

PHARMACOECONOMICS OF ANTIMICROBIAL USAGE IN  
THE SECONDARY CARE SECTOR

Sharon Elizabeth Parker

A Thesis Submitted for the Degree of PhD  
at the  
University of St Andrews



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**Sharon E. Parker**

**Thesis submitted for the degree of Doctor of  
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**September 1997**



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*I dedicate this work to my mother who always gave total unconditional love and support.*

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Much appreciation goes to my husband, Tim Williams, and my family and friends for their continued moral support and encouragement.

## Abstract

With the advent of regular antimicrobial usage there has been recognition, world-wide, that they are overused and misused. The worries of inappropriate usage centre on increased antibiotic resistance with consequent loss of efficacy, unnecessary exposure to toxic side effects and latterly, financial waste.

The two studies undertaken for this thesis have attempted to demonstrate how the combination of the costs of treatment with clinical and process measures of outcome could be used to avoid resource wastage.

The first study was an audit of aminoglycoside utilisation and the general antibiotic management of gram-negative bacteraemia. The aminoglycosides were found to be poorly managed and associated with several opportunity costs. Three readily measurable indicators of adverse outcome of hospital antibiotic therapy associated with marked increases in hospital treatment costs were characterised.

These were: -

- Change to an alternative iv drug regimen,
- Retreatment with antibiotics in hospital,
- Readmission with infection.

Another area of resource wastage was the excessive use of the intravenous route for antibiotic administration.

Detailed feedback of these findings to selected clinicians was used in an attempt to heighten awareness to the management problems and associated cost of the aminoglycosides and to persuade prescribers to reduce the overall use of intravenous antibiotics by taking advantage of oral administration.

The second study examined the feasibility of non-inpatient intravenous (NIPIV) antibiotic care and compared the costs and benefits of this type of programme with traditional, hospital inpatient treatment. The study concluded that NIPIV care is feasible, appropriate criteria for patient selection were developed and provision of a quality service was shown to be practical. The issue of 'safety' was raised; as a result, the notion of 'acceptable risk' deserves exploration in the further development of NIPIV care. Sensitivity analysis was used to explore the bias introduced to the costings in this study by commercial sponsorship.

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## Chapter 1

### 1. Introduction

In most countries, resources for healthcare are finite. Consequently, as the ability to treat and prevent diseases increases, the greater the pressure is to ensure these limited resources are used in the most efficient manner. Healthcare is a complex interplay of many dimensions and it is necessary, therefore, in the pursuance of efficient resource allocation to be able to evaluate both the costs and benefits of each dimension.

An aspect of healthcare which has seen much technological advancement is drug treatment. With this advancement, both healthcare benefits and costs have been accrued but because, primarily, cost-containment techniques have been used to control rising expenditure little is known about the cost-effectiveness of individual drug therapies. There is a need therefore, to value both existing and future treatments, in terms which go beyond acquisition costs alone.

From an acute, secondary care perspective, a therapeutic group of drugs which urgently require this form of evaluation, is the antimicrobials. Firstly, because drug budget expenditure is proportionally greater for antimicrobial agents than for any other therapeutic group and rationalisation of use based on cost-effectiveness would assist in more efficient resource allocation. Secondly, inappropriate use of antimicrobials can induce bacterial resistance which in turn, severely limits the future usefulness not only of the inducing agent but of other antimicrobials also. This problem is not experienced with any other group of drugs. The burden of costs caused by this phenomenon is largely unknown, however, Phelps (1989) estimated for 150 million annual antibiotic prescriptions in the US, the unrecognised costs of bacterial resistance could realistically range from \$.1 billion to \$30 billion.

This thesis aims to show how pragmatic application of basic economic principles to antimicrobial use, which involves assessing both costs and outcome of treatment, can be used to improve the efficiency of resource allocation for this group of drugs.

Chapter 2 describes the development of international interest in economic evaluation of healthcare with particular reference to drug budgets. The measures used by the UK government to exert downward pressure on NHS drug expenditure are discussed in detail. It is also shown how the UK government is attempting to introduce and encourage the application of economic principles to drug expenditure and highlights the difficulties associated with this initiative. Governmental measures introduced to control NHS drug expenditure however, have been of principal relevance to the primary care sector. Responsibility for controlling drug expenditure in the secondary care sector has fallen to this sector itself, consequently hospitals have developed and used their own cost-containment methods to limit drug expenditure. Chapter 3 discusses the effectiveness and failings of these methods and suggests that the ability to allocate available funds in the most efficient manner can only be further progressed by including outcome assessment as well as cost data, in the decision making process. Chapters 4 and 5 specifically discuss the various economic issues of antimicrobial use and show why this therapeutic group should be subject to more intense evaluation than they have been. Chapters 6 and 7 describe and discuss the practical application of economic evaluation to antimicrobial use. Chapter 6 reports a two phase observational study of antimicrobial utilisation. Phase I involved data collection and analysis, meaningful outcome measures were identified which in turn distinguished areas of resource wastage. The outcome measures identified were not institutional specific and could readily be applied to antimicrobial use in other secondary care institutions. Phase II endeavoured to modify current clinical practice by an interactive educational programme which utilised the information gathered and analysed in Phase I. The impact of this study on local practice and its weaknesses are discussed as are the implications for future research. Chapter 7 reports on a feasibility study of non-inpatient intravenous (NIPIV) antibiotic care. The direct variable costs and the benefits of NIPIV antibiotic treatment are compared and contrasted with traditional inpatient hospital treatment. The weaknesses of the study are discussed as are the implications for future research. Chapter 8 summarises the findings, critically appraises the two studies reported and suggests how their study design could be improved. Additionally a suggestion

is made for the way in which a national database for the economic evaluation of clinical practice could be readily constructed. The purpose of the database being to provide information to aid decision-makers in their quest to distribute funds in the most efficient manner.

## Chapter 2

### 2. **Governmental methods used to control drug expenditure and the role economic evaluation can play.**

Depending on the country and system of financing healthcare, the methods used to control the escalation of drug expenditure, at governmental level, varies. This chapter will briefly examine the development and use of the systems and control measures of several different countries but will largely focus on those in the UK.

#### 2.1 **The US approach**

Prior to 1966, 80% of healthcare provision in the US was privately financed by either the patient or by personal medical insurance. It is now a mixed model of federal and private provision. In 1966 two programmes were introduced by the US government to finance healthcare services for particular groups of people. These programmes were Medicare, which finances services for the aged and Medicaid, which finances services for the underprivileged. Medicare was extended in 1974 to cover all persons with chronic renal disease. With the enactment of these two programmes, the aged and poor had increased access to medical care. Hospitals were paid according to their costs, and physicians received their usual fees.

Coverage under Medicare is incomplete and the services covered are not comprehensive, in addition, a copayment is required for both hospital and physician services, There are limited benefits for post hospital care, such as skilled nursing and home care, and outpatient prescription drugs. All aged people, regardless of their income are presently covered by Medicare. Those aged with higher incomes can afford to purchase medical services and to buy supplementary coverage for those gaps not covered by Medicare. However, because Medicare benefits are not income-related, many aged find it difficult to pay the necessary out-of-pocket expenses. The result is that approximately 20% of the aged must rely on Medicaid (Feldstein, 1993).

Medicaid is financed through general tax revenues from the states and from federal income taxes. It is administered by each state, which in turn sets the

eligibility criteria for persons in receipt of Medicaid. There are wide variations in eligibility requirements and in services covered. Medicaid expenditures have risen rapidly and states have found themselves under pressure to reduce their share of the costs, they have attempted to do this by limiting eligibility, reducing benefits and by paying medical providers less. This latter approach has reduced the poor's access to medical care; lower reimbursement levels have limited the willingness of many providers to serve Medicaid patients (Feldstein, 1993).

Since the introduction of Medicaid and Medicare, uptake of private medical insurance, primarily through the workplace, has also increased. This increase in third party payers has led to an increased demand for healthcare which in turn has led to a rapid increase in overall healthcare expenditure. In 1965, 5% of the US gross national product (GNP) was being spent on personal medical services, by 1990 this figure had reached 12% (Feldstein, 1993). Both private insurance and government payments lessened the financial burden on the patient. Direct patient payments for all medical services declined from 51.6% in 1965 to 23.2% in 1990. As more of the bill for medical services was paid for by government and private insurance, the importance of price on the patients use of the service and choice of a provider from whom to purchase that service diminished. As a result, there were few constraints remaining to hold down the use of services and prices charged by providers. The lack of incentive, i.e. financial responsibility by the decision makers, patients and physicians, to substitute less costly care when medically possible, led to rapid increases in hospital costs, duplication of facilities and services and excess hospital capacity. It has been suggested (Feldstein, 1993) that hospitals avoided bankruptcy due to their excess capacity by exerting downward pressure on the admitting physicians to extend lengths of stay as well as admitting additional patients unnecessarily.

The US government has sought controls for holding down hospital costs. There was an attempt to rationalise the expansion of healthcare systems by reducing capital investment by stronger planning regulations. This culminated in the enactment of certificate-of-need (CON) laws in the mid 1970s (Feldstein, 1993). In essence this not only reduced competition for existing hospitals but also enhanced their market power by providing a barrier to entry. CON legislation

assumed that no changes were required in the method of hospital reimbursement and provided no new incentives to change patient or physician behaviour. It is not surprising that CON turned out to be unsuccessful in controlling hospital expenditures, which was the problem it was intended to redress. Other cost-containment measures were sought.

Prior to 1983 Hospitals in the United States (US) were reimbursed for healthcare services by Government agencies, insurance companies, and patients, either on the basis of charges or on the basis of costs. The Hospitals operated a practice called "cost-shifting" whereby the costs not met by certain insurance policies e.g. Medicare, Medicaid, Blue Cross, who paid what they considered basic hospital care costs, were shifted to that segment of the patient population who paid what they were charged (Finkler, 1982). Hence by escalating charges for various services, the Hospitals recouped unreimbursed costs. The clinical laboratory is an example of what was considered a convenient profit centre that could be used to support unrelated deficit-producing hospital operations (Conn, 1978). On October 1, 1983, the Prospective Payment Scheme (PPS) was introduced into the US as a form of hospital rate regulation for hospitalised Medicare patients. The PPS involves an average prospective payment made to the Hospital for treatment of a disease state which falls into a specific Diagnostic Related Grouping (DRG) rather than an individualised payment per patient treated. For example, the costs of managing a broken neck of femur in an elderly patient can vary widely for lots of different valid reasons, however, under the PPS a Hospital treating this indication now only receives a population averaged payment. For the obvious reason of profit maximisation the advent of the PPS necessitated that Hospitals rigidly control their costs such that every reimbursed dollar is used optimally. Cost-shifting was no longer an option, corrections in distorted charges had to be made and all cost components of diagnostic and therapeutic interventions had to be determined. Basically, the very last sticking plaster used in the care of a patient had to be accounted for. If the cost of treating a patient exceeds the DRG price, the hospital loses money. Hospitals therefore, have a financial incentive to produce care at a cost below the fixed DRG price, since the difference can be kept.

The DRG system is based on the assumption that patients with the same DRG would use similar hospital resources. DRG's are developed according to patient characteristics and the treatment received. DRG's are determined empirically; they were created according to whether the primary and secondary diagnosis, age and existence of a surgical procedure affected the patient's length of stay. Within each DRG there is assumed to be a certain resource use associated with a patient's treatment, and the use of those resources is assumed to vary according to such factors as the patient's age, sex, primary and secondary diagnoses, and discharge status. There are approximately 480 Medicare DRG's. Under DRGs, a fixed amount is paid to a hospital for each patient within a DRG. However, there are a number of concerns with the DRG system. These concerns revolve around the classification of assigned DRG, patients frequently have multiple diagnoses, the fact that DRGs do not take account of severity of illness and that the actual payment system is based on average costs over a large number of hospitals rather than the lowest production cost by the most efficient hospital for a given DRG. Facing a fixed price, a hospital has an incentive to minimise its costs of caring for the patient. It can do this by reducing a patient's length of stay, treating them as outpatients and restricting the amount of ancillary services used. In addition, it is also profitable and possible for a hospital to manipulate the DRG coding for patients with multiple pathology to select the higher price attracting DRG classification. This has been termed DRG creep' (Donaldson *et al*, 1991). Exclusion of more severely ill patients from the institution will increase net profits.

A study by Assaf *et al* (1993) carried out in 7 New England hospitals looked at the assignment of discharge diagnostic codes for patients with coronary heart disease (CHD), both before and after the inception of the PPS. These workers found that the frequency of assignment of codes for the acute forms of CHD, which entail higher reimbursement, had increased significantly. Conversely, the frequency of assignment of codes for the chronic forms of CHD, which entail lower reimbursement, had decreased reciprocally. These workers concluded that the PPS had influenced the assignment of hospital discharge codes in a way that would increase payment. It was not possible, however, to distinguish from the data

whether hospitals began to assign more precise diagnoses with the advent of the DRG system, or whether they began to favour diagnoses of acute conditions solely for financial reasons.

It has been demonstrated by several groups (Jacobs *et al*, 1992, Falcone *et al*, 1992) that there is a definite financial disincentive to hospitals to treat severely injured patients as the DRG-based reimbursement is substantially lower than the actual treatment costs. Jacobs *et al* (1992) examined the charges associated with treating trauma patients over a 5 month period and compared this with actual reimbursement. Only 65.5% of the total charges were reimbursed. Falcone *et al*, (1992) showed that surgical review of trauma patient DRG assignment can improve reimbursement rates but even so there remains a short fall from total calculated charges.

More effective ways of using drugs has been one mechanism by which hospitals have sought to reduce the costs of care. Several studies evaluating the impact of certain drugs on the cost of treatment began to appear in the literature shortly after introduction of the PPS (Crist *et al*, 1987, Quintilliani *et al*, 1987, Dannenhoffer *et al*, 1989). It was at this point that pharmacoeconomic evaluation i.e. the application of economic evaluation to drug use, came to be of high profile within the American Health Care Institutions (Bloom, 1992). The necessity of cost control had to be reconciled with the maintenance of quality of care of the patient (Conn *et al*, 1985), pharmacoeconomic evaluation enables this from the perspective of drug treatment however, it does not cover the entire culminated costs of care. Friedrich *et al* (1992) examined the hospital, pharmacy and antibiotic costs for 46 patients with penetrating abdominal trauma admitted over a 4 year period and compared them with reimbursement received. Less than 10% of patients were responsible for 43% of the hospital costs. The antibiotics represented only 0.5% of the DRG reimbursement received. For 4 patients costs exceeded DRG reimbursement by a median of \$8210 leading to an average net loss of \$295 per trauma patient. It was concluded that cost-containment practices for this set of patients should be directed at other ancillary services and length of stay as any antibiotic cost-containment modification would have negligible impact on reimbursement monies.

DRG reimbursement can be further maximised by 'unbundling' of services. Unbundling occurs when the hospital shifts part of the treatment to another setting while still receiving the full DRG payment. For example, patients may be discharged earlier and admitted to a nursing home or to their own home; the patients can then purchase, through Medicare, additional services, such as home care or additional outpatient services. Unbundling reduces costs in the regulated sector and shifts costs to the unregulated sector. Costs are shifted to the patient in the form of additional out-of-pocket expenses and to family members who have to care for the discharged patient. Unbundling increases total Medicare expenditures, since hospitals receive the full DRG payment while Medicare incurs additional costs for nursing home and home health care for services previously provided in the hospital.

Another governmental initiative during the 1970s, to contain healthcare costs was the inception of health maintenance organisations (HMO's) (Feldstein, 1993). HMO's are capitation prepaid health plans. They are a heterogeneous mix of companies which are organised in a variety of ways (Luft, 1991). For an enrolled population, the contractual responsibility of an HMO is to assure the delivery of a range of medical services and to reimburse patients incurred costs. HMOs can own their own hospitals and employ physicians on salary. Alternatively, an HMO can contract separately with hospitals and physicians for their services and reimburse them on a fee-for-service basis and have a profit sharing bonus. The economic incentive of HMO's is to retain the difference between the capitation payment and the costs of providing medical services. The organisation and its physicians have a financial incentive, therefore, to minimise the cost of medical care provided to its enrollees. A key aspect of the HMO concept is that providers control the whole range of benefits. HMO's attract enrollees by a variety of methods, they generally cover a wider range of preventative services and prescription drugs than conventional insurance plans usually offer. They also have minimal copayments and lower premiums than conventional fee-for-service insurance plans. The lack of financial barriers can be an attraction to consumers. The negatives that must be considered against the lower costs are longer waits for an appointment and less continuity of care with the same physician.

The one mechanism that the US government has put in place to directly control drug expenditure has been the federal Omnibus Budget Reconciliation Act of 1990. This Act was designed to reduce and control federal and state outlays for prescription drug products provided to Medicaid outpatients (ASHP Govt. Affairs Div., 1991). From January 1, 1991, for the drug product line of a manufacturer to be eligible for any coverage under Medicaid, the manufacturer must agree to provide rebates to all state Medicaid agencies i.e. a rebate is made to the state by the manufacturer towards the state's expenditures for the manufacturer's drugs. The amount of rebate a manufacturer must give is a proportion of the drug price charged to the retail supplier. This Act does not relate to drugs prescribed in hospital, however the Act may have an impact on the hospital drugs budget as the pharmaceutical industry may choose to maintain its profit margin by offsetting its rebates with price increases for new products.

In summary, prior to 1966 access to healthcare in the US was limited by an individual's ability to pay. Changes within the US system have to some extent increased access to healthcare although Iglehart (1986) reports that some 30 million citizens still lack healthcare insurance. The changes in access have increased overall healthcare expenditure. Various mechanisms have been sought by the US government to contain this expenditure which in turn has forced Hospitals to improve their internal efficiency of resource utilisation such that profits can be maximised. From a governmental perspective the current DRG-based reimbursement system is not entirely successful in controlling healthcare costs and would appear to be open to abuse as evidenced by DRG creep and unbundling techniques. Enrolment of Medicare patients with HMO organisations removes the problems associated with DRG reimbursement away from the government. However this shifts costs to the enrollee as the range of healthcare services provided are limited to those set by the HMO.

Because of the way in which patient treatment costs are reimbursed the US government has only been motivated to implement mechanisms which directly control outpatient drug expenditure. The control of inpatient drug expenditure has become the concern of the providers i.e. the Hospitals, HMO's etc. and it is these

organisations who have become increasingly interested in the role pharmacoeconomics can play in assuring efficient drug use.

The evolution of Canada's scheme of hospital and physician insurance dates from 1914, when the first Municipal Doctor Plan was introduced in Saskatchewan. Through the intervening years public policy developed between federal and provincial governments culminating in 1965 in a publicly administered, universal program for medical services. All of Canada's 25.5 million citizens received care through its health scheme irrespective of their circumstances. The provinces were made responsible for administering the health insurance plans, the funds for which, come partly from the federal government and partly from taxation of provincial citizens. The ten provinces have broad constitutional authority to spend the revenues as they deem best, and to regulate health programmes. Citizens can still undertake private health insurance plans for extended benefits, but under the provincial health plans, individuals have had virtually unlimited access to care with the physician of their choice. It is understandable that Canadians report a high level of satisfaction with the municipal health care programme (Iglehart, 1986, Wyman *et al.*, 1995).

Problems have developed with the funding of the health insurance programme, not only because of increased health expenditure but also because the country's federal government faces a massive budget deficit (Iglehart, 1986). The government has transferred the health care expenditure problem to the provincial governments to deal with. This has been done by capping the federal financial contribution to the health insurance plans and by implementing legislation that protects patients from paying for any part of their care (Iglehart, 1986). Provincial governments however, are transferring the responsibility for many services to third parties by de-listing services which were previously covered by the public health insurance programmes (Carruthers, 1995). These third-party payers include employers, insurance companies, no-fault automobile insurance companies and the public, which now pays directly for services such as in vitro fertilisation (Carruthers, 1995).

Ontario is Canada's most populated province and its most influential region in terms of establishing trends. Early in 1992 Ontario's Health Minister outlined various health care reforms (Martin, 1992). Strategic priorities included major reviews of the hospital system, laboratory services and the drug-benefits programme. Governmental drug expenditure to date has been restricted to specific patient populations (Carruthers, 1995).

In Ontario, residents are eligible for drug benefits if they are over 65 or if they have low incomes. The provincial government plan pays for the entire cost of the prescription including the pharmacist's dispensing fee for this group of patients, so long as the drug is listed either as a benefit in the Ontario Drug Benefit Formulary or as a nonformulary benefit for specific indications, or special permission has been received from the Ontario Drug Programs Branch after written clinical justification by the attending physician. Recommendations about listing of pharmaceutical products in the Drug Benefit Formulary are given to the Minister of Health by the Drug Quality and Therapeutics Committee (DQTC). The committee, which considers issues of effectiveness, safety and cost, is made up of a group of experts representing academic and community-based physicians, pharmacists and biostatisticians (Detsky, 1993).

The provincial drug programmes are the largest purchasers, on behalf of their beneficiaries, of drug products in Canada. The pharmaceutical industry has now come under the spotlight for cost-containment measures. Pharmaceutical manufacturers who submit an application for consideration of a drug to be added to a provincial Drug Benefit Formulary are now expected to provide economic information beyond simply listing the unit price of the product. Not all submissions require economic analysis, but the submitting manufacturer is expected to justify its absence (Detsky, 1993). At the present time each province performs a separate review of the submission information on effectiveness, safety and cost. An inter-provincial economic working group proposed that a single review committee be established for the purpose of reviewing economic components of pharmaceutical drug listing submissions (Detsky, 1993). Detsky (1993), in recognition of the fact that experience and expertise in the use of economic analyses was still in its infancy, for both the pharmaceutical industry

and government, published proposed guidelines for the economic analysis of pharmaceutical products. Deregulation of a larger number of drugs from prescription status to over-the-counter status has been proposed recently (Morgan *et al*, 1995) as a method to reduce costs to the Canadian government. It would appear however, that there is some initial resistance by the medical fraternity to this suggestion.

As in the US, governmental initiatives to control drug expenditure have largely focused on outpatient use rather than in the secondary healthcare setting.

### **2.3 The Antipodean approach**

Australia's public healthcare system is similar in many respects to the British National Health Service. It is funded by a special tax levy on income and provides universal access to doctors, hospitals and most ethical pharmaceuticals. Many sections of the community (low income, pensioner and other social welfare groups) receive healthcare at no cost to themselves.

As with other countries there has been concern in Australia about the level of public expenditure on healthcare, in 1990-1991 this totalled A\$21.7 billion (Parry 1994). Although the pharmaceuticals budget accounts for less than 9% of recurrent healthcare expenditure (Parry, 1994) it has been the object of vigorous cost containment by the Government. Bloom (1992) argues the reason for this is because it is a highly visible component of healthcare expenditure unlike other portions of the expenditure and therefore becomes an easier target for academics and policy makers looking for ways to cut costs. Credence is given to this statement by Rafuse (1995) who reported on a project evaluating where major savings could be made in the Canadian Health Care System. The project suggested that the biggest saving would be made by a major reconfiguration of health care facilities such as reducing the number of acute care hospital beds, reducing the time spent in hospital and using alternatives such as residential and community care for the elderly. Logistically this is a more difficult area of expenditure to deal with than the pharmaceuticals budget.

In Australia 70% of prescription pharmaceuticals are reimbursed by the Pharmaceutical Benefit Scheme (PBS) (Parry 1994). The PBS makes available to patients a wide range of prescription drugs at subsidised prices. Although there is a small capped co-payment by general users, certain categories of patient are not charged at all. Although the PBS was designed to provide low-cost access to a core range of drugs, the system has effectively replaced the free market with regard to prescription drugs. Products not covered by the PBS are in competition with drugs available on the PBS and have little chance of significant prescribing by practitioners.

The Commonwealth of Australia exercises control over the ethical pharmaceuticals market by virtue of the fact it is the only purchaser under the PBS. A variety of mechanisms have been used to restrain expenditure on new pharmaceuticals (Parry 1994). These include:

- 1) Authority requirements' on drugs costing more than A\$30 per prescription, whereby the more costly drugs can be prescribed only by the physician with explicit authority from the Department of Health. This is purely a budgetary device designed to suppress use of newer, more costly drugs, the cost of which is borne largely by the Government under the PBS.
- 2) Delayed listing of newer, more expensive drugs by the Australian Drug Evaluation Committee. The needs of tight budgetary constraints are met by delays of up to 5 years in approval status.
- 3) The traditional pricing mechanism of the PBS. After general marketing approval, a drug will be listed on the PBS subject to negotiations with the Commonwealth of Australia with respect to its value to the PBS and the price that will be reimbursed by the Commonwealth.
- 4) Imposition of an economic analysis requirement for PBS listing. An application for a new drug to be added to the PBS must now demonstrate cost-effectiveness compared with existing medical treatment(s), including existing drug

therapies. This control mechanism is recognition of the importance of economic evaluation in the allocation of resources by policy makers. Australia is the first country to issue mandatory guidelines of this nature.

Bloom (1992) in an analysis of the guidelines stated that although the requirements are seemingly appropriate several issues relating to them are raised. If studies of cost and benefit are to be done in tandem with controlled clinical trials of safety and efficacy, it is difficult to translate the artificial results of efficacy into effectiveness criteria so that 'appropriate' policy and other decisions can be made by political authorities. Clinical use of a drug and consequently the economic ramifications of that use can be far different from the rigid, prescriptive use of the drug under study conditions (Strom *et al*, 1985). A further issue is how the results of economic evaluation will be used. The criteria for registration and pricing purposes must necessarily be complex because of the many different types of medications and the effects they have ranging from life-saving through to those that ameliorate symptoms alone.

#### **Cost-effectiveness requirement for PBS listing**

The new pharmacoeconomic policy requirement for PBS listing infers that the federal Government considers various areas of expenditure within the context of the global healthcare budget. Parry (1994) suggests that this is not the case, he states that policy expenditure decisions on pharmaceuticals are taken in isolation from any implication for their effects on expenditure on medical or hospital services despite the new requirements. Although a new product may lead to significant savings elsewhere in the healthcare system, such as reductions in physician visits or reduced hospital stays, commitment to additional expenditure on that new drug is driven by PBS budgetary constraints only. Parry (1994) argues that this is because federal government budget allocations for each area are separate from each other and the inter linkages between categories of healthcare are almost completely ignored. If this is the case, it makes a nonsense of the cost-effectiveness requirement for PBS listing and substantiates one of the conclusions made by Drummond (1991) prior to the introduction of the guidelines. He concluded that inappropriate implementation would be nothing more than an

expensive way of slowing down the entry of new medicines into Australia and of reducing pharmaceutical expenditure. In essence the guidelines achieve the objective of reducing the drug budget but the effect on overall healthcare expenditure remains unknown.

#### **2.4 The UK Approach**

The British National Health Service was introduced in 1948 to provide a comprehensive health service available to all, free at the point of delivery and financed mainly from taxation. Since its inception there has been a steady increase in the understanding of diseases, the development of healthcare technology and the ability to treat diseases. Consequently there has been an escalation in demand for public financial resourcing of healthcare. Responsibility for managing healthcare services is delegated by the Government's NHS Management Executive as far as possible to local health authorities. Until April 1, 1996, Family Health Service Authorities (FHSAs) were responsible for assessing the needs of their populations for primary medical and dental care and for developing services to meet those needs, through liaison with medical and dental practitioners. District Health Authorities (DHAs) were responsible for assessing the needs of their populations for all other community and secondary care, and for purchasing care from public and private providers to meet those needs. Since April 1, 1996, FHSAs and DHAs were structurally reorganised into unified Health Authorities (HA) with the previous remits being retained by the new HAs (Curtis, 1996).

On a percentage basis the proportion of spending on drugs to total National Health Service (NHS) spend in the UK has remained relatively constant since the establishment of the NHS. It was 9.3% in 1949-50, 9.9% in 1959-70 and 11.1% in 1989-90 (Health Committee, 1994). However, this disguises the fact that actual drug expenditure is on the increase. In England in 1992-3 gross NHS spend was £29.4 billion of which expenditure on drugs amounted to £3.3 billion (see Table 2.1).

The increase in the drugs bill is due to two factors, an increase in the number of drugs prescribed and an increase in the average price of medicines. The increase in the volume of drugs prescribed can be explained by an increase in the ageing population (Mulley, 1995), an increased rate of diagnosis and an increased use of drugs in preference to other treatments. The increase in the average price in medicines is due in the main to the introduction of new products, as the average price of existing drugs rises slowly. The average price of drugs bought by the Hospital and Community Health Services (HCHS) sector (otherwise known as the secondary care sector) rose by 13.4% in 1992-93 and by an average 7% each year over the preceding 11 years (Health Committee, 1994).

The largest proportion (80%) of the NHS drugs budget is accounted for by medicines prescribed by General Practitioners in the Family Health Services (FHS) sector (otherwise known as the primary care sector). Such drugs cost £2.6 billion in 1992-3. The figure for drugs purchased by the HCHS in the same year was £634 million (Table 2.1).

**Table 2.1 Cash spent (millions) on drugs bill in England**

<b>Cash spent (millions) on drugs bill in England</b>			
<b>Year</b>	<b>FHS (primary care)</b>	<b>HCHS (secondary care)</b>	<b>% increase on preceding year</b>
80/1	766	185	
81/2	876	214	15
82/3	1009	245	14.5
83/4	1130	267	10.9
84/5	1192	274	2.6
85/6	1275	297	8.4
86/7	1378	318	7.0
87/8	1536	352	10.7
88/9	1744	380	8.0
89/90	1942	414	8.9
90/1	2080	460	11.1
91/2	2317	591	28.5
92/3	2641	634	7.3
93/4	2951	696	9.8
HCHS - Hospital & community health services      FHS -Family health services			

Personal communication, Norman Taylor, DoH, London, 1995.

### 2.4.1 Cost containment

The continuous real terms increase in the drugs bill has led the Government to explore ways in which these costs might be contained. The two principal means at the Governments disposal for doing this are by influencing the price of drugs and by seeking to reduce the use of expensive drugs. Table 2.2 summarises the ways in which the Government has endeavoured to influence the price and prescription of drugs in an attempt to limit the NHS drug bill.

**Table 2.2 UK governmental methods for influencing the price and prescription of drugs**

<b>Price modifying schemes</b>	Pharmaceutical Price Regulation Scheme (PPRS) Drug Tariff
<b>Prescription modifying schemes</b>	Selected List PACT Data Indicative Prescribing Scheme Deregulation of Prescription Only Medicines to Pharmacy Medicines (POM to P) Greater use of generic drugs
<b>Patient Demand Limiter</b>	Fixed charge co-payment

#### **2.4.1.1 Price modifying schemes**

##### **Pharmaceutical Price Regulation Scheme (PPRS)**

The Pharmaceutical Price Regulation Scheme (PPRS) is a voluntary arrangement between the Department of Health (DoH) and the pharmaceutical industry. It controls prices indirectly by controlling companies profits, however as it is primarily a profit control scheme, the price of an individual drug is entirely a matter for the company concerned (Wolfson *et al*, 1983).

##### **The Drug Tariff**

The Drug Tariff is a Government publication which amongst other information provides guidance on how pharmacists will be reimbursed for dispensing NHS prescriptions received from GPs. The Drug Tariff sets generic drug prices for reimbursement of pharmacists at levels that reflect those available in the market place. It follows rather than leads prices. In the view of the DoH it will exert some downward pressure on prices especially for those drugs for which there is competition as suppliers will be aware of the level at which pharmacists will be reimbursed and that they will be reluctant to buy alternative generic products at significantly higher prices than those set in the Tariff.

#### **2.4.1.2 Prescription modifying schemes**

##### **The Selected List Scheme**

In 1986 regulations were introduced which limited the range of drugs available for prescription and supply on the NHS in several therapeutic categories, this included the benzodiazepines because it was felt there was a specific problem with this group of drugs. The rationale behind the selected list was that the Government decided firstly, £120 million were unnecessarily spent each year on a range of medicines which were used for minor or self limiting ailments which did not require medical intervention and could be bought over the counter, for example, tonics, cough and cold remedies. Secondly, £40 million a year were spent on benzodiazepines which included expensive proprietary brands of a similar nature to and no advantage over the small number of generic benzodiazepines which

were available. The principle of the Selected List is that drugs which are ineffective or which are more expensive than other equally effective drugs should not be prescribed, these drugs essentially form a 'blacklist' i.e. the NHS will not pay for these drugs. The proviso within the scheme is that a patient may request a branded drug that is not available on NHS prescription, to be prescribed privately. For this the patient incurs the full cost of the drug and dispensing charge. Introduction of the limited list was estimated to save the NHS approximately £100 million each year (Deitch, 1984). In addition to the 'blacklist' of drugs there are drugs called 'borderline' substances which may not be prescribed on the NHS unless the drug is for a specific medical condition. The NHS prescription for the borderline drug has to be annotated indicating that it is for the treatment of an allowed medical condition, for example, the mucolytic acetylcysteine can be prescribed for the treatment of patients with cystic fibrosis but cannot be used for any other type of patient.

#### **Indicative Prescribing Scheme**

Family Health Services Authorities (FHSA's) were charged by the Government both with promoting rational prescribing and with keeping general practitioners (GPs) prescribing expenditure within budgetary allocations agreed with regions. Although a GP is limited to some extent by the selected list, GPs can decide how much and what they prescribe. The government sets an in-year Reserve to cover overspends in the drugs budget but access to the Reserve cannot be regarded lightly. The Reserve is limited in size and is intended as a contingency to deal with unforeseen circumstances, for Treasury to permit access to it, it has to be demonstrated that any overspending which has occurred is despite best efforts to promote effective and economical prescribing (NHSME, EL(95)8, 1995).

From 1991 each GP practice has been asked to keep expenditure within its indicative (target) drugs budget. This budget was set for all GPs by their FHSAs. The methodology deriving indicative prescribing amounts, however, has been subject to criticism because until 1992/3 it was based on the historic expenditure of a given practice adjusted for price and volume changes and for local factors. This led to inequity between those prescribers who had historically attempted to rationalise their prescribing and those who hadn't. Little incentive was created for

doctors who were over prescribing to review their habits (NHSME, EL(93)4, 1993). Since 1993 historic costs have been supplemented by weighted capitation benchmarks, taking into account the age and gender structure of each GP's practice list (NHSME, EL(93)4, 1993). The purpose of weighted capitation benchmarks was to enable FHSA advisers to make more systematic and demonstrably fair reductions to the indicative (target) drugs budget of historic high prescribers.

GPs are only guided by the indicative prescribing amounts set annually and FHSAs have had virtually no power in the last resort to compel GPs to prescribe in a particular way unless it could be proved that their actions were harmful to patients. However, for those GP's who joined the voluntary fund-holding scheme which was part of the Governmental healthcare reforms of 1989 there has been a powerful incentive to prescribe rationally. The GPs of a fundholding unit directly manage the practice budget for all aspects of healthcare. The fundholders themselves become purchasers of care for their patients rather than this being done on their behalf by the local FHSA. The economic incentive to the fundholder is that savings made in one area, for example pharmaceuticals, can be redeployed elsewhere to improve the range of services offered by the practice. This incentive has been shown to have a definite impact. A study specifically designed to examine the effect of the fundholding scheme was carried out over a four year period. Six fundholding units were compared to non-fundholding units as controls. Amongst other findings it was demonstrated that the fundholding units had a reduced volume of prescribing, were more cautious in the prescription of new and more expensive preparations yet maintained quality of prescribing as measured by their increased prescribing volume in 3 clinical areas recommended by consensus (Howie *et al*, 1995). These findings are supported by a review of primary care prescribing by Walley *et al* (1995). In summary, fundholders were found to make savings on their budget by either reducing prescribing costs or containing prescribing cost increases.

An incentive scheme for non-fundholders was devised for the 1995-96 budgetary allocation following the perceived success of the incentive scheme for fundholders. Under the new arrangements all non-fundholding practices were given their prescribing allocation as a range of expenditure within which it was

reasonable to expect the practice to meet the needs of their patients by rational, cost-effective prescribing. Practices which contained their prescribing expenditure within the range were eligible to receive an incentive payment subject to certain conditions (NHSME, EL(95)8, 1995). The type of condition that a FHSA could attach to the award of an incentive payment were, for example, the achievement of specific levels of generic prescribing/dispensing, audit of repeat prescribing systems, attendance at prescribing seminars etc. It was stated that these conditions were to be made known to the practices before the start of the scheme (NHSME, EL(95)8, 1995). For the year 1996/97, introduction of the unified HAs has essentially not changed the arrangements for prescribing allocations and incentives to GPs (NHSME, EL(95)128, 1995).

#### **PACT (Prescribing Analyses and Cost Tabulations) data**

Summary PACT data has been supplied on a monthly basis since 1988, by the Prescription Pricing Authority, to all FHSAs and most GPs. There are 3 levels of data, summary, detailed and full. The data provides GPs with information about their prescribing patterns and costs as well as information about FHSA and national averages. More detailed data are automatically sent to expensive prescribers, which might include, for example a breakdown of prescribing costs by therapeutic group. Any GP can request full details.

PACT data can be used as a tool by GPs to monitor performance against their target budgets, it also enables them to compare their prescribing behaviour to that of their colleagues, both in their own area and nationally. In Scotland the equivalent to PACT data is SPA data which is disseminated on a quarterly basis.

PACT data reveals only what GPs prescribe, in what quantities and at what cost. It does not reveal what conditions the drugs were prescribed for, in what dosage, or for how long, or how many patients have been treated, all of which are central to any assessment of appropriateness, effectiveness and cost-effectiveness. Many prescribing errors would escape unnoticed in a scrutiny of PACT data alone.

#### **Deregulation of Prescription Only Medicines to Pharmacy Medicines**

Under the Medicines Act 1968, medicines are assigned one of three legal categories when they are licensed: prescription only (POM), pharmacy sale (P) or general sale (GSL). Medicines in the latter two categories may be supplied over

the counter (OTC) without a prescription with the proviso that the P medicine is sold under the supervision of a pharmacist. Many of these two categories may also be prescribed through the NHS. The government eventually realised that deregulation of medicines from POM to P provides a benefit both to the NHS and to the patient. The NHS benefits by shifting the costs of the medicine to the patient and the patient benefits by the convenience of being able to obtain the medicine without referral to a GP, in addition, for those patients who pay prescription charges, this may also be a less expensive way of acquiring the drug (Bradley, 1995). A driving force for deregulation, therefore, was government policy to contain the NHS drugs bill. In the late 1980s the government made it easier to reclassify certain drugs from POM to P. Initially progress was slow with only 10 medicines being reclassified between 1988 and 1992. However, the criteria which govern whether a medicine should be POM or P became the subject of an EC directive (1992) which was incorporated into UK law by way of amendment to the Medicines Act 1968 (Medicines Act 1968 Amendment, 1992), since this amendment a further 40 medicines have been reclassified (Blenkinsopp *et al*, 1996).

The likely NHS expenditure consequences of increased deregulation are unclear. In some instances, savings in the drugs budget have resulted:- for instance £1.8 million per year when hydrocortisone and loperamide became available from pharmacies without prescription; in others prescription expenditure has continued to rise (Audit Commission, 1994). Another potential saving is in GPs time. A survey by the Proprietary Association of Great Britain (PAGB) estimated that appropriate self medication with an OTC drug would reduce GP's workload by sixteen consultations a day. One estimate is that 100-150 million general-practice consultations per year are for conditions that are potentially self treatable (Anon, 1994).

The deregulation of drugs has not been unopposed (Erwin *et al*, 1996), with many GPs disagreeing that the supply of certain medicines should be allowed without a prescription. However, the level of opposition has decreased since the inception of fundholding practices. The reason suggested to support this reduction in opposition is that fundholding practices have a greater concern for containment of

prescribing costs than non-fundholding practices and therefore support the proposal that a wider range of drugs be available for purchase by a patient without a prescription (Erwin *et al*, 1996).

### **Fixed charge co-payment**

Unless a patient is exempt, a fixed charge co-payment has to be paid towards each item prescribed for them by a GP. There are several categories of exemption, for example, old people, children, low income, certain medical conditions etc. At present the cost per item for a patient not exempt is £5.50. This flat-rate charge bears no relationship to the amount of medicine prescribed or its actual cost to the NHS. For those patients who receive medication on a regular basis but who are not exempt and have to pay the fixed charge there is a facility called a pre-payment certificate. This is rather like an insurance policy which limits the amount the patient co-pays over a given time period towards their medication. Once a pre-payment certificate is purchased no further co-payment is required for a prescription regardless of the number of items prescribed within the twelve months covered by the certificate. At the present moment a pre-payment certificate costs £82.00 for 12 months, provided the patient is prescribed more than 15 items within the year then the pre-payment certificate is a cheaper option than paying the fixed £5.50 charge per item.

The total revenue raised by prescription charges in 1992-93 was £242 million, which amounts to 7.3% of the NHS drugs budget, and 0.8% of the entire NHS budget (Health Committee, 1994). Information about the cost of collecting this revenue is not available. In 1992 over 24 million people were estimated to be eligible for free prescriptions by reason of belonging to one or more categories. It is not known how many people were exempt from charges specifically on medical grounds. In 1992 80% of items were dispensed without charge (Health Committee, 1994).

### **2.4.2 NHS Management Executive (NHSME) Letters**

Another method the Government uses to exert downward control over the NHS health care budget is dissemination of NHS Management Executive (NHSME)

Letters. The NHSME issues guidance directives in the form of 'executive letters' to the local health authorities concerning amongst other matters the management of the drugs budget. It is in this way that the call for action on national initiatives is disseminated. It is also through these letters that the Management Executive informs the local health authorities of changes in the fiscal management of the annual budget allocations. The success of these guidance directives appears to be dependent on the degree of coercion associated with these communications.

A recent executive letter (EL(93)115) stated that the NHSME **wished** to see better use made of research-based evidence about clinical effectiveness. The letter provided a list of core information services concerning 'clinical effectiveness' which are available for consultation by purchasers and providers to aid them with this initiative. However, the adage 'a horse can be led to water but cannot be forced to drink' is rather true in this instance Maynard (1993) suggested that most purchasers were not translating established performance guidelines into purchasing practice as is evidenced by unnecessary insertion of grommets into children with glue ear and unnecessary D&C's (Lewis, 1993). Maynard (1993) further suggested that there is a general failure to support the development of national initiatives to identify effective therapies that are also cost-effective. One reason for this maybe that research findings are difficult to interpret and apply. To highlight this, Scezepura (1994) used the example of the various interventions which can be used after myocardial infarction. Coronary heart disease is the most common cause of death in Britain, consuming approximately 2.5% of NHS resources and costing nearly £10 billion a year in lost production and hospital care (Scezepura 1994). The literature contains few studies of the cost-effectiveness of the various interventions in myocardial infarction, and those that have been reported show little consistency in methods, costs measured, discounting of future costs and benefits, or how costs are related to outcomes. Standardisation of instruments to measure both clinical and economic factors is obviously a critically important next step in the evolution of useful research based information (Scezepura 1994).

It could also be said that there is a degree of resentment by healthcare professionals who are expected to implement the government initiatives. An

editorial in a leading medical journal (Ham, 1995) following the publication of EL(93)115 on clinical effectiveness, suggested that it is not only the use of medical treatments which needs to be evidence based but also the policy making for health services as a whole at Governmental level. It certainly does appear that the Government is capable of sending out mixed messages, an example of this is the NHS Executive Letter which directs Health Authorities to ensure that Beta-interferon, a drug used to treat multiple sclerosis, is available on the NHS despite the fact that many consultant neurologists consider this drug to be neither clinically proven nor cost-effective (Butler, 1995). There needs to be a mechanism for transferring the results of research into policy. Ham (1995) suggested that the only way in which the NHS could progress was for evidence-based policy making and evidence-based medicine to go hand in hand.

In contrast to EL(93)115 which was not associated with any direct form of coercion, the directive EL(95)5 about the purchase of high-tech health care for patients at home will most definitely be implemented because it includes mandatory financial guidelines. In fact EL(95)8 stated that resources available for allocation to GP practices had been reduced because of the initiatives in EL(95)5.

### **2.4.3 Other forms of control for restraining drug expenditure**

#### **2.4.3.1 Guidelines for Economic Analyses of Drug Treatment**

The DoH in conjunction with the Association of British Pharmaceutical Industries (ABPI) have issued guidelines (DoH Press Release, 1994) for the conduct of economic analyses of drug treatment, but it would appear that this issue is little more than rhetoric. The guidelines are for the conduct of clinical trials but there is neither incentive or a mandatory requirement for their implementation (Freemantle *et al*, 1995). Without a facilitative or coercive approach it will be surprising if their use becomes widespread.

### 2.4.3.2 Expert Body Evaluation of the Drugs Budget with their findings and recommendations for the future

#### 2.4.3.2.1 Governmental Audit

The Audit Commission was set up by the Government in the early 1980s to audit and assess whether local authorities were delivering value for money. The Commission was to promote economy, efficiency and effectiveness. The Government's white paper on the NHS published in 1989 announced that the Audit Commission was to take on the external audit of the health service. The responsibility began on 1st October, 1990 (Smith, 1990). The Audit Commission uses 3 criteria in deciding which issues to study, these are:-

1. The issue must carry substantial financial costs,
2. There is an opportunity to achieve improvements, and
3. There is the possibility of change, (Smith, 1990).

The NHS drugs budget fulfils all 3 criteria and as the largest proportion of the NHS drugs budget is accounted for by medicines prescribed by GPs it is not surprising that this became the focus of an Audit Commission evaluation.

A report of the GP study (Audit Commission, 1994) stated that more rational prescribing by GP's would lead to better quality care for patients and to major economies in drug expenditure. It was suggested that a saving of £425 million would be made throughout England and Wales if all doctors were to prescribe in a cost-effective manner similar to those GP practices classed as 'good' prescribers in the evaluation. The report identified opportunities which could lead to better patient care and more effective use of NHS resources. One of the areas of patient care identified which required **increased** drug expenditure was that of the preventative treatment of asthma. It was estimated that if all GP's were to increase their prescribing of inhaled steroids for preventative treatment to 50% of the prescribed bronchodilator rate, then drug expenditure would increase by £75 million. However, it was considered that it would be cheaper for the NHS as a whole as fewer patients would be admitted to hospital with severe asthma attacks or complications. Each year 2,000 people die in the UK as a result of an asthma

attack, of which 80% are avoidable. It was also felt that there was a general under diagnosis of chronic conditions which if reversed would have additional prescribing resource implications (Audit Commission, 1994). Table 2.3 summarises the opportunities for rationalising resources as identified by the Audit Commission.

**Table 2.3 Opportunities for more rational prescribing with implications for resources (from Audit Commission, 1994)**

<b>Opportunity for modification</b>	<b>Resource implication (compared to 'good' prescribers)</b>
Over prescribed drugs	£295 million saving
Less prescribing of drugs of limited therapeutic value	£45 million saving
Substitution of alternative drugs	£25 million saving
More generic prescribing	£50 million saving
More selective use of expensive formulations	£30 million saving
More inhaled steroids for asthma	£75 million spending increase
Additional prescribing resulting from a reduction in the under-diagnosis of chronic	£ not estimated

### **Hospital/GP interface and cost-shifting**

GP prescribing is influenced by medicines initiated in hospital or recommended when patients are referred to hospitals for an opinion. The full expenditure implications are difficult to quantify (Audit Commission, 1994). There are two reasons why hospital doctors prescribing behaviour should initiate more prescribing, and more expensive prescribing amongst GP's than is necessary. Firstly, drugs may be available at a lower price in hospitals than in the FHS (primary care) sector. The drug companies offer 'loss-leaders' to hospital pharmacies at an artificially low price so that the drug replaces others, which are often cheaper in the primary care sector, in the hospital formulary. Because hospitals are cash limited there has been a strong incentive to persuade their doctors to prescribe the cheapest, clinically appropriate drugs. Formularies are used to limit or guide their choice. By offering 'loss-leaders' the drug companies

are attempting to get their products initiated by the hospital based doctors (Wolfson *et al*, 1983). When a patient goes to the GP for further prescriptions it is very difficult for the GP to change the prescription even if there is a cheaper and equally effective alternative as the patient sees the consultant as the ultimate decision maker on therapy (Health Committee, 1994). Lower hospital drug prices may also result from hospitals using their position as bulk purchasers to negotiate lower prices. Whichever way the hospital drug price is lowered, the drug company will attempt to recoup 'lost profit' by raising the price of their drugs in the primary care sector (Wolfson *et al*, 1983). Secondly, hospital drugs budgets are cash limited whereas those of FHSAs are not. Although fundholders have specific budgets, the majority of GP's (non-fundholders) are subject to looser financial limits in their spending on medicines. They do have target budgets but as already explained there is a contingency budget for overspends. This has provided an incentive to the hospitals to shift prescribing on to FHSA's in order to remain within their budgets. The lack of a unified system of funding between the primary care sector and the secondary care sector has led to a cost-shifting approach. Many drugs initially prescribed for patients by hospital doctors are continued for some years after discharge. The authors of one study (Jackson, 1993) estimated that between 15 to 20% of GP prescribing is hospital initiated; in total 40% may be strongly influenced by hospitals, since a GP's choices of drugs when prescribing for their own patients are also likely to be guided by local consultants. In addition to the ubiquitous drugs, GP's have been increasingly called upon to prescribe expensive specialist drugs to treat more exotic conditions that until recently would have been treated by hospital doctors. These include treatments for infertility, growth deficiency, malignant disease and HIV; also drugs used as adjuncts to organ transplantation, cancer chemotherapy and home dialysis. Nationally, such 'high-tech' drugs, normally prescribed only under specialist supervision, now represent 4% of GP prescribing expenditure, although there are big local variations (Audit Commission, 1994). GP expenditure on these drugs rose by 20.5% between 1991/92 and 1992/93. The Audit Commission (1994) recommended that the FHSA and DHA should jointly agree with the medical professions the circumstances in which such expensive drugs should be provided

on the NHS and who should be responsible for the cost. It was considered that GP's should not be asked to make political decisions on an ad-hoc basis. A further recommendation by the Audit Commission (1994) was for the prices at which drugs are reimbursed in the community to be taken into consideration when agreeing regional purchasing contracts and when compiling and reviewing hospital formularies. Formularies should distinguish drugs considered suitable for routine prescribing by GP's from those intended primarily for specialist hospital use and that both sets of drug prices, hospital and community, should be shown.

The Audit Commission report frequently referred to the need for cost-effective prescribing and considered that *'FHSA's should continue to foster.....the realisation that prescribing decisions must be taken within the context of the overall resources available to the NHS'*.

The recommendations of the Audit Commission are not unreasonable and can be practically put into operation. The inclusion of GP's and FHSA medical advisers on the drugs and therapeutics committees of major hospitals are a useful way of ensuring that community interests are represented in hospital decisions about inclusion of new drugs in formularies or about prescribing responsibilities. Surrey is one FHSA that has promoted the formation of a joint co-ordinating committee on which all hospital units in its area are represented and which takes the lead on issues of common interest to the community (Jackson, 1993). However, joint general practice/hospital formularies are thin on the ground, a survey of acute general hospitals in the UK found that although 90% had a formulary, less than 4% operated a joint one (Joshi *et al*, 1994). The Grampian formulary, which was completed in 1992 (Ferrow *et al*, 1996), was one of the first reported joint general practice/hospital formularies and although compliance with the formulary by Grampian GPs is voluntary, it appears to be working quite well. A recent survey (Ferrow *et al*, 1996) showed 84% of drugs being prescribed to patients admitted to local hospitals were joint formulary items. All Scottish Health Boards were supposed to implement joint formularies by the end of 1995 but it is difficult to assess whether this has actually happened because the only published paper advertising this event is the one for Grampian region (Ferrow *et al*, 1996).

#### 2.4.3.2.2 Health Committee

The Health Committee was set up in 1992 by the Government to examine the expenditure, administration and policy of the DoH and associated public bodies. A major focus for the Committee's activities was the issue of priority setting in the NHS. It examined the ways in which decisions were being taken on the assessment of need and the level of Government funding required to meet that need. The Committee specifically considered '*whether the measures introduced by the Government to control the NHS drugs budget are leading to more appropriate and cost-effective use of drugs in terms of current NHS resources and future patient needs*'. Central to the inquiry was how the Government might best carry out its multiple responsibilities: those of simultaneously promoting welfare, containing costs, encouraging rational and effective prescribing and supporting a vigorous UK pharmaceutical industry. The conclusion and recommendations of the inquiry included the statement that an important constraint upon the Government's freedom to take action to reduce the drugs bill was that it is committed to the principle that patients have an 'entitlement to receive all the medicines they clinically require' (NHSME, EL(94)2, 1994). The 1994 Annual Report of the DoH states that it is 'policy that no patient be denied the medicines needed' (Health Committee, 1994). The Health Committee (1994) restated this Governmental mission statement that in no circumstances should a patient be denied a medicine for which there is evidence of genuine need. The Committee further stated that insufficient research has been conducted to allow the cost-effectiveness of recent drug developments to be quantified but acknowledged that the Selected List ('blacklist') was an attempt to introduce the criterion of cost-effectiveness into decision-making on the purchase of medicines in the NHS. It was suggested that a logical and desirable extension of the Selected List policy would be the development of a NHS Prescribing List ('whitelist') covering all therapeutic categories. This would contain a wide spectrum of products which the NHS was prepared to buy. The list would automatically include all drugs at the time of their launch and for five years thereafter. All new products would be prescribable on the NHS. After five years, a time sufficient to allow formal assessment of the therapeutic value of the product, each drug would be reviewed

according to the criteria applied to drugs in the current NHS Selected List. Those drugs which were found to be less effective, or more expensive with no therapeutic advantage, than competitor drugs would then be excluded from being prescribed on the NHS. In this way a 'national formulary' would be gradually built up in a predictable, rational way. The Committee considered that the introduction of cost-effectiveness criteria legislation at the point of licensing as flawed due to the fact that it is not always possible to assess the comparative efficacy of a drug until it has had a reasonable amount of time to establish its value. The interests of the pharmaceutical industry would also be protected by allowing a lengthy and predictable period for a new drug to prove its worth. A further recommendation was that the DoH should allocate more resources for outcome studies and for the examination of cost-effectiveness and that these findings should be disseminated.

#### **Have the recommendations had an effect?**

Following the two expert reports (Audit Commission, 1994, Health Committee, 1994) the NHS Executive has issued two directives (EL(94)72 & EL(95)5) to the local health authorities which are a direct consequence of the expert recommendations. The directive, EL(94)72, marks an important point in the way medicines should be handled in the NHS as the emphasis is on bringing primary and secondary care much closer together in the management of medicine use. The directive requests that purchasers develop and agree strategies for improving the cost-effectiveness of prescribing across the primary/secondary care interface. It specifically asks that Health Authorities ensure the appropriateness of hospital-led prescribing and that an authority wide policy be developed for the managed entry of new drugs into the NHS. The directive states firstly, that purchasers need to ensure hospitals, when establishing their policies on prescribing, take account of the total costs of drugs to the NHS. Secondly, the directive requires that purchasers make use of evidence of the clinical and cost-effectiveness of new medicines when managing their entry into the NHS. The publication of EL(94)72 appears to be making an impact to some extent in that North West Health Authority (NWhA) has taken the lead in making explicit their intentions to change the way in which clinical trials are conducted across the region. NWhA

intends to have input from GP's and professional advisers in primary care at the design stage of clinical trials and will make sure that everybody is aware of current developments and have advance warning of any new products. The aim of changing the conduct of clinical trials is to get an early and effective assessment of where a drug fits into clinical practice and how cost-effective it is likely to be (Jackson, 1995).

The directive, EL(95)5, has instructed the local health authorities to re-organise the way in which 'packages of care' to patients at home are provided. These packages of care which normally involve the use of specialist drugs tend to be initiated at hospital level with the GP retaining responsibility for the care of the patient at home through agreed shared care arrangements. Until the 1st. April, 1995, it could be either the GP's financial responsibility for the prescription of items in the package of care (e.g. drugs, other products, equipment) or the hospitals responsibility. EL(95)5 changed these financial arrangements making it no longer permissible for the provision of these packages of care by GP prescription. District Health Authorities have been charged with this responsibility. The DHA has to make the appropriate logistic arrangements and contract negotiation with whoever they deem fit to provide the 'package of care' service to the 'at home' patients. The service can be provided by contract with a Trust or directly with an NHS or commercial supplier. The funding for these changes will be made by transferring monies from the FHSA (primary care) drug budget to the hospital and community health service (HCHS) (secondary care) budget. The FHSAs will need to adjust downwards GP target budgets and GP fundholders budget *allocations* to reflect these changes.

## **2.5 Economic appraisal of healthcare: its use and lack of use**

Economic evaluation is increasingly being acknowledged by policy makers as a potential aid to priority setting and resource allocation but is it actually being taken into consideration when making a decision?

Davies *et al* (1994) reported on a survey which was designed to measure the impact that economic evaluations in EC countries have had on decision and policy

making in health care since 1987. Health Service researchers in 10 EC countries were asked to locate economic evaluations reported or undertaken since 1987 in their country and to comment on whether the study was known to have had a visible impact on decision-making. Subject to exclusion criteria 66 studies were eligible for inclusion into the survey. The main topic area covered by the evaluations was methods of prevention (n=35, 54%) followed by drug therapy (n=15, 23%) with various other subjects making up the remainder. Just over a quarter of the drug studies were perceived to have had an impact on decision-making. This contrasts to those studies looking at the location or organisation of care, of which 50% were perceived to have had an impact.

The source of funding of the studies was thought to be a strong determinant in whether the study influenced policy making. All of those looking at the location or organisation of care were funded by government ministries whereas none of the drug studies were. Other important factors thought to have an influence on decision-making were the dissemination of the research findings, the time taken to conduct an analysis, and whether the topic addressed and the form the evaluation took, were relevant to the decision makers. Evaluations commissioned or funded by decision makers were more likely to have an impact. It was concluded from the results of the survey that economic evaluation currently has a relatively low impact on health care policy or decision making.

Ross (1995) carried out a novel piece of work in exploring Australian key health care decision makers' perceptions of economic evaluations which reinforced the findings of Davies *et al* (1994). The decision makers interviewed had responsibility for major health service expenditure decisions or for the provision of policy advice in which such expenditure decisions were made. It was found that although there was a high level of awareness of economic evaluation amongst the group only 38% had used or were in the process of using this type of analysis. Generally the evaluations used had been done as the result of regulatory requirement or under the auspices of a national health advisory body and had been specifically commissioned.

In the decision makers view major barriers to the use of economic evaluation included:

- i) Lack of time in the decision making process, political imperatives or no appropriate study or no time to commission one, these reasons have also been expressed by decision makers in the UK (Watson *et al*, 1996).
- ii) Lack of expertise and education, this was also voiced albeit from a different perspective by Salkeld *et al* (1995).
- iii) Lack of credibility of technique.

Ross (1995) concluded that there was a communication gap between the advocates of economic evaluation and decision makers which could only be bridged by education and the use of demonstration studies.

The conclusions of Ross are supported by Salkeld *et al* (1995) who reviewed all 33 health related economic evaluations carried out in Australia since 1978 in terms of their rigor and usefulness. These authors found that a significant number of studies had an ambiguous analysis, results could not be generalised, sensitivity analysis was carried out in an ad hoc fashion and conclusions were irrelevant. There were also problems associated with the interpretation of league tables. However, it was concluded that the quality of studies had improved in the last few years in methodological terms and decision makers could be reasonably well informed by current studies. However there was still room for improvement in the application of methods and in reporting the results of economic evaluation.

Henshall & Drummond (1994) in a discussion of economic appraisal in the British NHS clarified some of the problems experienced by decision makers in the UK when using this type of evaluation and offered suggestions to overcome the barriers. These authors feel that it is necessary for economists to resolve certain methodological issues in economic evaluation as the existing uncertainties both lessen the impact of economic appraisal results and cause confusion when economists liaise with clinical researchers and NHS decision makers. The methodological areas prioritised are:-i) discounting of health benefits, ii) valuation of health states, iii) relevance of and measurement of indirect costs and benefits and iv) methodological issues in integrating economic appraisal with clinical research. It was also thought that economists need to develop methods for dealing with uncertainty in economic appraisal. Recognition was given to the fact that

decision makers also need to know enough about economic appraisal methods so that they can interpret study results intelligently. The implication was that certain groups had training needs on the appreciation of economic appraisal rather than detailed methodological instruction.

A UK study carried out in mid 1995 to determine what information was used by senior health board managers making purchasing decisions supports the discussion of Henshall *et al* (1994) (Farmer *et al*, 1996). Purchasers were asked to consider from a given list the influence of various factors on their purchasing decisions. Although finance resources were weighted as the third most important, health economic information was weighted as the least important being the lowest of all 16 factors. Respondents in the study identified that there was a need for *better data on costs and prices* and *'meaningful economic analysis tools'*.

Should all the methodological issues become resolved, responsibility for making use of economic appraisal will still remain with the decision makers and to quote Sheldon (1996) *'The challenge for managers is to get into the habit of using...information resources for their decision-making'*.

### **What is the British Government doing to address the information gap?**

In 1991 a new strategy for research and development (R&D) in the NHS was launched by the DoH. Inclusive in the objectives of the strategy is the purpose to improve the scope, relevance and quality of R&D to inform policy and practice in health and social care and to ensure that the benefits of research are systematically and effectively translated into practice (Peckham, 1993). The launch of the NHS R&D strategy has marked a shift in emphasis away from the NHS as a passive recipient of new technologies to a Service which is going to develop a strong research infrastructure and competence capable of critically reviewing its own needs. The programme is intended to correct existing deficiencies in knowledge and provide a basis for improvements in the approach taken to health care by managers, health care professionals and the users of health services. Intrinsic to the objectives of the R&D strategy must be the development and integration of economic appraisal of healthcare. In the report 'Research for Health' (Peckham, 1993) it is stated *'If patients are to benefit from worthwhile new developments, it*

*is essential that clinicians and managers know which interventions are cost-effective and which are not so that resources can be focused appropriately*'. The report also noted that a vast array of interventions are undertaken each day which have not been systematically assessed for either effectiveness or cost. The evaluation of these procedures presents a major challenge.

Information systems are being set in place to support the R&D strategy. These include the National Register of Research, the Cochrane Centre, a facility for commissioning research reviews and a Dissemination and Enquiry Unit.

The National Register of Research will be compiled by a Projects Registers Co-ordinating Unit which has been commissioned to assemble regional registers of all research projects that Regions fund or manage or which otherwise attract service support. A database of the regional registers can then be interfaced with databases of the MRC, the major charities and other health departments. This is supposedly to enable a complete picture of applied health research to be assembled, however, this does not encompass that research undertaken funded by means other than through the NHS.

Since 1978 a team of researchers led by Iain Chalmers in Oxford have systematically reviewed all research findings on pregnancy and childbirth. This team has been the single good example of research results being collated, rigorously-quality assessed, compared, synthesised, and then disseminated to health professionals and patients in formats they can use. This body of experts provided the nucleus to the Cochrane Centre which was opened in 1992. The Centre has been established to assist specialists in a wide variety of fields to prepare, maintain and disseminate systematic, up-to-date reviews of randomised, controlled trials of healthcare information essential to decisions in healthcare and research.

'Effective Health Care' bulletins sponsored by the NHS Management Executive has been found to be very useful in making known information relevant to clinical and managerial decisions. To further this initiative, a new facility for commissioning research reviews has been established. The purpose is to complement the work of the Cochrane Centre by commissioning reviews of

available research beyond the area of controlled trials ensuring that the information is of good quality and of practical application

A Dissemination and Enquiry Unit was established in 1993 to focus on the systematic transfer of accessible and up-to-date overviews of R&D information to NHS managers and clinicians. It also provides enquiry-based access to the results of R&D. This new facility is to conduct research on how to make research-based information more accessible to all those working in the NHS.

Despite the existence of these information sources there appears to be a lack of clarity regarding the roles of the various agencies involved in producing effectiveness information. A recent National Association of Health Authorities and Trusts (NAHAT) report states *'Both the number of information sources and the volume of information on clinical and cost-effectiveness are growing, and there are already some indications that this is resulting in duplication of effort.....Ideally users should only have to deal with a single access point for information on clinical effectiveness'*.(Appleby et al, 1995).

## **2.6 Summary**

The various methods used by different countries at governmental level to limit healthcare expenditure, which includes the curbing of drug expenditure, reflects how the healthcare systems in operation are financed. Table 2.4 summarises these methods.

**Table 2.4 Governmental methods designed to exert downward pressure on healthcare expenditure**

Country and Governmental control measures	Effect of control
<p><b>United states</b> Prospective payment scheme introduced in 1983 (DRGs etc.).</p>	<p>Fixed price reimbursement per DRG has forced hospitals to improve their internal efficiency of resource utilisation such that profits can be maximised. As a result of this a major focus for hospitals has been to seek methods aimed at reducing pharmacy expenditure.</p>
<p><b>Canada</b> Federal government has transferred responsibility for healthcare expenditure to the Provincial governments by capping the federal financial contribution payable to the Provincial governments whilst in tandem implementing legislation which protects patients from paying for their care provided the healthcare service is a 'listed' service.</p>	<p>Provincial governments in turn have transferred responsibility for healthcare expenditure to third parties (employers, insurance companies, public etc.) by delisting services previously covered by them.</p> <p>Pharmaceutical manufacturers are also expected to now provide economic information when submitting a drug to be added to a Provincial Drug Benefit formulary.</p>
<p><b>Commonwealth of Australia</b> Mandatory economic analysis guidelines have been issued to specifically restrain expenditure on new pharmaceuticals.</p>	<p>Pharmaceutical companies have to demonstrate cost-effectiveness of new drugs to gain Pharmaceutical Benefit Scheme (PBS) listing. Without this listing a product has little chance of significant prescribing by medical practitioners.</p>
<p><b>United Kingdom</b> Drug price modifying schemes, prescription modifying schemes, publication of NHS Executive Letters (which may or maynot be coercive).</p>	<p>A degree of cost containment has been achieved but cost-shifting practices from the secondary care sector to the primary care sector has also occurred.</p>

Although, the drugs budget represents only a small proportion (approximately 10%) of total healthcare costs, it is a highly visible component and as such has become a defined target for control. Several methods have been used by the British Government to exert a downward pressure on the NHS drug budget with varying degrees of success. It would appear that the government does recognise the role that economic evaluation could have in controlling drug expenditure and indeed promotes its use to purchasers and providers of healthcare by referring to 'cost-effectiveness' frequently in executive letters. However, as yet, there is a lack of a well developed formal framework and support mechanism to ensure these exhortations are applied. It is left to individual purchasers and providers of healthcare to use or not use economic information in their decision-making as they so desire. As already discussed there can be many reasons for the lack of use of economic appraisal in policy making. These can range from a complete lack of data in the therapeutic area being considered to a lack of expertise in interpreting appraisal data. The decision-makers may feel the information available is not valid for the decision under discussion or there may be a lack of awareness of what economic appraisals have been undertaken. Without a centralised structured approach in the clarification of methodological issues, the commissioning of studies, the dissemination of research results and the training of decision making personnel in economic appraisal interpretation, the existing framework will remain ad hoc and piecemeal. It is to be hoped that the new R&D strategy will provide this much needed centralised structure, initial indications are that a single point access is required for all the information being generated.

An important suggestion made by the House of Commons Health Committee (1994) was for all drugs to be allowed on formularies and be prescribable on the NHS from the time of their launch and for five years thereafter so that sufficient time is allowed to assess the therapeutic value of the product. Those drugs which were found to be less effective, or more expensive with no therapeutic advantage, than competitor drugs would then be excluded from being prescribed on the NHS. In this way a 'national formulary' would be gradually built up in a predictable, rational way. This would appear to be supported to some extent by the medical community and was highlighted in a letter to the *Lancet* by chest physicians

(Spencer *et al*, (1995) in response to the suggestion by an anonymous review in an influential journal, that Dornase-alfa for cystic fibrosis should not be allowed onto formularies. The physicians felt that the opinion expressed in the review did not reflect the views of specialists caring for patients with cystic fibrosis. Dornase-alfa is a novel agent in the treatment of cystic fibrosis for which there are no long term data. In the short term there are data to show a degree of improvement for some patients treated with this drug. Spencer *et al* (1995) made the point that unless experience is gained long-term within regional specialist centres for Dornase-alfa, it will not be possible to fully assess its impact on well-being and quality of life indices. It was felt that there could be an improvement in life expectancy of up to 15 months for some patients. Only through experience would it be possible to target patient selection so that prescription of the drug could be restricted to those patients who would benefit and to therefore maximise cost effectiveness. In Australia, this option does not exist for medical practitioners and experience cannot be gained with this drug. Dornase-alfa has already been excluded from PBS listing brought about by the Australian Guidelines. The method suggested by the UK Health Committee is more flexible and allows for a more realistic assessment of a drug compared to the rigid, mandatory guidelines recently introduced by the Australian government.

A related issue raised by Naylor *et al* (1993) which requires 'real-time' monitoring is 'technology creep'. Drugs are frequently used for conditions other than those for which they were originally approved or for which clinical trial data were obtained. The costs and outcomes of using a drug assessed over a five year time period would therefore take this into account and give a more realistic idea of its true cost-effectiveness than that projected from artificially controlled conditions. A concern raised by Laupacis *et al* (1992) though, is that it is generally easier to withhold funding for a new technology than it is to withdraw funding from an existing one.

In the UK there are medico-legal ramifications associated with the existing attempts to apply economics to resource allocation. Society is having problems coming to terms with the concept that all healthcare will no longer be fully funded and that decisions will be taken on the grounds of the extent to which a patient can

benefit from treatment. The initial reaction to overt rationed healthcare has been litigation. Early in 1995, a child with leukaemia was denied further NHS treatment by her local health authority. The decision was based on the medical grounds that her chance of survival with treatment would be around 2% and that the cost of treatment approximated to £75,000 (Hunter, 1995). The child's parent challenged the decision in court. The final judicial ruling was that the decision lay firmly with those responsible for allocating the resources, which in this instance was the local health authority. Under these circumstances it may well be that savings achieved through rationalisation will be lost through litigation.

A national policy on healthcare resource allocation is needed in the UK, the criteria for which are accepted by society. Otherwise the decisions of local health authorities will continue to be challenged in court. Inefficiencies of the system will result as the costs of litigation will have to be borne not only by the pursuers bringing the action and the health authorities which the action is against, but also the Government, because some of the pursuers will be eligible for legal aid.

To summarise, the largest proportion of drug expenditure occurs in the primary health care setting in the UK, however, prescribing in the secondary care sector can have a substantial impact on primary care prescribing costs. Government recognition is given to the role economic evaluation could have in contributing to cost-effective healthcare resource allocation, however, governmental controls aimed at the national drug budget have principally been of a cost-containment nature directed at the primary care setting. The drug budget in the secondary care sector has not been subject to direct governmental control in the same way. Other forms of control, again of a cost-containment nature, have been used in the secondary care setting to restrain the drug budget, these controls are examined in the next chapter.

## Chapter 3

### 3. **Methods For Controlling The Hospital Drug Budget - Cost Containment**

Prior to April 1, 1996, NHS governmental monies were devolved to District Health Authorities (DHAs) for the purchase of secondary healthcare. With these monies, DHAs then allocated an overall cash limited budget to each hospital unit in their area, assessed on the perceived secondary healthcare needs of the population in their catchment area. How each hospital then used this monetary allocation to provide the purchased healthcare became a matter for the hospital management structure. Essentially, the departmental head of each cost centre (e.g. radiology, pharmacy etc.) would be charged with ensuring that the budget allocated to their cost centre was adhered to.

#### **The Hospital Drug Budget**

The total cost of the hospital drug budget is a function of two variables, the quantity of drugs consumed and the price of those drugs (see Equation 1).

#### **Equation 1**

$$\text{Total cost of Drug budget} = (\text{Quantity Drug a} \times \text{Price Drug a}) + (\text{Quantity Drug b} \times \text{Price Drug b}) + (\text{Quantity Drug c} \times \text{Price Drug c}) + \text{etc.}$$

The quantity of drugs consumed is determined by the number of drugs prescribed which includes dose used and duration of treatment. An important factor affecting the prescription of drugs is the advent of new chemical entities. The availability and active promotion of new drugs obviously leads to an increase in prescribing which in turn increases the size of the drug budget. The impact of a new drug on prescribing costs will vary depending on whether the drug is an alternative agent for a condition where a drug treatment already exists or whether it is an entirely novel therapeutic agent. The prescribing costs of an alternative therapeutic agent will be partially offset by the decrease in prescribing cost of the agent it is replacing, conversely the introduction and use of a novel therapeutic agent which does not replace an existing drug will not have a direct offset cost. However, it may have an indirect offset cost. A new drug, although not a replacement for an

existing drug may be a replacement for some other form of treatment, for example, the advent of the H<sub>2</sub> antagonists replaced surgical intervention for gastric ulcer disease. Consequently a reduction in surgical intervention costs for this indication will have occurred. This represents a cost-shifting between the surgical budget and the drug budget. In the pursuit of efficiency, savings accrued in the surgical budget through the use of the H<sub>2</sub> antagonists could be used to offset the cost of these drugs. However, this does not occur.

As with other component cost centres within the hospital, the drug budget has been viewed in isolation from other budgets, specific measures undertaken to control its rise have therefore been of a cost-containment nature. These measures, to revert to equation 1, have primarily concentrated on reducing the quantity of drug prescribed by restricting access, attempts to reduce the price of drugs has also been made. Table 3.1 summarises these measures. Each of the strategies and how they interact with each other will be considered in turn.

**Table 3.1 Strategies used by Hospitals aimed at reducing both drug consumption and drug price**

<b>Schemes to reduce drug consumption</b>	<b>Scheme used to reduce drug price</b>
Formularies Consultant approval Automatic stop date Therapeutic substitution Policies Drug utilisation review Behaviour modification	Generic substitution

### **3.1 Consumption Reduction**

#### **3.1.1 Formulary Introduction**

The concept of a hospital formulary can be traced back several centuries for the UK and over two for the US (Pearce, 1992, Nash, 1993). The purpose of a formulary has become more sophisticated over the years from merely providing a list of available drugs through to dynamic policies which provide guidance on

selection from within a therapeutic group, dosage, adverse reactions, cost and other pharmaceutical areas of interest. Cost information has usually been limited to acquisition cost.

In the UK a societal desire for the 'economical' use of drugs was made explicit as early as 1929 when the National Formulary for Health Insurance Purposes (NFHIP) was produced. The NFHIP was stimulated by the National Health Insurance Acts. Prior to the Acts, many prescribers had their own private arrangements with pharmacists in their immediate locality by which personal formulae abbreviations could be used and understood by doctor and pharmacist respectively. When the Insurance Acts came into force, many of the prescriptions formerly made up by the doctor or pharmacist came to be written on National Health Insurance forms, and since there was free choice of pharmacist had to be comprehensible by all. This dictated that Insurance practitioners could no longer use their own abbreviated formulae.

The new system caused a marked increase in prescription time writing which was felt to be unnecessary effort, because of this many Health Insurance Panel Committees compiled formularies which held valid for their respective areas. Before long a plethora of formularies existed which in turn caused difficulties because some doctors had to use several formularies. The same prescription had different titles in adjacent areas and conversely the same title often covered different prescriptions. To overcome this problem a number of adjacent Panel Committees combined to form a formulary for their group, 5 formularies were produced to cover 58 areas of England. It soon became the opinion of the Retail Pharmacists' Union, the Insurance Acts Committee of the British Medical Association and the Ministry of Health that this example of group action could be taken further by the compilation of a National Formulary to which all areas could conform. The 1927 Conference of representatives of Local Medical and Panel Committees instructed the Insurance Acts Committee to expedite the production of a such a formulary.

The National Formulary for Health Insurance Purposes was published in 1929. A recurring theme through the publication was that of economy. The publication was seen as a method of promulgating cost awareness amongst prescribers. Point 9f of

the preface states '*That therapeutic efficiency be obtained with due regard to economy*'. In Notes for the guidance of Medical Practitioners in Prescribing there is reference to therapeutic substitution and generic prescribing as an aid to cost containment, as is the avoidance of elaborate prescriptions and the prescribing of undue quantities. This section concludes '*it is hoped that practitioners will adopt the above suggestions, and thus assist in effecting a measure of economy which will relieve practitioners in general of any reproach on the subject of excess cost in prescribing*'. As resources remain scarce the same exhortations have been made repeatedly through the following 60 years.

The NFHIP provided the roots for the present British National Formulary (BNF). Due to technological advances in medicine the type of medicines and advice the BNF provides is vastly different from its forebears and is recommended as a rapid pocket reference guide only, to be supplemented with other sources of information when necessary. Basic net costs are provided with the medicine listings in order to provide an indication of relative cost between agents. These costs are not actual but calculated from basic costs used in pricing NHS prescriptions and do not reflect the cost of drugs in the hospital setting as these tend to be purchased in bulk. These costs can therefore mislead the user when selecting between agents. Furthermore the preface in the BNF goes onto state that '*cost-effective*' prescribing needs to take other factors into account that can also affect the total cost of treatment. The provision of basic net costs does not appear to serve any useful purpose. The BNF although an excellent therapeutic reference guide is of little use for economic guidance.

In an attempt to rationalise drug use and therefore limit costs, Hospitals have resorted to the production of local formularies which list selected or preferred drugs available to prescribers. The range tends to be much more restricted compared to the BNF. Selection of drugs for inclusion in the formulary is normally made by a multidisciplinary Drug and Therapeutics committee. Crooks (1983) reported a 15% reduction in drug costs in medical wards following the introduction of a formulary at Ninewells hospital, Dundee in 1981. This included an initial once and for all saving resulting from reduction of ward and pharmacy stocks, savings in subsequent years were reported as less. A method used to

encourage adherence to this formulary was the requisite of a separate prescription justifying the use of a non-formulary drug. Consequently unnecessary drug expenditure could be identified and restricted. This experience was repeated by Feely *et al* (1990) in Ireland. Wandsworth Health Authority also found a formulary useful in reducing drug expenditure and improving the quality of prescribing (Collier *et al*, 1985). The Drug and Therapeutics Committee of this Health Authority under certain circumstances not only consider the cost to the hospital when appraising a new drug for possible entry to the formulary but also consider whether the drug may have cost implications for general practitioner prescribing. The background to this is the financial inducement offered to hospitals by manufacturers, occasionally the market price may be reduced to 1/80th. What the manufacturers lose to the hospitals they hope to gain in the primary healthcare market. This precise issue was highlighted in the Audit commission report on primary care prescribing (1994). Subsequently, a recommendation by the Audit Commission (1994) was for the prices at which drugs are reimbursed in the community to be taken into consideration when agreeing regional purchasing contracts and when compiling and reviewing hospital formularies. Furthermore it was recommended that formularies should distinguish drugs considered suitable for routine prescribing by GP's from those intended primarily for specialist hospital use and that both sets of drug prices, hospital and community, should be shown.

By 1986 an audit by Ridley (1986) showed a wide range of local formularies to be in use throughout the UK. Equally the formularies varied in their content from a limited list of one or two drugs in each major therapeutic group through to many drugs in each group. Reports of formularies to reduce drug expenditure continued, Trounce *et al* (1987) reported a reduction in their drug bill from \$3.04m in 1982/3 to \$2.57m in 1986/7. Conversely others (Bateson, 1987) have reported an increase in drug expenditure despite the presence of a formulary and have questioned their usefulness, what this author did not consider is that the increase could have been even greater but for the presence of the formulary.

A formulary requires to be adaptive to changing prescribing needs. In 1970 the Westminster Hospital formulary was compiled by a subcommittee of the medical

executive and pharmacy stocks were restricted to approved items (Baker *et al*, 1988). If a non-formulary item was requested the prescriber would be contacted by a pharmacist and offered an approved alternative, if the clinician confirmed the request for the non-formulary item the drug would be supplied but a record of the request was kept. By 1978 because of the increased requests for non-formulary drugs and rising drug expenditure of 10-15% a year it was felt that the formulary was not adaptive enough to cater for changing clinical needs. The strategic preparation and management of the formulary was changed such that representatives from all specialities had an input to the formulary thus creating one mechanism by which the need for change could be swiftly recognised. The formulary now covered both hospitals in the district. Regular seminars and workshops were held with all levels of staff to educate them in the aims and workings of the system. Another mechanism for updating the formulary was regular monitoring, analysis of prescribing patterns could then identify potential areas requiring change. Monthly compliance with the formulary was found to be consistently over 99%. In each successive year after the fundamental redesign, drug expenditure either fell or was held stable despite the release and approved use of several new drugs with high acquisition cost. Comparison with other London teaching districts showed the Westminster district pro rata drug expenditure to be consistently lower, no other district had a fully operational drug rationalisation policy.

Baker *et al* (1988) made explicit that the initial reason for formulary introduction to the Westminster Hospital was a method to curtail rising drug expenditure. The purpose of containing costs by rationalising prescribing is to make the most efficient use of a set resource yet some physicians appear to be uncomfortable with the concept of making cost limitation explicit to support formulary usage. An editorial by Turner (1984) states that the purpose of a formulary should be the improvement of patient care by increasing the level of rational prescribing and not economy, as if the two goals were separate. Mooney *et al* (1984) reporting on a workshop for senior NHS staff discuss the misconceptions that abound about economics in the NHS and propose that it is the separation of professional and financial accountability which fails to foster the need for efficiency in health care.

The previous comment by Turner (1984) lends additional credence to the Mooney *et al* (1984) proposal. Inefficient prescribing practices are perpetuated by the cry 'freedom to prescribe'. Many doctors prescribe in ignorance, unaware of the constituents of combined preparations, of common side effects and of drug interactions, confusion from the vast range of alternatives available is one cause of the poor standard of prescribing (Anon. 1978). The use within a hospital of a restricted list of drugs solves several problems at once. In terms of cost-containment, expensive drugs for which there are cheap, equally satisfactory alternatives can be excluded, so too, can drugs and drug combinations thought to have an unacceptably high risk of side effects or addiction.

The use of formularies is extensive in the US, with over 80% of surveyed hospitals employing some type of formulary system (Nolte *et al*, 1991, Rascati, 1992). A US survey of multidisciplinary pharmacy and therapeutic committees reported that the two most important factors in decision making for formulary drug inclusion were effects on the quality of drug treatment followed by impact on hospital costs (Segal *et al*, 1988). As pointed out by Feely *et al* (1990) despite the primary objective of formularies being quoted as improving drug use, analysis has concentrated on the purported secondary aim, which is to reduce drug costs. A telephone survey of pharmacy directors from a random sample of 150 community hospitals reported the most frequently stated purposes of a formulary were to decrease costs (54.8%) and to ensure appropriate therapy (37.1%) in that order (Rascati, 1992). This is the opposite way around to the P&T committees priority (Segal *et al*, 1988) and obviously reflects the pharmacy directors primary responsibility for controlling the drug budget (Plumridge *et al*, 1984).

Different cultures can bring different arguments to the formulary concept. In the US, health care provision is primarily private, Martucci (1987) promotes the delimitation of certain drugs in a formulary as a method of marketing the hospital to the public. He suggests that although greater pharmacy operating and inventory costs may be increased by such a manoeuvre they would be offset by intangible benefits such as the patients comfort factor and would encourage admitting physicians to use the hospital. Because of the widely differing health care system in Britain this argument would almost certainly never be used. In Norway the

presence or absence of a hospital formulary appears to have little impact on the drug budget (Bakke, 1984). Norway has strictly regulated the introduction and marketing of drugs for more than 50 years. The system is a state owned wholesale monopoly with nation-wide distribution. Because of such strict regulation, the total number of drug products available is smaller than other Western European countries, yet, only a few therapeutic classes are not represented. Since the number of chemical entities and drug products in the market are low compared to most other countries, the possibilities for further simplification and narrowing of the spectrum of available drugs at the hospital level are limited. The aim of the drug committees has mainly been to identify a 'core' of products recommended for routine use in most patients, without unduly obstructing the acquisition of other drugs when required for special purposes. Repeated ordering patterns are discussed by the committee before it is decided whether administrative action should be taken to improve compliance or add medicines to the formulary. Although money can be saved by selecting appropriate and reasonably cheap established products instead of the most recently introduced and expensive medicines, the overall impact of the drug committees on expenditure has not been impressive. There has not been a discernible change in the rising trend in spending coinciding with the selection process, nor evidence of a lower per day or per patient drug bill in hospitals with committees as compared with those without (Bakke, 1984).

In those countries not subject to as strict regulations as Norway the impact of a formulary is dynamic. A survey of formulary presence in major Australian acute-care hospitals by Plumridge *et al* (1984) led these authors to conclude that although two thirds of all these hospitals had a formulary '*effectiveness could be improved markedly*'. The results of this survey cast serious doubt on whether formularies were being adequately prepared or introduced in an appropriate manner. Evidence presented by others (Zilz, 1975) had already demonstrated that user acceptance is essential for successful formulary implementation and can be obtained only by continual consultation with physicians throughout the preparation phase. Although the task is complex and time consuming it is both essential and achievable. However, in the survey by Plumridge *et al* (1984) only

50% of formularies had been prepared by a committee which incorporated specialist physicians. Furthermore only 35% of the formularies surveyed were regularly revised to allow admission of new drugs and deletion of outdated ones. The method of introducing a formulary has also been shown to be important for its acceptance with personalised communication achieving a far higher success rate when compared to impersonal written announcements (Check, 1980). Despite this, the two most frequently used methods of communication for introduction of formularies in the survey undertaken by Plumridge *et al* (1984) were administrative memoranda (74%) and pharmacy bulletins (38%).

To reiterate, success of a formulary has been demonstrated to be dependent on its acceptance and active implementation by those prescribers who are intended to use it (Plumridge, 1984). A formulary alone is not capable of modifying prescribing behaviour in a sustained way (Wyatt, 1992, Nash, 1993). Other educational techniques are required.

### **3.1.2 Strategies used to augment a formulary which further reduce consumption**

#### **Consultant Approval**

The purpose of requiring a drug (usually high acquisition cost or high probability of toxicity) to have consultant approval prior to prescription is restrictive. The prescriber is required to justify and make explicit the need for that particular drug to be used thus gaining specialist approval (Scher, 1990). By providing this barrier to free prescribing of selected drugs, inappropriate use is targeted.

#### **Automatic stop orders**

Automatic stop orders are primarily used in the US and are a power strategy to stop an indefinite prescription from continuing, the drug categories subject to this form of control are usually antibiotics, narcotics, barbiturates, sedatives, anticoagulants, oxytocics and antineoplastics (Myers, 1988). The purpose is to protect the patient from extended treatment in addition to preventing unnecessary waste of resources. The prescriber is notified prior to drug cancellation. Jewesson

*et al* (1985) after a quality of use study suggested that an automatic stop of prescriptions for prophylaxis within 24 to 48 hours after elective surgical procedures would reduce by 20-25% the use of all antimicrobial drugs in their hospital and would result '*in a savings of several thousands of dollars annually*'. An automatic stop order is used as part of a strategy to control prescribing rather than a means to an end by itself (Scher,1990, Coleman, 1991).

### **Therapeutic substitution**

Therapeutic substitution is the substitution of a drug with a different chemical identity from the one prescribed but is believed to have the same action. The purpose of substitution being to reduce costs by limiting the number of drugs used within a given therapeutic class. There is strong opposition to this form of substitution (Committee on Drugs, 1987, Ballin,1987, Nelson, 1989). Concerns devolve around the fact that the same drug may be used for multiple indications therefore the person who is making the substitution cannot necessarily identify the drugs immediate intended purpose without access to a patients case history. Nonetheless, a case may be made for substitution within certain therapeutic groups such as antibiotics.

Wright (1991) reported on a successful therapeutic substitution program for the second generation cephalosporin, cefoxitin. A decision was made by a multidisciplinary Pharmacy and Therapeutics Committee to substitute all orders for cefoxitin with another second generation cephalosporin, cefotetan, which was considered equally efficacious. Cefotetan has a longer half-life than cefoxitin and need only be dosed twice daily compared to four times daily for cefoxitin so although the acquisition costs are similar total daily costs are lower for cefotetan. Infection surveillance data were reviewed during the substitution period, no change in infection rate or antibiotic failure rate was found.

The prevalence to which therapeutic substitution is carried out is largely unknown. In an attempt to quantify those hospitals carrying out this type of program Doering *et al* (1982) undertook a national questionnaire survey of all short-term hospitals in the United States. Thirty nine percent returned usable questionnaires, of these 31% reported that their formulary system allowed therapeutic substitution without

contacting the physician for permission. Federally owned hospitals were twice as likely (62.5%) to engage in therapeutic substitution than those hospitals of other ownership types (23-32%). Two of the major reasons given by non substituting hospitals for not engaging in therapeutic substitution were firstly, that it would not be accepted by the physicians and secondly that it interferes with the physician's right to select the drug which is best suited to the patient. Respondents were asked to estimate the dollar savings of their therapeutic substitution programs, less than 35% could give an answer and those that did answer did not necessarily base the response on actual accounting data. Doering *et al* (1982) concluded that two critical aspects of therapeutic substitution needed further evaluation, these being cost savings and drug therapy outcomes. With the exception of some antibiotic programs (Guastella, 1988, Smith, 1989, Wright, 1991, Achusim, 1992a) and a few H<sub>2</sub> antagonist therapeutic interchange programs (Rich, 1989, Oh, 1990, Berkowitz, 1992) this does not appear to have been undertaken (Achusim, 1992b).

### **Policies**

A policy is a refinement within a formulary which provides a systematic approach to the treatment of a specific indication. It suggests a defined course of action to be taken usually with the recommendation of a first, second and third line drug. The aim of a policy is to promote the safe, effective and rational use of drugs. Policies are quite widely used for the treatment of infection. In a national survey of 88 hospitals in the Netherlands, Janknegt *et al* (1994) found that 66% incorporated an antibiotic policy into their formulary. In the UK, 51% of responding hospitals to a national survey carried out in 1990 had a written policy for surgical prophylaxis (BSAC Working Party Report, 1994).

### **3.1.3 Strategy used to augment a formulary which reduces Price**

#### **Generic substitution**

The definition of generic substitution is the supply of a drug by its approved name rather than by its prescribed proprietary brand name, the drug has the same chemical entity as the proprietary brand but may be manufactured by an

alternative drug company to the manufacturer who owns the proprietary patent. The acquisition cost of a generic pharmaceutical is usually much less than its proprietary equivalent (Hepburn, 1990). As a measure to contain costs, generic substitution within given limitations is now a widely accepted practice in the hospital setting, although it has been a contentious issue throughout the world (Retief, 1984, Pincus, 1983, Schwartz, 1985, Maddock, 1986). The problems with generic substitution devolve around bioequivalence and bioavailability and concerns that a patient stabilised on a branded product may be subject to intoxication due to greater bioavailability of the generic product (Anon, 1972, Tyrer, 1970) or to therapeutic failure due to lesser bioavailability (MacDonald, 1987). However, exact bioequivalence is essential for relatively few drugs with a narrow therapeutic window (Walley, 1993). Despite this, generic substitution can be the cause of an intangible cost to the patient. For example, another problem which can be encountered with substitution relates to the excipient ingredients that can change from formulation to formulation. Excipients constitute a medication in addition to the active substance, such as colouring agents or propellants, and are considered to be inert. However, hypersensitivity reactions to various excipients have been reported (Anon, 1985, Anon, 1992). A patient stabilised on a branded drug and is changed to a generic drug which contains different excipients in its formulation has the potential to develop an adverse reaction. Generic substitution can also cause anxiety to the patient because the drug is a different colour, shape, or have a different taste from the branded medicine they are used to taking.

As with automatic stop orders generic substitution is used as part of a strategy to control the costs of prescribing.

As part of a clear national policy to ensure the optimal use of drugs within the country's resources, South Africa, became the first in the world to legislate at a national level, that generic substitution by pharmacists will be allowed both in the public and private sectors. It will be incumbent on the pharmacist, prior to dispensing a prescription, to inform the patient on the benefits of generic substitution (Edinburg, 1996).

### **3.1.4 Strategies to reduce consumption by modification of behaviour**

There have been many studies carried out to determine the most effective method for influencing the clinical practice of drug prescribing. Kunin *et al* (1973) reviewed the inappropriate use of antibiotics in the US and concluded that this was a major problem. These workers reported methods used in their hospital to counter this problem. Methods included 'a strong drug formulary system' and 'continuous education of students, house staff and practising physicians in the use of drugs', however the authors did not expand on the operational details. The success of a restrictive drug formulary depends on the intervention strategy used to re-inforce it.

#### **3.1.4.1 Written**

Written information has been used to modify prescribing. In an American study to rationalise the use of iv ranitidine, an educational memo suggesting the use of oral ranitidine was placed in all patients charts who were receiving concurrent oral or nasogastric medications and iv ranitidine. Over an 8 month period a 61% change was induced by this method resulting in a cost saving of approximately \$US3,100 (Baciewicz, 1991). A study carried out previously reported similar findings (Dannenhoffer, 1989). The effectiveness of 'therapeutic newsletters' in influencing hospital drug expenditure has been examined in the UK (Wilson, 1991). The newsletters considered gave a clear recommendation to use one particular drug rather than another and emphasised situations in which the comparative drugs were and were not interchangeable. Analysis of defined daily doses of the drugs before and after circulation of the newsletters showed prescribing practice changes. Post circulation there was an increased usage of the recommended alternative drug with a corresponding decreased usage of the more expensive comparator. For the three pairs of drugs examined annual cost savings were estimated to be £26,000. Criticisms of this study can include that the changes were not shown to be sustainable, that there was no attempt to examine how rational the changes made were and whether there were any changes in the use of other drugs in the same therapeutic class as the pairs of drugs considered. Shenfield *et al* (1980) demonstrated that reduction in use of one drug in a therapeutic class

through a restriction policy can lead unexpectedly to an increased use of an alternative drug in the same therapeutic class. This has been described by others (West, 1977).

The timing in which written information is presented appears to be important. An Israeli study (Rubinstein, 1988) demonstrated that monthly distribution of information to hospital prescribers concerning antibiotic costs and rates of usage had little effect on reducing overall antibiotic costs. However, when the average daily cost of each antibacterial agent was supplied on individual patient microbiological culture test result forms there was an overall reduction in monthly antibiotic costs. The timely presentation of the data obviously assisted the prescriber to make an informed decision about which antibiotic to choose at individual patient level and at the time of treatment. The data presented previously on a monthly basis may not have had an impact for two reasons, firstly, because it did not relate to an individual situation, and secondly, the information was not provided at the point of delivery of care. In support of this are findings of McDonald (1976), this worker studied the effect of prospective computer generated suggestions about the management of simple clinical events on the rate of clinical errors. It was found that physicians responded to 51% of 327 events when given the computer reminder and to only 22% of 385 events when not given the reminder. Mugford *et al* (1991) in a review of the effects of feedback of information on clinical practice also concluded that feedback is more likely to have a more direct effect on practice if presented close to the time of decision making.

#### **3.1.4.2 Person to Person contact**

Physician tutorials have been used with effect by Klein *et al* (1981) to modify the prescribing of certain antibiotics in the treatment of urinary tract infection. What these workers found important was to base educational intervention on those factors influencing current prescribing. Avorn and Soumerai (1983) found that in office practice, doctors who received face-to-face visits by 'academic detailers', together with attractively-presented printed material, significantly reduced their

prescribing of target drugs when compared with control subjects. No changes were seen in the prescribing of physicians who received printed material only. Schaffner *et al* (1983) also found that doctors who were visited by a 'physician counsellor' showed a marked change in the targeted prescribing behaviour, whereas doctors who received mailed brochures showed no significant difference in behaviour from that of control subjects. Conversely, in a study of three approaches for marketing smoking cessation programmes to Australian general practitioners, which included an educational facilitator approach, a volunteer courier and a mailed approach, there was a failure to show a significant advantage between the various approaches (Cockburn *et al*, 1992).

The professional standing of the individual providing the personal contact was thought to be important by Martin *et al* (1980). These workers thought that one reason for the success of their weekly chart reviews in reducing the use of diagnostic tests was that the reviews were led by senior clinicians whose views were respected by junior staff. In support of this Eisenberg *et al* (1977) postulated that one of the reasons they failed to reduce the inappropriate use of tests for lactate dehydrogenase in a hospital was because feedback was provided by junior and not senior staff in the hospital. They thought that house officers would be more likely to respond to figures of authority. Pharmaceutical company sponsorship has been shown to weaken the educational effect a program can have (Friis *et al*, 1991). Written material was disseminated between three groups of physicians. In addition this material was followed up by 10 lectures given by the same person to two of the three groups. One group received lectures arranged by the local department of clinical microbiology, the other group received lectures sponsored by a pharmaceutical company. Overall prescribing habits changed significantly. However, the changes were significantly higher for the group who received the lectures arranged by the microbiology department. The prescribing habits of the group who received the lectures sponsored by the pharmaceutical company did not change further when compared with those physicians who received written material only.

### 3.1.4.3 Commercial style advertising

In one Australian hospital, Harvey *et al* (1986) used a commercial advertising type campaign to both promote an *Antibiotic Guidelines* booklet and to change the prescribing of iv amoxycillin in primary pneumonia to iv benzylpenicillin. A course of iv amoxycillin averaged 37 Australian dollars compared with 7.30 Australian dollars for a course of iv benzylpenicillin. The campaign used techniques of the pharmaceutical industry, such as posters, give-away pens and writing pads and was based on the findings of Avorn *et al* (1982) that non-scientific forces can be a powerful influence on clinicians prescribing behaviour. The posters, using catchy slogans, clear messages and powerful imagery, were placed where staff congregated such as dining rooms, nursing stations, surgeons lounges, resident and student quarters, toilets and urinals. Campaign material provided a conversation piece for staff members and created a general awareness of the issues, not just by medical staff members but by students, nurses and other health professionals. The closed nature of the hospital environment facilitated the campaign's impact and this institutional awareness may have provided extra pressure on prescribers. In addition, campaign material provided opportunities for microbiologists, clinical pharmacologists and pharmacists to reinforce the desired messages on a person-to-person basis. After the campaign 91% of patients were receiving benzylpenicillin as compared with 44% of patients before the campaign. However, the proportion had dropped to 68%, 18 months after completion of the campaign, however, this was still significantly higher than the proportion of benzylpenicillin recipients before the advertising campaign. Despite the drop off rate the campaign costs of \$A10,000 were recouped within 12 months by savings on drug costs. A staff questionnaire aimed at identifying those areas of the campaign least and most effective was circulated to staff one month after the campaign. Representative responses for the most effective area included cost data, posters in the urinals rated high for the least effective.

This interventional campaign had been so successful it was decided to perform a controlled cross-over study in 12 Victorian public hospitals, to examine the power of the educational marketing techniques, and to promote specific recommendations made in the *Antibiotic Guidelines* booklet (Landgren *et al*,

1988). This study re-confirmed the findings of the first study (Harvey *et al*, 1986), that the campaigns used were associated with a significant improvement in the use of antibiotic agents. This type of campaigning has been so effective that a modified version has also been used to improve the timing of conversion from intravenous to oral administration of antibiotics (Allen, 1992). A series of posters showing antibiotic costs and annual expenditure, postcards mailed to all medical staff, medication chart stickers and publication of campaign details in the pharmacy bulletin were used. As a result, the potential annual wastage in the total hospital budget due to delayed conversion from the intravenous to oral route of administration was estimated to have fallen from \$130,435 Australian before the campaign to \$60,596 after it. The campaign costs of \$3,060 (which came from existing budgets) were minimal when compared with the potential annual savings.

#### **3.1.4.4 Drug Utilisation Review (DUR)**

DUR is the examination of prescribing patterns with subsequent feedback to prescribers. It is a quality assurance process designed to compare patterns of drug use in a given medical care delivery system against predetermined standards. Patterns of drug usage can be used to demonstrate the impact of formulary guidelines on drug usage or show the effect of the introduction of a new drug (Cooke, 1991). This type of data does not give information on the quality and appropriateness of prescribing but can provide useful information concerning the adherence of prescribers to formulary sections and guidelines and can be used as part of the audit process (West, 1977, Dobrzanski, 1991, Baker, 1988, Klein, 1981, Riley, 1991, Coleman, 1991, Adu, 1993). Unless a computerised system is used to collect data, even for the most basic of reviews, the process becomes prohibitive in terms of time (Fish, 1992).

Blackburn (1993) published a comprehensive review of DURs in institutions and in the ambulatory care setting. The consensus, internationally, was that DUR programmes are generally accepted as important components of the quality assessment processes but there is a general deficiency in quality evaluation components with few clearly defined clinical and economic outcomes. The

primary aim of most DUR programmes has been to reduce the direct drug costs to a specific institution or drug programme and has ignored its relation to total healthcare costs and benefits.

Sacristan *et al* (1994) suggested that drug utilisation studies could be used to aid pharmacoeconomic analysis, a rather glaring flaw in this suggestion is that the studies are not commonly used to study the benefits of drugs (Gross, 1984). An intrinsic component to any pharmacoeconomic evaluation is an assessment of outcome, so until the time that drug utilisation databases record outcome information their contribution to any economic analysis would be limited.

#### **3.1.4.5 Combined strategies**

Check (1980) reported a combined strategy for influencing prescribing practice of antibiotics to be highly effective. Avorn *et al* (1988) also found a combined paper based strategy aimed at improving parenteral antibiotic usage to be cost efficient. Three commonly used parenteral antibiotics were selected as targets for dose interval recommendations. A new parenteral antibiotic order form was designed to bring the relevant educational message to the physicians attention each time a prescribing decision was made. Several months in advance of the implementation of the new order form, written and poster materials containing appropriate information about the targeted antibiotics were placed in every patient chart in the hospital, mailed to all physicians and posted in new display cases in all patient care areas. This method produced a staggeringly high compliance with recommendations, inappropriate dosing of the targeted antibiotics which pre-strategy ranged between 60-90% was reduced to less than 10% post-strategy. \$US59,300 was realised annually as a result of the changes in drug and excipient costs alone. Staff time and supply cost savings amounted to a further \$US17,000. In part, because of introduction of this approach, total antibiotic expenditures at this hospital declined by 4% in the year after introduction of the form (Avorn, 1988).

A comprehensive program to change the type of intravenous nitrate used at a large English general hospital was carried out by Riley *et al* (1991). In the first instance the support of consultant cardiologists and the drug and appliances committee was

sought. This was followed by oral presentations to nursing and junior medical staff which encouraged two way exchange. Written guidelines for the use of the new nitrate were circulated and a specific date set to implement the changeover to the nitrate of first choice. Clinical pharmacists visiting the wards where nitrates were used re-inforced the guidelines by one to one contact with prescribers. Compliance with the changeover was almost 100%. Savings of £24,000 and £21,000 for the fiscal years 1988-89 and 1989-90 were estimated by comparing actual intravenous nitrate expenditure with projected expenditure had the changeover not taken place.

Workers in Ireland (Feely *et al*, 1990) also found that active intervention promoted formulary adherence. Specific forms of intervention used included feedback of prescribing habits to individual prescribers and consultants in charge of units. Additionally, peer comparisons and examples of specific savings were provided to prescribers and prescribing habits were discussed at monthly medical committee meetings. A drug information note was prepared in conjunction with the hospital's microbiologists on the use and abuse of third generation cephalosporins. When a prescriber wished to obtain a drug not included in the formulary a separate requisition was required. Selected aspects of prescribing were subject to intervention with special attention given to generic prescribing and the use of third generation cephalosporins. Comparison of prescribing practice before and after formulary introduction, with and without active intervention showed that generic prescribing increased by 50% and without feedback fell to its previous level. Aspects of prescribing practice not subject to feedback did not change at all. Once prescribers became familiar with the formulary, non-formulary requests constituted 5% of all prescriptions however with feedback the percentage was reduced further but rose again, further intensive feedback reduced the requests to 2% but rose anew to 5% when the feedback stopped. Third generation cephalosporin use was reduced during active intervention as did the annual cost, however without intervention the use increased as did the annual usage cost despite a reduction in suppliers acquisition cost. These workers showed that change is related to the amount of feedback prescribers receive and continuous

intervention is required if a formulary is to continue to achieve its objectives of improving drug use and reducing costs.

American hospitals appear to be more prepared to include a power strategy (i.e. a degree of coercion) within their combined approach to ensure prescribing conforms to a formulary/policy. Scher *et al* (1990) found that voluntary adherence to prophylactic antibiotic guidelines was poor in their hospital. In order to control rising costs of prophylactic antibiotics these workers implemented a four part program. The program consisted of limiting the number of cephalosporins on formulary, requiring consultant approval for any non-formulary cephalosporin, designating the use of a special order form to order any antibiotic on which its purpose as prophylactic, empiric or therapeutic had to be included and lastly all prophylactic antibiotics were automatically discontinued 24 hours after the initial dose. Six months prior to initiation of this program direct antibiotic costs averaged \$US16.80 per case, in the twelve months following inception of the program direct antibiotic costs averaged \$US10.45 per case. Total savings during this twelve month period, which included preparation and supply cost avoidance, was estimated to be \$US32,163. No detrimental effect was observed on wound infection rates. The reverse of this type of program i.e. removal of a restriction policy for antimicrobials has been shown by Himmelberg *et al* (1991) to result in an increase in the inappropriate use of these agents and total expenditure to increase by 103%.

In the evaluation of savings brought about by reduction of wasteful practices it is important to consider the costs incurred by the campaign, without doing so it is not possible to know whether the intervention is cost-effective. Cockburn *et al* (1992) studied three approaches for marketing smoking cessation programmes to Australian general practitioners. The educational facilitator approach cost \$A142 per general practitioner with \$14 for the volunteer courier and \$A6 for the mailed approach. There was a failure to show a significant advantage between the approaches and it was concluded that educational facilitators and volunteer couriers did not appear to be cost-effective. The added benefit in terms of smoking cessation in patients of general practitioners in the educational facilitator approach would need to be high to justify the expense.

Coleman *et al* (1991) found that a limiting formulary within the framework of restricting the usage of new expensive antibiotics and promoting the use of selected antibiotics achieved only a limited success in controlling the costs of parenteral antibiotics in an American VA hospital. The perceived reasons for this failure were considered to be threefold. Firstly, the policy allowed starting therapy with controlled antibiotics before infectious disease service (IDS) review. Second, the IDS team did not continue to monitor control policy patients unless called to consult by the treating physician. Third, the IDS team was composed of a rotating staff who could not provide continuity of care and had little incentive to strictly enforce medical centre antibiotic control policy. Based on these perceptions a change in enforcement protocol was initiated. IDS review prior to the prescription of restricted antibiotics was required, prospective and continuous review of antibiotic usage with authority to discontinue selected antibiotics on receipt of culture results, evaluation of the clinical condition, or both, and the appointment of a permanent IDS team member to deal with antibiotic-related issues. The average monthly antibiotic costs during the 26-month post enforcement change period were \$US7,600 less than during the 16-month pre-enforcement period, resulting in an average yearly cost reduction of \$US91,200. This new control procedure added 50 to 70 patients per month to the IDS workload. The medical centre's administration added a clinical pharmacist to the IDS team to help deal specifically with antibiotic issues when it was realised that the 23% reduction in drug acquisition costs during the first 4 months post enforcement was twice the salary expense of the position. Others have also found that cost savings accrued through a combined strategy can be used to more than justify the personnel costs associated with a combined strategy (Pillans *et al*, 1992). In the first year of a rigorous strategy to contain drug expenditure, Pillans *et al* (1992) reported savings of 3.3 million Rand.

### **3.2 Summary**

Both passive and active measures have been used by Hospitals to contain drug expenditure with varying degrees of success. Within these measures, five basic types of intervention have been used to influence and modify the prescribing

behaviour of clinicians. The different types of intervention have been described by Plumridge (1984) as re-educative, persuasive, facilitative, power and combined strategies. Studies using these types of intervention have been reviewed by Grimshaw and Russell (1993). These workers identified and systematically reviewed 59 published evaluations of clinical guidelines that met defined criteria for scientific rigour. Their conclusion was that explicit guidelines do improve clinical practice but the successful introduction of guidelines is dependent on many factors including the clinical context and the methods of developing, disseminating and implementing those guidelines. Different methods being appropriate in different contexts. Grimshaw & Russell (1993) suggested a classification that highlights the more effective strategies. Within this classification those strategies with a high or above average probability of being effective had a dissemination strategy which was a specific educational intervention or was of a continuing educational nature.

The cost-containment methods found to be most successful in controlling the hospital drug budget substantiates the findings of Grimshaw & Russell (1993). That is, a formulary can be an effective tool for containing costs provided it is dynamic, reflects current therapeutic needs, is augmented by measures such as consultant approval and generic substitution and is supported by continuing educational techniques aimed at streamlining prescribing practice.

In the reports of effective formulary cost containment there have been few accounts of treatment outcome. One of the few was by Scher *et al* (1990), these workers examined the effect of restricting the use of certain prophylactic cephalosporins on wound infection rates. No change was found in the rate. In this instance therefore, the cost containment practice was also cost-effective.

Although it may be possible to achieve effective cost containment, without knowing treatment outcome it is just not possible to determine whether the cost containment practice is cost effective. It could be argued that although a cost containment practice is effective in limiting drug expenditure, it could be having a negative impact on some other budget elsewhere in the hospital.

The next logical step within hospitals is to stop viewing drug expenditure in isolation and to take a wider view of the impact drug usage has within the

framework of overall treatment cost. To do this the outcome of drug treatment has to be considered alongside both the obvious costs and the not so obvious costs of treatment. A recent report from one hospital (Delaney, 1996) demonstrates how undertaking this exercise aided the decision to add what appeared to be an expensive acquisition cost drug (enoxaprin) to the drug formulary. Without the pharmacoeconomic evaluation the drug would almost certainly have been excluded as it was estimated that raw drug cost alone per annum would have increased the drug budget by almost 5% (IR£21,500). However, because enoxaprin reduced the incidence of post-operative deep vein thrombosis from 20% to 6%, annual treatment costs of IR£96,350 for this adverse event were averted, these savings more than offset the acquisition cost of the drug.

To summarise, a major deficiency of current formularies is that they have been compiled and operate without knowledge of how they impact on the utilisation of other healthcare resources. A way forward in the selection of drugs for formulary inclusion would be to systematically apply economic evaluation to each therapeutic category of drug. With this decision a starting point needs to be identified. Almost without exception, the largest single group of drugs used in acute care hospitals is the antibiotics and there are many reasons why this group of drugs should be subject to economic evaluation. These reasons are examined in the next chapter.

## Chapter 4

### 4. The economic issues of antibiotic use: part I

Spending on prescription pharmaceuticals by the National Health Service (NHS) in England in 1996 was £3,780 million (Government Statistical Service, 1997), for the same period in Scotland the spend was £427 million (Prescription Pricing Authority, 1996).

**Table 4.1 Prescription pharmaceutical costs by therapeutic classification (British National Formulary) in England (Government Statistical Service, 1997) and Scotland, 1996 (Prescription Pricing Authority, 1996).**

BNF Therapeutic Category	England	Scotland
	Total cost (£ million) (% of total)	Total cost (£ million) (% of total)
Gastro-intestinal system	578.9 (15.3)	85.6 (20.0)
Cardiovascular system	740.1 (19.6)	75.3 (17.6)
Respiratory system	485.8 (12.9)	52.3 (12.2)
Central Nervous system	527.6 (14.0)	60.5 (14.2)
Infections	225.5 (6.0)	28.7 (6.7)
Endocrine system	337.5 (8.9)	33.6 (7.9)
Obstetrics	77.7 (2.1)	9.2 (2.2)
Malignant disease and immunosuppression	118.1 (3.1)	10.9 (2.6)
Nutrition and blood	122.5 (3.2)	11.4 (2.7)
Musculoskeletal	200.8 (5.3)	24.0 (5.6)
Eye	50.3 (1.3)	4.3 (1.0)
Ear, Nose and oropharynx	44.3 (1.2)	5.1 (1.2)
Skin	171.8 (4.5)	20.0 (4.7)
Immunological/vaccines	88.8 (2.3)	5.7 (1.3)
Anaesthesia	1.8 (0.05)	0.2 (0.05)
Other	9.0 (0.2)	0.3 (0.07)
Total	3780.5	427.1

It can be seen from Table 4.1 that the contribution made by anti-infectives to the spend is in the range of 6% to 7%. Despite this, a lot of effort has been directed at controlling the use of antibiotics particularly in the hospital setting where they are

used in high frequency and have been reported to account for up to 34% of an acute hospitals drug budget (Kunin, 1988, Kunin *et al*, 1973, Hess *et al*, 1990, Coleman *et al*, 1991).

As with any class of drug financial waste occurs when antibiotics are used inappropriately, that is when the costs exceed the benefits accrued. However, there are more complex economic issues involved in the use of antibiotics which are not experienced with other classes of drug. For example, the very way in which antibiotics are employed can have an impact on their future usefulness i.e. ecological changes can be brought about by the injudicious use of a particular agent, these changes i.e. bacterial resistance, can nullify not only the future usefulness of that particular agent but the whole class to which the agent belongs. The ramifications of inappropriate use are therefore much further reaching than the limited immediate resource wastage experienced with other drug classes. These economic issues are now discussed.

Antibacterial (antimicrobial) agents are derived either from bacteria or moulds (the antibiotics) or from total chemical synthesis. They are used to eradicate pathogens which cause infection. The first range of agents to be introduced into medicine were the synthetic cupreines, these were produced by Morgenroth in the early 1900's (Sneider, 1985). Although these drugs were highly effective against pneumococci, streptococci and staphylococci they were associated with a high degree of toxicity which severely limited their use. Through the following years a wider range of synthetic antibacterial drugs were developed which had lower toxicity therefore making them more suitable for generalised use. The first antibiotic to be introduced into regular clinical practice was penicillin during the second world war. Soon after the introduction of penicillin many other antibiotics were discovered, for example, the cephalosporins, aminoglycosides, chloramphenicol; these rapidly became used on a regular basis.

Widdison *et al* (1993) stated that antibiotics are the largest single group of drugs used in hospitals in the UK. A nation-wide survey through England and Wales showed 22% of all hospital inpatients to be the recipients of antimicrobial therapy (Anon., 1981). This figure seems to be a relatively accurate assessment as a one day prevalence survey carried out in a single English hospital some two years later

reported 21% of all in-patients to be receiving an antibiotic (Cooke *et al*, 1983). Similar findings have been reported in the US (Kunin *et al*, 1973). A three month prevalence study in a teaching hospital showed 27% of patients admitted to the medical service to be treated with an antibiotic (Kunin *et al*, 1973). Elsewhere in the US the proportion of patients treated with an antimicrobial has been reported to be higher (Tanner & Nazarian, 1984). A series of studies at Boston hospital showed that the percentage of patients receiving antibiotics increased from 26% in 1964 to 42% in 1974 (Tanner & Nazarian, 1984).

With the advent of regular antimicrobial use there was a recognition that they were being overused and misused and that this was a world-wide problem. In an evaluation of antibiotic use, Scheckler & Bennett (1970) showed 62% of patients receiving antibiotic treatment to have no evidence of infection at all. By 1974 Lockwood (1974) had described the syndrome of compulsive antibiotic prescribing and advocated the formation of an organisation called Antibiotics Anonymous to deal with the issue. A former Commissioner of the American Food and Drug Administration recommended that a National Task Force on the Clinical Use of Antibiotics be set up (Kunin *et al*, 1973). The problem was considered to be of such magnitude that this was subsequently done. It is not only first world countries which are experiencing antimicrobial misuse, an international network for the rational use of drugs (INRUD) in third world countries exists, one of the major problems this network is trying to address is that of antibiotic misuse (Quick *et al*, 1991).

The worries of inappropriate antibiotic usage have centred around increased antibiotic resistance with consequent loss of efficacy, unnecessary exposure to toxic side-effects and latterly, financial waste. No other group of drugs has such an effect on society by its legitimate misuse. There is thus, a societal perspective as well as individual patient implication from continued misuse (Price *et al*, 1970).

Unlike other drug treatments the therapeutic outcome of antimicrobial treatment is soon known, a patient either gets better or they die. Contrary to this, for example, the cerebrovascular drugs, it can be many years before knowledge of their outcome is known. Because of the tangible outcome available for measurement and their ubiquitous use, antimicrobials are very amenable to pharmacoeconomic

evaluation. This tool could be readily employed to assist in the rationalisation of their use and therefore limit resource wastage.

#### **What are the fiscal implications of antibiotic use?**

All facets of antibiotic use, for example, the purpose of use, ecological impact of use, adverse effects, the method of administration, the location of administration, all have economic implications. Each of these aspects will be discussed.

### **4.1 Prophylaxis and Treatment**

With the discovery, development and introduction of an increasing number of antibacterial agents the choice available for treatment of a particular pathogen continues to widen. Many agents exist which have similar spectra of activity and selection between the various agents can become ad hoc unless set criteria are used to rationalise selection. Without rational criteria antibacterials can very easily be inappropriately employed. A crucial point which needs to be considered prior to choosing between the alternatives, however, is whether the patient actually needs to be in receipt of an antimicrobial.

Eradication of a pathogen can be achieved in one of two ways, prevention or active treatment. Prophylaxis is the use of an antimicrobial to prevent an infection occurring where there is a high probability that one might occur. Active treatment is used when an infection already exists. Of all antibiotic use, prophylactic antibiotics account for 30-40% (Shapiro *et al*, 1979, Cooke *et al*, 1983, Widdison *et al*, 1993). The striking difference between the use of an agent for prophylaxis and its use for active treatment is the **duration** of time the agent is used for. A prophylactic agent is recommended for use no longer than 24 hours as little additional benefit is obtained from extending this duration (Stone *et al*, 1979). An antibiotic used for treatment purposes ranges usually from 5 days upwards depending on the cultural background of the physician and the infection it is intended to treat (Davey *et al*, 1992, Janknegt *et al*, 1993).

The economic ramifications of prophylactic antibiotic use centre around the cost of employing these agents versus failure of prophylaxis, the incidence and cost of infection in the absence of prophylaxis, inappropriate selection of agent and the

inappropriate use of prophylaxis. The economic ramifications of antibiotics used for treatment are similar to those used for prophylaxis and centre on inappropriate use (lack of need, unsuitable agent selected or more efficacious agent available, incorrect dosage etc.) and failure of treatment.

#### **4.1.1 Prophylaxis**

Prophylactic antibiotics are used in several settings, for example, in the immunocompromised host, in patients with cystic fibrosis etc., but mostly they are used to give cover during surgical procedures. Although antimicrobial prophylaxis has a place in surgery its efficacy has only been scientifically demonstrated in certain procedures and conditions (Kunin, 1979, Wilson, 1995). Wasteful resource consumption may occur when prophylaxis is used without prior evaluation (Wilson, 1995).

It has been shown that time of drug administration, blood supply of tissue to be challenged and appropriateness of antimicrobial spectrum are factors crucial to the success of surgical prophylaxis (Stone *et al*, 1979,). Classen *et al* (1992) determined the lowest risk of postoperative infection to be associated with administration of a prophylactic antibiotic in the time period two hours either side of surgery. The relative risk being increased sixfold (6.7, confidence interval 2.9-14.7) if the prophylactic antibiotics were administered 2-24 hours pre or post-operatively. An additional risk factor which can affect the success of prophylaxis is duration of operation (Garibaldi *et al*, 1991). As part of a 'snapshot' survey of antibiotic use, Cooke *et al* (1983) reported that not only were 15% of surgical prophylactic antibiotic courses deemed inappropriate there was evidence that prophylaxis was started too late thereby negating its usefulness. A study by Jogerst & Dippe (1981) carried out in a community hospital considered 64% of prophylactic antibiotic courses to be inappropriate, 28% by virtue of being started too late.

#### **Costs of prophylaxis in various surgical specialities**

A study to determine the cost of prophylaxis was carried out for a cohort of patients undergoing both elective and emergency abdominal surgery (Stone *et al*,

1979), this included costing the failure of prophylaxis and the subsequent treatment of infection. These workers found that preventative antibiotic treatment was the most cost-effective option. It was further determined that almost two extra hospital days per patient were required by those individuals denied preoperative antibiotic, the excess being entirely due to potentially avoidable surgical infections. The extra medical expenditures caused by a single operation-related infection were calculated. The excess cost per patient incurred by prophylactic antibiotic and postoperative infection was \$129 for those patients receiving a preoperative antibiotic and \$429 for those patients not receiving a preoperative antibiotic, a difference of \$300 in favour of prophylaxis. It was noted that the indirect/intangible costs to the patient of being subject to infection had not been assessed but even so these existed in the form of losses of income due to prolonged incapacitation and a recognised increase in morbidity and mortality. These workers further discussed that greater savings could be made if the duration of prophylaxis was limited, financial waste occurred to the extent of \$92 per patient when antibiotic was continued in the postoperative period in those patients who had received prophylaxis. It was found that antimicrobial therapy continued beyond the day of operation was neither a benefit nor a detriment to the subsequent hospital course, or to any risk for development of a postoperative infection within the wound and/or abdomen proper.

Mansfield *et al* (1992) clinically reviewed the consequences of infection developing after vascular graft surgery. The incidence of infection was reported as between 0.7% and 7%. Although the occurrence may not appear very high the consequences of infection in this setting are catastrophic. Management of the infection can range from extended antibiotic treatment in the hospital setting through to major reconstructive surgery and intensive care support. Although not quantified in any form, the financial burden alone, in terms of staff time, hospitalisation and drug costs must necessarily be huge. The cost to the patient is also extensive. Mansfield *et al* (1992) reported a mortality rate of 24% and an amputation rate of 20% associated with late infection of vascular grafts at their hospital. Other workers have evaluated the direct cost of infection in clean vascular surgery. Kaiser *et al* (1983) compared the use of cefazolin prophylaxis vs

placebo. The excess cost of hospitalisation due to preventable wound infections rose precipitously and was directly related to the severity of infection. The excess cost ranged from \$3,600 per 100 operations for the mildest grade of infection through to \$6,200 per 100 operations for the most severe grade. In this study the observed infection rate and subsequent cost of treatment exceeded the cost of prophylaxis for all classes of infection.

A trial which looked at the financial costs of failed prophylaxis was one which rather than comparing prophylaxis with no prophylaxis compared the efficacy of different active agents (Roach *et al*, 1990). Cefazolin, which was cheaper to acquire and administer, was compared with cefamandole for prophylaxis in cardiac surgery. It was found that although the acquisition cost and administration charges related to the use of cefamandole were in excess of those incurred with cefazolin, differences in the charges associated with treating the wound infections that occurred despite prophylaxis with each regimen made cefamandole the more cost-effective prophylactic agent. There was a statistically significant difference in the perioperative wound infection rate between the two antibiotics in favour of cefamandole. The average excess charge above the charge of using cefamandole was \$401 per patient receiving cefazolin. These excess charges were mainly attributable to readmissions for sternal wound infection. In this study, costs and charges were reported, because of this it is not possible to determine the true fiscal difference between the two agents. The reasons for this are covered comprehensively in a paper by Finkler (1982) which explains the difference between costs and charges. Essentially in financial terms, costs refer to actual resources consumed in producing a product or service, for example, the cost of an iv administered drug will be the sum of the cost of the drug, the cost of consumables required to administer the drug, a proportion of any fixed costs (such as any equipment employed) and the cost of the staff time involved in the preparation and administration of the drug. Charges by comparison are essentially list prices for a product or service which may or maynot bear a direct relationship to the 'true' costs of producing the product or service. Charges will almost always exceed the 'true' costs. In addition to the 'true' costs of production, charges can include such things as equipment depreciation and other overhead costs such as

laundry which may not bear any direct relationship to actual resources consumed. Although in any economic evaluation it would be ideal to use 'true' costs rather than charges, the amount of time and effort required to determine these may be prohibitive because of the difficulties encountered in the determination (Whynes *et al*, 1995). For those situations where 'true' costs of resource consumption cannot readily be determined, charges can be used as a proxy measure provided this is made explicit. As such an indication of cost difference between comparators can be achieved (as in the Roach *et al* (1990) although the precise magnitude of that difference can not be assessed.

Shapiro *et al* (1983) analysed the costs and benefits associated with antimicrobial prophylaxis in both vaginal and abdominal hysterectomy. These workers found that excess in-hospital infections occurred in 29% of women undergoing vaginal hysterectomy who did not receive prophylaxis and in 18% of those undergoing abdominal hysterectomy. These results reflected the findings of others (Shapiro *et al*, 1983). The excess infectious morbidity costs were \$1,777 for vaginal hysterectomy and \$716 for abdominal hysterectomy. It was calculated that routine prophylaxis would translate to an average net benefit of \$492 per vaginal hysterectomy patient and \$102 per abdominal hysterectomy patient. These results would support the conclusion that prophylaxis in vaginal hysterectomy is more effective than prophylaxis in abdominal hysterectomy. Importantly, the benefit analysis was found to be sensitive to baseline infection rate, the efficacy of prophylaxis, the cost of antibiotic and the cost of treating the infections. An alternative conclusion was reached by Davey *et al* (1988). In this study the reduction in infection rate using cephadrine prophylaxis in vaginal and abdominal hysterectomy followed a similar pattern to that shown by Shapiro *et al* (1983) with a greater reduction being seen in the vaginal group. However when the costs of treating infections, which occurred despite prophylaxis, both in hospital and after discharge to the community were considered, prophylaxis in vaginal hysterectomy was found to be more costly than placebo yet prophylaxis in abdominal hysterectomy was found to save both hospital and community resources. The conclusion in this case appears to be that prophylaxis in abdominal hysterectomy is to be favoured above that in vaginal hysterectomy. As stated by Davey *et al*

(1992) the apparent conflict between the cost-effectiveness analysis and the traditional analysis in terms of cases of infection prevented illustrates two important points. The first is that there is no real basis for equating pelvic infections after vaginal hysterectomy with wound or pelvic infections after abdominal hysterectomy. The second is that use of continuous variables for measurement of outcome e.g. financial costs of treating infection, are preferable to using discontinuous variables such as infection/no infection. The discontinuous variable does not take into account the severity of infection or speed of recovery and as shown by the Davey *et al* (1988) study these are factors crucial in determining the use of resources. An important point discussed in the Davey *et al* (1988) prophylaxis study report was that only 5% of operations lasted more than 1.5 hours and therefore the results may not be relevant to centres with longer operation times. In the Shapiro *et al* (1983) study 66% of operations lasted greater than 1.75 hours. This may be one source of discrepancy between the two studies, Garibaldi *et al* (1991) demonstrated that duration of operation is important in terms of prophylactic success rate. Another source of discrepancy maybe the very different costs of management. It is obvious that the results of both studies (Shapiro *et al*, 1983, Davey *et al*, 1988) need to be considered within the context of other variables.

Until recently antibiotic prophylaxis in fracture surgery was controversial, however a prospective, double-blind, multicentre study of over 2,000 patients has provided evidence that the costs of treatment for closed limb fractures could be substantially reduced by employing single dose prophylaxis (Boxma *et al*, 1996). A single preoperative dose of ceftriaxone 2gm versus placebo was shown to be associated with significantly lower wound infections and a lower incidence of nosocomial infection within 30 days of surgery. These workers estimated that if all patients in the study had received prophylactic antibiotic, total direct cost avoidance would have been US\$535,550, which equated to savings of US\$486 per patient.

It can be seen that the judicious use of prophylactic antimicrobial therapy assists in the efficient use of resources, their inappropriate use achieving the entire opposite. Oral antibiotics before and after prophylactic parenteral antibiotics have

not been shown to be of additional benefit in reducing the infection-rate (Achong *et al*, 1977). Yet a study by Achong *et al* in 1976 (Achong *et al*, 1977) showed 56% of patients in their surgical wards and 75% of patients in their gynaecological wards to be receiving oral antibiotics after receiving prophylactic parenteral antibiotic. It is accepted by many workers that prophylaxis extended beyond the 24 hour postoperative period is unnecessary (Stone *et al*, 1979, Crossley *et al*, 1981, Cooke *et al*, 1983, Widdison *et al*, 1993). Crossley *et al* (1981) in a multihospital survey of all surgical patients receiving prophylaxis reported that 32% of 1,021 patients received prophylaxis for greater than 72 hours. The cost of this superfluous use can be estimated using the figure calculated by Stone *et al* (1979). Financial waste of \$92 per patient was considered to occur when antibiotic was continued in the postoperative period, a crude estimate of unnecessary monetary expenditure in the Crossley study is approximately \$30,000.

Although the efficacy of a prophylactic agent and the process by which it is administered are important issues in cost-effective evaluations there is another dimension which in economic terms receives little attention, that is the occurrence of adverse events. If an antimicrobial is used routinely in a large number of patients, there will eventually be side effects in some persons that have a measurable cost. To date these do not seem to have been considered (Ehrenkranz, 1989).

#### **4.1.2 Treatment**

Various studies have shown that patients receive medication unnecessarily, as mentioned earlier, Scheckler & Bennett (1970) showed 62% of patients receiving antibiotic treatment to have no evidence of infection whatsoever. The proportion of patients considered to have no indication yet, were in receipt of treatment was somewhat lower (16%) in a study by Jogerst & Dippe (1981). Resource wastage occurs when patients are treated both inappropriately and unnecessarily (Kunin *et al*, 1973, Achong *et al*, 1977, Jogerst & Dippe, 1981, Jewesson *et al* 1985, Dunagan *et al*, 1991, Shrimpton *et al*, 1993).

Several studies have documented the costs of hospital antibiotic treatment, including hidden costs such as cost of preparation, frequency of administration,

monitoring and toxicity (Tanner & Nazarian, 1984, Eisenberg *et al*, 1987, Hoepelman *et al*, 1988, Wright, 1991, Davey *et al*, 1990, Plumridge, 1990, Robson *et al*, 1992, Kerr *et al*, 1993, Malek *et al*, 1992, Smyth *et al*, 1995) and the information from this type of study has indeed been used at individual hospital level in an attempt to contain antibiotic prescribing costs (Abramowitz *et al*, 1982, Tanner & Nazarian, 1984, Jewesson *et al*, 1985, Coleman *et al*, 1991). One study, a cost description of an adult cystic fibrosis unit, which included the antibiotic costings for patients requiring different levels of care was used to secure funding and also facilitated the prediction of future requirements. Medication accounted for 57% of the total cost of caring for these patients, yet in the discussion of this study the authors state that the benefit of treatment used in this way is unproven (Robson *et al*, 1992). However, what is missing from the literature is information about total cost-effectiveness. Most clinical trials of therapeutic antimicrobials use outcome measures such as improvement or cure but very few provide any further information about the consequences of failed antibiotic treatment either for the patient or the health services. A prospective audit of costs and outcome of aminoglycoside treatment and of therapy for gram-negative bacteraemia by Davey *et al* (1995) does however demonstrate the rebound costs caused by failed therapy. In this study a patient was treated for a wound infection in hospital for six days at a cost of £186 (drugs, consumables, staff administration time) and was then discharged. Within two days the patient was readmitted with gross suppuration of the wound, total treatment cost for the second admission was £1,757 (drugs, consumables, staff administration time) (Davey *et al*, 1995). In addition to this treatment cost, other costs which are more difficult to evaluate need to be taken into account, namely, the opportunity cost to other potential patients denied access to the hospital bed taken up by the readmission and the intangible cost to the patient who has been subject to failed therapy. It has been suggested by some (Copley-Merriman *et al*, 1992) that this sort of health resource data should be collected prospectively at the time a drug is undergoing final clinical trials, the practicality of this suggestion however, is somewhat suspect.

## 4.2 Adverse effects of antibiotic use

Antibiotic use, be it either prophylaxis or treatment, can be associated with various adverse effects. These can range from the change in bacterial resistance patterns seen with the overuse of antibiotics and the ecological impact this can have through to the idiosyncratic adverse effects experienced at individual patient level.

### 4.2.1 Resistance, Ecology & Infection Control measures

The ramifications of the injudicious use of antibiotics can be highlighted by a serious outbreak of cross-infection due to *Klebsiella aerogenes* in a neurosurgical unit in the late 1960s (Price *et al*, 1970). Large numbers of patients within this unit regularly received prophylactic and therapeutic antibiotics both because of the severity of their medical condition and the fact that certain patients were at increased risk of infection. During 1968-69, of 228 patients on the unit almost 30% became subject to serious infection with *K. aerogenes*, 8 patients died. Extensive measures were taken to control the cross-infection but all to no avail, to further compound the problem the infecting *Klebsiella* species were resistant to all chemotherapy. Drastic measures were sought and it was decided to withdraw the use of all prophylactic and therapeutic antibiotics. The rationale behind this was that *K. aerogenes* is an opportunist ready to colonise the respiratory tract of patients whose normal bacterial flora has been suppressed by broad spectrum antibiotics. Within four weeks *klebsiella* urinary tract infection fell from 20% to 0% and *klebsiella* chest infection was reduced from 28% to 2%. Another unforeseen benefit was that the total infection rate for other organisms was also drastically reduced. Price *et al* (1970) suggested that by withdrawing all antibiotics, the more antibiotic sensitive and less virulent bacteria were allowed to thrive. In turn, the changed ecological situation resulted in a reduction in the numbers of infections due to the more resistant *K. aerogenes*. Although not considered in the report of this outbreak, the costs of additional care to the hospital and the costs of morbidity and mortality to the patients must by definition have been high. In a discussion of the prevention and control of nosocomial infections Dixon (1985) reported that almost 300 thousand patients acquire a nosocomial respiratory tract infection (RTI) each year in the US, with associated hospital care

costs of approximately \$10 billion. Similar additional hospital care cost estimates for nosocomial infections throughout the UK do not exist, but the account of an outbreak of hospital acquired RTI in 8 debilitated elderly patients reported the mean monthly antibiotic bill for one ward to have more than doubled. Once the outbreak was finished antimicrobial costs were more or less reduced to the former level (Millar *et al*, 1994). It can be seen therefore that costs of treatment alone rapidly escalate.

In 1972 Finland published an extensive review of bacterial susceptibility patterns to existing antibiotics at that time. His conclusion was '*that excessive use of antibiotics; the use of multiple, highly active, and broad spectrum agents; the use of excessive dosages; and particularly their widespread use for prophylaxis are primarily responsible for the increased proportion of the most resistant strains of many species and for the increasing prominence of species with innate resistance to the antibiotics so widely used*'.

The reports of bacterial resistance world-wide has continued (Jacobs *et al*, 1978, Moller, 1989, Courcol *et al*, 1989, Eady *et al*, 1993, Burke, 1995, Anon, 1996) with accompanying exhortations that processes be used to stem further development. Eady *et al* (1993) reported that there are 23 ways of prescribing antibiotics for acne based on oral, topical, or combined use of available preparations. The relative risk of developing resistance with each regimen is unknown. These authors proposed guidelines for antibiotic treatment of acne which firstline involved not prescribing antibiotics at all if a non-antibiotic topical treatment would suffice and that patients expectations for an endless supply of antibiotics needed to be changed, without following a policy it was felt that the bacterial resistance now seen in acne would only worsen.

Antibiotic formularies and policies have been introduced into institutions in an attempt to control antibiotic usage and limit bacterial resistance (Bendall MJ *et al*, 1986, Coucol *et al*, 1989, Lamikanra *et al*, 1989, Moller JK, 1989, Sturm AW, 1990, Neu HC, 1992, O'Brien TF, 1992, Eady *et al*, 1993). The success with which these work are dependent on more than just their existence, this is discussed in full later.

### **Infection Control measures**

Although bacterial resistance can be related to the use of antibiotics, nosocomial infection can be limited by other infection control practices such as good hand-washing, barrier nursing, single patient use of instruments and limiting the use of invasive procedures (BSAC Working Party, 1995, Sanderson, 1995). Isaacs *et al* (1988) demonstrated how readily resistance can develop when infection control measures are compromised. This study was prompted by two babies developing life-threatening systemic infections with gentamicin resistant *Klebsiella oxytoca*. Analysis of factors from prospectively collected surveillance data showed that the proportion of babies colonised with gentamicin resistant gram-negative organisms did not correlate with either the quantity or duration of aminoglycosides used but rather that the proportion of babies colonised correlated with two indicators of workload: the number of babies in the unit (expressed as baby days) and a score based on the level of nursing care required. As the workload score increased so did the number of babies colonised. Isaacs *et al* (1988) suggested that the spread of resistant organisms between the babies was likely to be due to normal aseptic precautions becoming compromised when the workload was high. The cost of this resistance to the neonatal unit was not evaluated. O'Donoghue & Allen (1992) costed the outbreak of 10 serious wound infections in an orthopaedic ward which were thought to be due to slack infection control measures. The wound infections had a high probability of being caused by 5 damaged and contaminated mattresses. The total cost of the outbreak was £22,199 which only included the direct costs of prolonged inpatient stay, additional operative procedures, dressings and chemotherapeutic interventions. Personnel costs, consumables associated with the chemotherapy, the costs of investigation of the outbreak such as environmental sampling and phage typing, and the intangible costs of pain and suffering to the patient and worry to the relatives were not included. The cost of replacing the 5 damaged mattresses was £182. Although the evidence was circumstantial that the damaged mattresses were the source of the outbreak no further patients developed wound breakdown after the mattresses had been discarded. An adequate infection control programme could have avoided this scenario and costs both to the hospital and patients would have been much reduced.

A study by the Center for Disease Control (Haley, 1991) found that up to one-third of nosocomial infections can be prevented by effective infection control programs. However Sanderson (1995) discussed that there is a point at which nosocomial infections are '*inevitable and irreducible*' and are a function of a hospitals procedures rather than cross infection. For example, the rate at which patients are catheterised and the expertise with which this procedure is executed will have an impact on the nosocomial level of UTI infection (Sanderson, 1995). From a societal perspective Stevenson *et al* (1988) discussed that a baseline surgical infection rate need not necessarily be the one which is the minimum attainable because the avoidance of infection is a costly process. These authors suggested that the optimum infection rate is that which balances the costs of infection control against the benefits achievable i.e. it is only beneficial to continue to reduce infection rates whilst the social and medical costs of infection exceed or equal the costs of avoiding them. This rationale has been endorsed by Davey *et al* (1995) in the discussion of which agent to select for surgical prophylaxis.

Infection control processes, of which antibiotic policies are one, should be used to limit the development of antibiotic resistance provided the benefits accrued exceed the costs of implementation.

#### **4.2.2 Idiosyncratic Adverse Effects**

Untoward toxic effects of antibiotics vary, they range from death from anaphylaxis or aplastic anaemia, with penicillin and chloramphenicol, to severe diarrhoea from lincomycin, rash from ampicillin, and nephrotoxicity and ototoxicity from the aminoglycosides. It has been reported that approximately 5% of the hospitalised patients who are given an antibiotic will experience some adverse reaction to the drug, and about 20% of patients requiring medical care give a history of having a past adverse reaction to an antibiotic (Kunin *et al*, 1973). Up to 10% of patients in whom prothrombin time has been prolonged as a result of antibiotic therapy have been reported to manifest some form of bleeding (Ehrenkranz, 1989). Rarely has the cost of adverse reactions been evaluated. However, Eisenberg *et al* (1987) measured the economic impact of

aminoglycoside-associated nephrotoxicity at six Philadelphia area hospitals. These authors found that 7.3% of patients treated with an aminoglycoside developed aminoglycoside-associated nephrotoxicity. The additional cost of hospital ancillary services per case of nephrotoxicity was \$446; the additional cost of hospital stay was \$825 for additional routine days and \$1152 for intensive care days. Additional consultations were \$78 per patient. The mean total additional cost was calculated to be \$2501 with the average additional cost per patient receiving aminoglycoside therapy being \$183.

#### **4.3 Non-compliance of prescribed antimicrobial therapy**

Compliance is the degree to which a treatment plan is adhered to. It has been estimated that 30-50% of patients do not comply with their prescribed medication (Merck Manual, 15th edn). This is related to the frequency with which a drug has to be taken and the occurrence of side-effects (Davey *et al*, 1992, Nightingale *et al*, 1994). When compliance is discussed it is usually in reference to patient compliance with oral therapy (Merck Manual, 15th edn) but it has been shown that staff within hospitals can have problems complying with a given regimen (Davey *et al*, 1992). An audit of IV antibiotic administration by Davey *et al* (1990) showed that between 16-45% of administrations differed from the prescribed time by more than an hour. This phenomenon of inaccurate administration times for IV injections has been described elsewhere ( Clark *et al.*, 1986, Cousins *et al.*, 1989, Li *et al*, 1989). Inaccurate administration times can affect the therapeutic activity of antimicrobials in different ways. For the aminoglycosides inaccurate administration times may lead to inappropriate dosage adjustment. For the B-lactams the time the drug concentration is maintained above the MIC of the infecting pathogen is important, if the concentration falls below the MIC then breakthrough bacterial multiplication can occur (Drusano 1988).

Non-compliance with prescribed antimicrobial therapy increases the probability of failure of treatment and failure of treatment is associated with various costs. These include additional drug treatment, the opportunity cost of unnecessary repeat visits to community or hospital practitioners, the costs of additional investigation and

the costs of long-term complications, such as ectopic pregnancy after untreated chlamydial infection in women (Washington *et al*, 1987).

#### **4.4 Method of administration**

Historical and cultural factors can have an impact on how antibiotics are utilised. Many of the original antimicrobials had very poor oral bioavailability, to ensure adequate serum levels it was necessary for these agents to be administered parenterally. This has left an implicit legacy of belief that this is a superior way to administer an antibiotic, however, with many antimicrobials which have excellent oral bioavailability, this belief is misplaced. Similarly whereas it is the norm for patients in the UK to be admitted to hospital to receive intravenous medication, in the USA it is considered regular practice for patients to receive intravenous (iv) care outside of the hospital setting.

The economic issues of both iv vs oral administration and non-inpatient vs inpatient care are now discussed.

##### **4.4.1 IV vs Oral**

Clinicians have long considered that the most effective route for the treatment of serious infections is the intravenous route, the problems of incomplete absorption that can occur in oral therapy are avoided, and it is widely accepted that peripheral shutdown, as occurs in severe sepsis, causes non-distribution of an intramuscularly administered antibiotic. However, this implicit assumption that the intravenous route is optimal can be disputed.

Recently several new oral antibacterial drugs have been developed which provide adequate cover to the whole range of Gram-negative and Gram-positive pathogens. Provided there are no manifestations of gut ischaemia and/or gross electrolyte disturbance there is no apparent reason why an appropriate oral antibiotic should not be employed. Where necessary dosage adjustments could be carried out for those patients exhibiting varying degrees of renal impairment.

The use of oral antibiotics in serious infection has been hotly debated. Arguments against the use of oral antimicrobials have centred around the bioavailability of the antibiotic and the belief that the absorptive capability of a patient may be compromised. However there is a paucity of literature concerning the use of oral

drugs in serious illness, this may be due in part to a section in the American Federal Register which reads '*bioavailability studies may be conducted on suitable non critically ill patients.....that studies on critically ill patients are inappropriate and contrary to the best medical interest of such individuals unless there is a potential benefit to the patient*' (Federal Register 1977), it can be argued that the potential benefit of oral therapy to the patient over and above iv therapy is the additional comfort of not being the recipient of repeated venepuncture and the associated phlebitis that can so readily result (Falchuk *et al* 1985; Backhouse *et al* 1987; Allcutt *et al* 1983).

#### 4.4.1.1 Clinical studies comparing iv and oral therapy

Depending on the agent, the bioavailability of an antibiotic can vary quite widely from a low percentage through to a high percentage. Table 4.2 gives some examples (from Principles & Practice of Infectious Diseases, 3rd Edn).

**Table 4.2** Some examples of antibiotics and their oral bioavailability

Antibiotic Group	Antibiotic	Oral Absorption %
Penicillins	Amoxycillin	89
	Ampicillin	50 (average)
	Dicloxacillin	37-74
	Nafcillin	10-20 (erratic)
Cephalosporins	Cephalexin	80-100
	Cephadrine	90-100
	Cefuroxime axetil	30-40
	Cefixime	50
Aminoglycosides	Gentamicin	minimal
	Netilmicin	minimal
	Tobramycin	0
Quinolones	Ciprofloxacin	69-85
	Ofloxacin	85-90
	Temafloxacin	100
Tetracyclines	Chlortetracycline	30
	Minocycline	95-100
Others	Metronidazole	95

Recent studies have shown the usefulness of oral antimicrobials in groups of patients who would otherwise have been candidates for iv therapy. In general, the quinolones have a high bioavailability and the clinical studies carried out in seriously ill patients comparing the use of these drugs orally with the iv route of administration have been encouraging. Fass (1987) used oral ciprofloxacin in a small group who had multiply resistant respiratory pathogens, the group showed 'consistently favourable clinical responses appropriate for their infections and underlying illness'. A study by Strandvik *et al* (1989) compared the efficacy of oral ciprofloxacin with iv ciprofloxacin for the treatment of chest infections in patients with cystic fibrosis. It was concluded that the oral form was preferable for treatment giving a slightly better bacteriological outcome. There was a dose difference between the oral and iv regimens which may explain the difference in efficacy but the point made is that serious chest infections can be adequately treated via the oral route.

Hodson *et al* (1987) conducted a similar study in 40 adult patients with cystic fibrosis who had acute exacerbations of chest infection caused by the bacterium *Pseudomonas aeruginosa*. These authors compared oral ciprofloxacin with conventional iv therapy and found that the oral group, 20 patients in total, showed equivalent improvements to the iv treated group, however lung function improvements were statistically greater after ciprofloxacin.

This study also included a quality of life component in that the patients who received oral ciprofloxacin were asked whether they preferred oral treatment to iv treatment if they had received iv treatment in the past. Of the 20 patients, 17 said they preferred oral treatment to previous iv therapy (1 had no preference, 1 had not had previously received iv treatment, and 1 patient did not answer).

One small study conducted by Johnson *et al* (1990) looked at the serum levels of oral ciprofloxacin in 6 neutropenic patients who had received chemotherapy for haematological malignancy. In 5 of the 6 patients, reduced serum levels of ciprofloxacin were found after cytotoxic chemotherapy treatment. This was thought to be due to reduced absorption of the ciprofloxacin which in turn was due to damage of the gut mucosa induced by the cytotoxic agents. The authors concluded that levels achieved were probably adequate for treatment of most

infections but caution should be used when treating systemic infections with oral ciprofloxacin in this group of patients.

A serious infection as compared with a non serious infection can be defined as one that causes substantial morbidity and mortality if allowed to proceed unchecked. Within the category of serious infection fall tuberculosis and pulmonary exacerbations of cystic fibrosis. Both of these conditions have been shown to respond successfully to appropriate oral antimicrobial therapy.

Another antibiotic with a high bioavailability (95%) is metronidazole. An audit of iv metronidazole therapy by Jewesson *et al* (1985) found that 29% of the courses were inappropriate in relation to the route of administration. The authors suggested that substitution of iv metronidazole with oral or rectal formulations in specific instances would result in substantial savings. Interestingly, Ridgway *et al* (1991) showed that cefuroxime axetil was suitable for treating lower respiratory and urinary tract infections in elderly patients despite the fact that this agent only has a bioavailability of some 30-40%.

It would appear that these studies lend support to the use of oral drugs for treatment of serious bacterial infections. What has not been fully investigated is the potentially higher bioavailability that may exist in the infected state: the increase in plasma free fatty acid level decreases drug protein binding and therefore more unbound drug is available to exert a pharmacological effect. Additionally, infection may inhibit drug metabolism so that it is inactivated at a lower rate (Smith, 1988). To ensure adequate serum concentrations of antimicrobial agents and therefore promote successful outcome of therapy, serum bactericidal titres at trough concentrations could be monitored (Davey *et al*, 1991, Drusano, 1988), the kinetic aim being that the free drug remain above the minimum inhibitory concentration (MIC) for the infecting pathogen. Others (Klastersky *et al*, 1974) have also concluded that the early evaluation of serum concentrations and antibacterial activity is very useful in leading to antibiotic dosage adjustment and therefore improving clinical outcome. More data are required comparing the efficacy of oral and iv antimicrobial formulations (Neu, 1989).

#### 4.4.1.2 Management/administrative issues with iv administration of antibiotics

##### Quality of preparation

Several studies (Davey *et al* 1990; Clark *et al* 1986; Cousins *et al* 1989) have shown that the ward environment is not suitable for the routine preparation of iv drugs. Stability, sterility and compatibility are all compromised when iv additives are prepared on the ward by non-pharmacy staff. The recommendations of the Breckenridge report (1976) on iv additives stated that *'the addition of drugs to iv infusion fluids is an aseptic procedure, which should ideally be carried out in appropriate environmental conditions, under the direct control of a pharmacist'*. Due to these recommendations and the growing awareness of the poor quality of iv drug preparation at ward level, a central iv additive service (CIVA) is now provided by a substantial number of hospital pharmacy departments throughout Britain. Where this service is provided there is a general acceptance of improved pharmaceutical quality, rate and time of administration and savings in medical and nursing time. All of these may lead to an improved quality of patient care (Clark *et al* 1986; Cousins *et al* 1989; Clark 1988).

### **Dosing intervals**

The Breckenridge Report (1976) further stated '*where intramuscular or oral administration is feasible, the iv route should be avoided*'. Where the iv route has to be used the precise method and rate of administration is sometimes critically important in determining the efficacy or safety of therapy'. This statement is pertinent to the use of antibacterial agents. As already discussed in the preceding section on compliance therapeutic efficacy for the B-lactam antibiotics depends mainly on the time that the bacteria are exposed to effective concentrations, long intervals between doses therefore lengthens the time that the concentration of antibiotic in the serum is below the minimum inhibitory concentration (MIC) of the target organism. A patient receiving B-lactam therapy under these conditions is put at risk of suboptimal treatment (Drusano 1988). The aminoglycosides and quinolones exhibit concentration-dependent bactericidal activity with a prolonged post-antibiotic effect. It is possible for these antibiotics to have an extended time interval between doses without compromising antibacterial efficacy (Bakker-Woudenberg *et al* 1988). In a study carried out within Dundee Hospitals to observe the utilisation of the aminoglycosides and the general antibiotic management of septicaemia, it was found that 44.5% of the study population experienced at least one missed/non recorded dose (Parker & Davey, 1992). The iv antibiotics were administered by house officers with the exception of the ICU where specially trained nursing staff administered iv therapy. The reason that so many doses should be missed/non-recorded can be related to the house officers remit. Their duties are often at a maximum, attending consultant ward rounds, clerking in patients, arranging x-rays and collecting blood samples or performing other tasks. Additionally, where several patients on the same ward are on what can be quite complex antibiotic regimens, it is not possible for the iv antibiotic boluses to be prepared and administered to all of the patients at the prescribed time.

For 63.9% of the non-recorded doses it was not possible to ascertain whether the dose had in fact been administered. In some cases the antibiotic may have been administered and just not recorded. This in itself has ramifications in that a second person may notice the omission of recording and seek to redress the situation by administering the dose, hence the patient receives two doses within a short period

of time. Although in a large number of cases this may not be of clinical importance, it is when the antibiotic has a narrow therapeutic index such as an aminoglycoside or a glycopeptide. The situation then becomes clinically significant. Examples of this additional dosing due to non-recording of the first dose has occurred within Dundee Hospitals; a patient received 140mg gentamicin at ward level prior to surgery but the dose was not recorded on the kardex, on receiving the patient in theatre the anaesthetist noticed the omission on the kardex and proceeded to administer a further 140mg gentamicin, the patient had therefore received two doses of 140mg gentamicin within one hour. It was not until later in the day when requesting the house officer involved to ensure that all patients received prescribed antibiotics prior to theatre that the incident of double dosing was uncovered. This type of incident was not an isolated occurrence.

Further implications of this non-recording/non administration of antibiotics include:-

1. The patient receiving inadequate treatment where the non recording reflects a non administered dose, therefore therapy may be further prolonged. Where the non recording is just that i.e. a dose actually has been administered, then the potential for toxicity exists should a second dose be given.
2. All procedures to a patient must be documented and the documentation retained for a set period of time, therefore there are medico-legal implications.
3. It may be necessary for various reasons e.g. interpretation of aminoglycoside levels, to know the exact number of doses a patient has received, incorrect recording can lead to incorrect dosage adjustments.

A publication by Denton *et al* (1991) highlights that these findings are not peculiar to Dundee Hospitals. These authors also found that the time intervals for multiple daily dosing regimens were highly variable. A practice was created whereby a long interval between successive doses overnight ensued and occurred on all units where nursing staff did not give iv antibiotics. Inaccurate administration times for iv injections has been described in other centres (Li *et al* 1989; Clark *et al* 1986; Cousins *et al* 1989).

#### 4.4.1.3 Cost factors in IV delivery

##### Drug cost/price

Costing of drug therapy is made difficult by failure to distinguish clearly between costs to the hospital and charges to the patient. This inconsistency of utilising costs and charges is highlighted by McCue *et al* (1985). These authors surveyed hospital charges for iv antibiotics in 71 hospitals in 25 US cities. They found that the percentage of patient charges due to drug cost ranged from only 6.9% to 38.8% and that it was impossible to estimate the cost of the drug to the hospital from the charges made to the patient.

The base price, the figure on which hospitals calculated their markups, was the actual drug acquisition cost in only 53.6% of the hospitals, the remaining 43.7% used one of the wholesale price guides to set their base price, even though none of them consistently paid the average wholesale price (AWP) for their drug purchases. 81.7% purchased at least one antibiotic through competitive bidding or a collective buying arrangement; of these hospitals, 67% passed savings onto patients, and the remainder put the profit generated by the differences between the actual drug acquisition cost and the price that was based on AWP into hospital or pharmacy operating funds.

In addition to the markup on the drug cost, 64% of the hospitals added a pharmacy dispensing fee for each dose of iv drug administered. When a pharmacy-prepared system e.g. minibag, the commonest method of antibiotic administration, was used, an additional charge of \$9.09 per dose was levied. Examples of the average hospital drug-related and pharmacy-related charges for selected iv antibiotic regimens are shown in Table 4.3, taken from McCue *et al* (1985).

**Table 4.3 Average hospital drug-related and pharmacy related charges for selected iv antibiotic regimens.**

Drug	Gentamicin	Cefazolin	Cefoperazone
Dose	80mg	1000mg	2000mg
Frequency	8 hourly	8 hourly	12 hourly
Drug cost (\$)	3.25	11.04	38.03
Amount markup (\$)	11.87	16.52	36.36
Dispensing Charges (\$)	32.20	31.20	23.63
Daily Charge to Patient (\$)*	47.30	58.67	97.93
% of Patient Charges due to Drug cost	6.9	18.8	38.8

\* Does not include dose preparation charge, \$9.09, or any iv-line related charges.

#### **Equipment/Consumables**

Intravenous administration of a drug involves not only the cost of the drug itself but the costs of the personnel time involved in the preparation and administration of the drug and the costs of consumables used during the preparation and administration i.e. syringes, needles, giving sets, in-line filters etc. Because of the large annual costs involved with iv therapy, one American 530-bedded hospital set up an interdisciplinary committee to look at infusion control devices. By rationalisation of the infusion control devices used, this group was able to show a total savings attributable to decreased use of \$142,223 for the fiscal year 1986 (Donnelly *et al* 1988).

In 1989, Cousins *et al* produced an average total cost for a ward based antibiotic bolus of £5.17 per dose and for a CIVA antibiotic bolus of £5.13. One year later Davey *et al* (1990) reported an average cost for a ward based antibiotic bolus of £5.66.

The overall costs of providing a CIVA service have been found to be of the same magnitude to the hospitals as the traditional bolus dose ward-based service, although the various elements which make up the overall cost varies markedly between the two operations (Cousins *et al* 1989).

Table 4.4, data from Cousins *et al* (1989), shows that the two elements of operational cost that differ mostly are nursing labour and consumables. The bolus nursing labour cost was based on the minimum theoretical time required for correct bolus dose preparation and administration of 10.5 minutes, compared with the average time of 5.25 minutes for nurses to obtain and hang a CIVA dose. The full administration time was not included for the CIVA dose as a nurse was not involved in administration after connecting the minibag and releasing the roller clamp. The variation in consumable costs is due to the cost of the minibag system, sterile gloves, alcohol wipes and bacteriological filters which are used in addition to the needles and syringes, during the preparation of a CIVA dose. Some of these additional items (sterile gloves, alcohol wipes) should be used at ward level but rarely are (Davey *et al* 1990).

**Table 4.4 Comparative costs (£) of ward-based iv bolus and central iv additive (CIVA) service (from Cousins *et al*. 1989)**

	Bolus	CIVA
Drug (£)	3.30	3.30
Consumables (£)	0.17	1.01
Waste (£)	0.26	0.18
Error (£)	0.43	0.05
Pharmacy labour (£)	0.00	0.27
Nursing Labour (£)	1.01	0.32
Nursing Time (min)	10.50	5.25

#### **IV Wastage**

Wastage occurs due to error and poor communication between medical and nursing staff. Depending on the system in use for iv preparation the report of iv wastage has ranged from 2.06% up to 19.98%.

Wastage is at a maximum when preparation is carried out at ward level, injections are frequently incorrectly prepared, badly labelled and incorrectly stored. Wastage at ward level has been reported to range between 6-19.98% (Davey *et al* 1990; Cousins *et al* 1989; Newhouse *et al* 1988). A consistent finding of utilising a CIVA service is the large reduction in drug wastage, the subsequent savings made from this reduction can be used to offset the increased cost of consumables. By initiating a CIVA service Cousins *et al* (1989) demonstrated a 50% decrease in drug wastage from 7.9% to 4%. Newhouse *et al* (1988) reduced iv wastage to under 2.25% using a similar system.

#### **Staff time**

Most manufacturers recommend iv drug boluses to be administered over three to five minutes. It has long been recognised that clinicians and nurses working under pressure on busy wards have difficulty in complying with these recommendations. Clark *et al* (1986) found that 78% of drugs given by iv bolus were administered in less than one minute. These findings were similar to those of Davey *et al* (1990). Additional to the administration time of the drug is the preparation time. Clark found an average time of 13.7 minutes for a nurse prepared/administered iv drug and an average time of 7.6 minutes for a doctor prepared/administered iv drug. It was calculated that the annual labour cost to the District Health Authority was £267,368.

Davey *et al* (1990) found that the average preparation time per injection at ward level was less for batches than for a single injection, the batch preparation mean being 2.1 minutes and the single injection mean being 4.8 minutes. The estimated annual nursing time was 54 hours on general medical wards and 91 hours on general surgical wards; house officer time was 163 hours and 159 hours respectively.

Cousins *et al* (1989) showed that the labour costs involved in the preparation and administration of a CIVA dose was almost half that of a ward prepared dose i.e.

59p per dose compared with 101p per dose. A CIVA service provides for batch preparation of injections thus allowing for a lower average preparation time per injection (Newhouse *et al* 1988).

#### **Additional costs**

Certain drugs because of their potential for toxicity require serum monitoring regardless of their route of administration e.g. digoxin, theophylline, phenytoin. This involves the personnel time and consumables used for sample taking and assaying. However, there are drugs that are given only by the iv route which also require serum monitoring e.g. aminoglycosides. The alternative oral drugs which can be used in place of the aminoglycosides do not require serum monitoring. Malek *et al* (1991) in a paper comparing two types of antimicrobial therapy showed that assay laboratory costs for patients receiving aminoglycoside therapy averaged £36.59 per patient.

Another additional cost is the element of patient discomfort experienced due to the additional venepuncture.

#### **Cost of treating adverse effects**

In addition to these operational costs a value has to be placed on the probability of the occurrence of an adverse event. Infusion-related phlebitis is a prevalent disorder and has been stated to affect over half of all patients receiving an infusion without an in-line filter. An in-line filter has been shown to reduce the incidence by 50-60%, this still means that approximately 25% of patients receiving iv therapy experience some degree of phlebitis. Garrelts *et al* (1994) in a study of patients receiving vancomycin calculated that the average cost of treating vancomycin induced phlebitis was \$93.72 which in turn equated to an additional cost of \$46.86 per patient receiving vancomycin.

The possibility of microbiologic contamination and pyrexia due to pyrogens is a serious concern in the use of intravenous administration.

Quercia *et al* (1986) carried out a cost justification study for the use of what appeared to be expensive in-line filters. This group demonstrated that nosocomial bacteraemias in a surgical intensive care unit increased hospital costs by approximately \$168,000 annually, based on the estimate that an average nosocomial infection cost \$4,000. They argued that the cost of placing in-line

filters on all possible iv lines in their surgical ICU, estimated at \$5,700 annually, would be more than offset by the savings made by reducing the incidence of nosocomial bacteraemia.

Final in-line filters do reduce microparticulate and microbiologic contamination but can cause technical problems of their own, e.g. reduced air flow rates, air blockages, drug adsorption.

As discussed earlier Eisenberg *et al* (1987) measured the economic impact of aminoglycoside-associated nephrotoxicity. The average additional cost per patient receiving aminoglycoside therapy at that time was \$183.

### **Methods for improving quality control**

US Hospitals have designated iv therapy (IVT) teams who are responsible for iv catheter insertions and administration of iv drugs throughout the hospital. Implementation of this team approach to iv drug administration was advocated in the 1970's in an attempt to control infusion-associated septicaemia. It was found that asepsis of iv fluid systems was most efficiently and effectively implemented by IVT teams who rigorously followed established protocols for cannula insertions, drug preparation and administration, frequent surveillance of infusions and cannula sites and any other follow up care required. Published data concerning the costs of this service are sparse. A paper by Tomford *et al* (1984) demonstrated that the use of an IVT team resulted in decreased morbidity and therefore improved the quality of patient care. The authors believed that the benefits accrued i.e. reduced phlebitis and bacteraemia, by employing an IVT team outweighed the opportunity cost of practising the mechanical task of iv catheter insertion. No attempt was made to actually quantify the costs of this service in dollar terms. However a call was made for further research into the evaluation of the cost-effectiveness of the IVT team. An alternative scheme to an IVT team has been a 'decentralized approach' suggested by Larson *et al* (1984). This study considered the integration of 'iv expert' nurses into the general nursing staff, i.e. selected nurses received additional education and training concerning venepuncture, catheter insertion and infusion therapy. These nurses continued with normal duties but when venepuncture, catheter insertion or general care of an iv line was required on their ward, they were called upon to carry this task out. It was found

that on those wards with an 'iv expert' on site there was a higher compliance with the iv guidelines and a lower risk of phlebitis. Equipment costs were found to decrease by 7.4%. Costs to start such a decentralized iv program on 10 clinical units was calculated to be about \$10,000. There is also a system of outpatient iv therapy in the States. A recent review by Balinsky *et al* concerning the cost effectiveness of outpatient parenteral antibiotics concluded that significant direct cost savings were made when inpatient therapy was replaced by outpatient therapy. Quantifying the benefits to the patient and including them in an analysis resulted in an increase in the overall cost-effectiveness of a home care based program. The authors make the point that costs were poorly defined in the studies evaluated. Both cost and charge data were utilised, making it difficult to determine the actual savings.

Table 4.5 summarises the cost factors associated with an average iv treatment with a gentamicin and ureidopenicillin combination.

**Table 4.5 Cost factors associated with an average iv treatment with a gentamicin and ureidopenicillin combination.**

	£
Drug*	171.95
Consumables*	45.50
Personnel time <sup>#</sup>	45.65
Wastage (12%) <sup>!</sup>	20.63
Additional costs (assays)*	36.59
Adverse events <sup>~</sup>	107.02
(potential for nephrotoxicity)	
Patient Discomfort	intangible
	-----
Total	427.34

\* taken from Malek *et al* 1991

<sup>#</sup> time taken from Malek *et al* 1991 i.e. 3 hours 54 minutes for preparation and administration of the drugs plus 1 hour 26 minutes for assay performance. A costing of £8.56 per hour was used based on surgical nursing costs for Scotland in the financial year ended in April 1990 (obtained from David Clark, Unit Accountant, Dundee Acute Hospitals)

<sup>!</sup> taken from Davey *et al* 1990

<sup>~</sup> taken from Eisenberg *et al* 1987, an exchange rate of \$1.71 = £1 was applied.

#### 4.4.1.4 Oral therapy as an alternative to iv therapy

Oral therapy has several economic advantages:-

- i) the initial purchase price is generally less expensive than the equivalent iv form of the drug. A comparison of iv and oral dosage forms of some commonly prescribed drugs can be seen in Table 4.6.
- ii) Patient comfort is increased and the potential problem of phlebitis is removed. Moreover it is more likely that the patient can be discharged home on oral therapy. All of these factors improve quality of life.

iii) A shorter hospital stay also results in a lower probability of contracting a nosocomial infection and a bed is released for further use. The only other way to achieve this is by setting up a home iv service, which is still likely to be considerably more expensive than oral therapy.

iv) Valuable medical and nursing time is saved due to ease of administration.

v) The consumables used during iv therapy are avoided.

vi) In hospital a patient has a reduced probability of missing a dose and an increased probability of receiving a dose on time as nurses administer oral medication under very regimented conditions.

vii) Adequate supervision of iv drug preparation and administration in hospital requires either a centralised intravenous additive service (CIVA) or a dedicated iv administration service, both of which add further to the costs of iv therapy.

**Table 4.6 Cost of one days recommended maximum adult dosage (from MIMS May 1991)**

Drug	Oral (£)	IV (£)
Amoxicillin	1.05	5.24
Flucloxacillin	0.52	14.85
Erythromycin	0.90	28.11
Ciprofloxacin	4.50	48.00
Cefuroxime	3.60	21.16

nb. these are not necessarily the doses regularly used, these doses were chosen to exemplify the differences in cost between iv and oral forms of the same drug.

Where it is totally unsuitable for a patient to be initially commenced on oral therapy, a shortened iv course with a change to oral therapy as soon as possible would also provide the economic benefits previously discussed. The economic implications of substituting parenteral therapy with oral antimicrobial therapy have been explored to some extent by others. Generally, the finding has been to support the use of oral antimicrobials in preference to parenteral therapy. Beneficial patient outcomes have been associated with substantial savings

(Quintiliani *et al* 1987; Leigh 1988; Cooke *et al* 1991; Powers & Bingham 1990; Chan *et al* 1995).

Clinical evidence supporting the use of oral treatment has mainly come from observational studies. Mandell *et al* (1995) critically reviewed the 'iv to oral switch' literature. Most of the studies were small, were for a mixed bag of infections and focussed on the use of quinolones, although some did use B-lactam agents. Of the 32 studies reviewed only 13 were randomised, controlled trials. Despite these drawbacks Mandell and co-workers concluded that early substitution of oral agents for iv treatment did have a place in patient therapy. Further experimental evidence supporting the use of oral therapy has been provided by Chan *et al* (1995). These workers demonstrated in a randomised, controlled trial that oral co-amoxiclav was as efficacious as iv co-amoxiclav for the treatment of community acquired lower respiratory tract infection.

Provided that equal patient outcome can be guaranteed with oral therapy it is difficult to imagine a scenario where use of the iv alternative would be more cost-effective. It is proposed therefore, that maximisation of valuable resources would be effected by the increased use of the oral route and that particular attention is paid to the increased use of oral drugs in the management of serious infection. What does remain a challenge is to change the intrinsic belief of doctors that iv antimicrobial therapy is preferentially better than oral therapy. A recent study by Solomkin *et al* (1996) demonstrates how this worry about oral therapy affected the prescribing behaviour of American surgeons. The study was designed to investigate the use of various antimicrobials in complicated intra-abdominal infections. One of the aims was to examine whether bioequivalent doses of oral therapy would provide equivalent efficacy to continued iv therapy for patients able to tolerate oral intake in the early postoperative period. Patients were randomised in a double blind fashion to one of three categories shown in table 4.7. Physicians were encouraged to initiate oral (po) therapy for all three treatment groups between 3 to 8 days after beginning iv therapy. It was found that oral treatment was commenced for those patients who became eligible for po treatment which initially indicated considerable physician acceptance to this approach. Furthermore, clinical success for those patients who received active oral treatment

was found to be equal to those patients who received only active iv treatment. What was of interest was a subset of patients who were prescribed oral and were then changed back to iv because the physician thought that the treatment was failing the patient, even though the patients were already receiving active iv treatment, it was the oral component which was placebo. The physicians carrying out the change from po to iv were unaware of this fact because of the double blind nature of the study. This would suggest that these physicians thought that it was the oral treatment that was failing the patients i.e. there is an intrinsic concern that oral therapy cannot be as effective as iv therapy. The results from this subset of patients being a measure of doctors behaviour rather than an assessment of a clinical endpoint.

**Table 4.7 Antimicrobial randomisation categories of patients in Solomkin *et al* (1996) study.**

<b>Randomisation</b>	<b>Initial treatment</b>	<b>Day 3-8</b>	<b>Continued treatment</b>
<b>Group 1</b> Ciprofloxacin iv + Metronidazole iv	Ciprofloxacin iv + Metronidazole iv	Continued iv  or sequential po	Ciprofloxacin iv + Metronidazole iv  Ciprofloxacin iv + Metronidazole iv + Placebo po
<b>Group 2</b> Ciprofloxacin iv + Metronidazole iv followed by Ciprofloxacin po + Metronidazole po	Ciprofloxacin iv + Metronidazole iv	Continued iv  or sequential po	Ciprofloxacin iv + Metronidazole iv  Ciprofloxacin po + Metronidazole po + Placebo iv
<b>Group 3</b> Imipenem iv	Imipenem iv	Continued iv  or sequential po	Imipenem iv  Imipenem iv + Placebo po

#### 4.5 **Alternative locations for the administration of iv antibiotics - Non-inpatient care vs Inpatient care**

In North America a non-inpatient iv (NIPIV) service has been available since the 1970's for a wide variety of indications. One of the first indications NIPIV care was used for was chronic bronchopulmonary infection associated with cystic fibrosis (Rucker & Harrison, 1974). These workers found that almost 70% of hospitalisations could be avoided and was associated with the benefits of fiscal savings in medical costs, lack of disruption of family routine and in some cases allowed continuation of schooling and employment. Soon after other workers (Stiver *et al*, 1978) reported the success of a pilot NIPIV care programme which was used for a variety of infections including osteomyelitis, endocarditis and bacteraemia. It was stated that all patients in this programme preferred home treatment as it allowed a return to a more normal lifestyle. Treatment was reported to cost one third of that in the hospital. This pilot study formed the basis for a continuing NIPIV service (Stiver *et al*, 1982). After four years experience Stiver and colleagues (1982) remained enthusiastic about the service continuing to report patient satisfaction, cost savings and increased hospital efficiency due to the release of beds vacated by those patients entering the programme. For the programme to run smoothly it was found that good communication channels between all team members was necessary. Other providers of NIPIV care support the fact that coherent teamwork is essential to the success of the programme (Rehm & Weinstein, 1983, Kind, 1985, Sharp, 1986), as is patient selection (Stiver, 1982, Kind, 1985, Sharp, 1986). Amongst others, important criteria to be met are; the infection to be resolving, the patient and family to be motivated to participate in the programme and to be educationally aware and that home circumstances are suitable.

Since these initial reports several studies have demonstrated the efficacy, safety, reduction in cross-infection and cost savings associated with this type of service (Chamberlain *et al*, 1988, Glick, 1991, Wiernikowski, 1991, Bernstein, 1991, Scully, 1992, Thickson, 1993 Rubinstein, 1993). Poretz *et al* (1984) performed a cost benefit analysis of home iv therapy in which all quantifiable benefits e.g.

increased productivity, return to work or school, etc. were measured. They determined a mean total benefit of \$6,588 per patient, a mean total cost of \$1,768 per patient, and an overall benefit/cost ratio of approximately 5:1. The conclusion of the study being that *"for all parties concerned, the benefits of outpatient iv therapy versus hospital iv therapy far outweigh the costs"*.

There are now many different NIPIV programmes within North America which are organised in a variety of ways, some are hospital based, some are organised by the family practitioner and some are run by independent companies (Poretz, 1993). Regardless of how the programme is organised the service appears to be well accepted by patients and third party payors provided it is organised in an efficient manner. However, worry and uncertainty can be an intangible cost to the patient and carers when a programme lacks organisation and a regular point of contact. This was amply demonstrated by Nolet (1989) who showed how lack of information and disorganisation of a NIPIV programme can lead to patient lack of confidence in the system and the subsequent desire to be treated in hospital. Table 4.8 compares and contrasts the various costs of NIPIV care with in-hospital care.

Because NIPIV care has now become such a large business in the USA, accreditation standards for providers have now been developed by the Joint Commission on Accreditation of Healthcare Organisations (JCAHO) (Malloy, 1990). The first home care surveys were conducted in 1988, organisations which operate to the JCAHO's standards and earn accreditation demonstrate to the consumer and the payor a commitment to providing the highest level of quality care and service.

In the UK NIPIV care is generally not an alternative option to in-hospital care for the vast majority of patients, however, it is used for cystic fibrosis and oncology patients in some instances and it is becoming an option for AIDS patients. One of the largest differences between North America and the United Kingdom is that of culture and the belief in the UK that serious infection and subsequent intravenous therapy necessitates hospitalisation. To some extent this can be related to the way in which the financing of healthcare is organised in these two countries. North American patients are primarily responsible themselves for ensuring that their medical treatment is financed, in the UK central government provides healthcare

monies. One of the driving forces for the development of a NIPIV service for serious infection in North America has been a desire to reduce the costs of treatment (Rucker & Harrison, 1974, Stiver *et al*, 1982, Poretz *et al*, 1982, Rehm & Weinstein, 1983, Sharp, 1986, Chamberlain *et al*, 1988). Contrary to this the driving force for the provision of NIPIV care for cystic fibrosis patients in the UK has been quality of life factors (Gilbert & Littlewood, 1988, BPA Working Party on Cystic Fibrosis, 1988).

Given the wide-ranging reports of cost-effectiveness of NIPIV care in North America its wider application in the UK deserves further investigation. It is not possible to extrapolate the experience directly from the North Americans as they administer a greater proportion of antibiotics by the intravenous route compared to the UK, also the different healthcare financing system may affect the final cost-effectiveness of the programme.

**Table 4.8 Comparison of the costs of NIPIV care**

	<b>Hospital</b>	<b>NIPIV</b>
<b>Direct Costs</b>	Hospitalisation	-
	Antibiotics	Antibiotics
	Consumables	Consumables
	Staff time	Patient/carer time
		IV technique training
<b>Indirect costs</b>	Loss of income	Commuting costs for clinic
	Interruption of education	follow-up
	Family commuting costs	
<b>Intangible costs</b>	Dependence	Worry and uncertainty
	Depression	
	Confinement	
	Separation from family	

#### 4.6 Attempts to control the use and costs of antibiotics

Despite this, several methods have been used world-wide to control the use of antibiotics, these have included educational campaigns, restricted sensitivity reporting, limiting drug lists by requiring consultant approval, automatic stop dates, pecuniary measures, generic substitution and last but not least local policy guidelines (Achong *et al*, 1977, Avorn *et al*, 1983, Manning *et al*, 1986, Harvey *et al*, 1986, Evans *et al*, 1986, Scher *et al*, 1986, Avorn *et al*, 1987, Sutters *et al*, 1989, Friis *et al*, 1989, Dammehofer *et al*, 1989, Wilson *et al*, 1991, Riley *et al*, 1991, Mugford *et al*, 1991, Friis *et al*, 1991, Coleman *et al*, 1991, Cockburn *et al*, 1992).

The introduction of an antibiotic policy in a group of hospitals in the UK was reported to have reduced antibiotic costs from 22% to 16% (Wolfson, 1980). However, as late as 1988 it was suggested that there was a general ignorance in the UK as to which methods of control are followed, whether they work to any degree and how to assess their true benefits (Gould, 1988). In response to this the British Society for Antimicrobial Chemotherapy (BSAC) set up a working party which would specifically look at these issues throughout the UK. The findings of this party were reported in 1994 (BSAC Working Party Report, 1994). Health professionals (medical microbiologists and pharmacists) at 733 hospitals were initially approached to participate in the survey. Responses which represented 427 identifiable hospitals within the UK were obtained. It was found that control measures used tended to reflect the size of the hospital, with a greater proportion of larger hospitals undertaking educational campaigns, antibiotic studies and having policies for surgical prophylaxis in place. Small hospitals (less than 315 beds) were only half as likely to have these as large hospitals (greater than 675 beds). Audit was five times more common in large hospitals. It was felt that respondents in the study were more likely to run control systems than non-respondents therefore extrapolation of the findings to cover the non-responding hospitals would probably give an over-representation of control systems used. For all respondents the most common control measure used (79%) is the antibiotic formulary with prior consultant approval for certain restricted antibiotics. Very few microbiology laboratories routinely reported antibiotic sensitivities for

antibiotics not included in their formularies. However, only 11% of respondents operated formal audit of antibiotic usage. Half of the respondents had a policy for surgical prophylaxis. Compliance with policies was monitored in 50% of responding hospitals with non-compliance being controlled by personal visits to the ward or by telephone contact with the non-complying prescriber. Ninety percent of respondents thought policies beneficial but offered no evidence to substantiate this belief.

The overall conclusion of the BSAC working party was that although control measures for antibiotic usage are commonplace their performance could be improved upon greatly. Education of prescribers was felt to be one way in which this may be achieved. As early as 1973, Kunin *et al*, discussed that this type of education needed to be continuous to have any lasting effect. The findings of a prospective Drug Utilisation Evaluation (DUE) of ceftazidime supports this call (Okpara *et al*, 1994), as has the reports of others (Coleman *et al*, 1991). Prescribing practice was successfully altered in the Okpara *et al* (1994) study provided a pharmacist continually intercepted and acted upon those prescriptions deemed to be inappropriate. In a follow up study some six months later when continuous intervention had stopped, prescribing practice was demonstrated to have returned to its previous poor standard, this was thought to be due to the constant turnover of staff. A study which demonstrated that a restrictive antibiotic policy can be used without a detrimental effect upon wound infection rates was carried out by Scher *et al* (1990). These workers reported a modest annual saving of approximately \$32,000 associated with the introduction of a restrictive antibiotic prophylaxis policy, and although wound infection rates were reduced for both clean (Class I) and clean-contaminated (Class II) to 1.8% (24/1,298) from 2% (12/605) and 2.1% (17/801) from 4.9% (16/327) respectively, this did not reach statistical significance. The savings made related to reduced drug and administration costs, no account was made of the cost of the extra staff time involved in wound surveillance procedures.

Multidisciplinary input has already been demonstrated to improve the quality of prescribing (Abramowitz, 1984, Fletcher *et al*, 1986, Briceland *et al*, 1988). All three of these studies combined the varying expertise of pharmacists and

physicians to successfully modify prescribing behaviour. A common theme between the three studies was the circulation of physician information sheets to prescribers composed by infectious disease specialists targeting specific antimicrobials, followed by personalised contact with a clinical pharmacist at ward level to review the content of the information sheets when prescribing did not meet information sheet criteria. Fletcher *et al* (1986) reported a net decrease in drug expenditures of \$161,396 and although a 0.5 full-time equivalent pharmacist was required for the program a return on investment for the service was greater than 10 to 1. Similarly, Briceland *et al*, 1988, reported projected annual drug cost savings of \$33,000 with an additional saving of \$7,000 in staff time.

Another recommendation of the BSAC report (1994) was '*if adequate control of antibiotics is to be achieved, the microbiologist who is aware of local sensitivity patterns, must work closely with the pharmacist who has knowledge of the day-to-day antibiotic prescribing patterns*'. This recommendation is almost identical to one made by Stobberingh *et al* (1993) which followed a similar study carried out in the Netherlands. A disturbing finding of the Dutch study was that almost 20% of hospitals surveyed did not intend to set up antibiotic guidelines at all (Stobberingh *et al*, 1993).

Staff time has an associated cost, efficient use of staff time dictates that the gains of using this time should be maximised. Savings made by a control measure should be weighted by all the costs of implementing the measure which includes staff time. Furthermore a sensitivity analysis of the implementation costs should be carried out to determine the point at which it is no longer cost-effective to use a particular control measure. Most reports tend to concentrate on the savings achieved without actually considering implementation costs although some accounts do allude to this. Okpara *et al* (1994) in a DUE of ceftazidime with clinical pharmacist intervention reported a cost avoidance of over \$9,500/month. The analysis of savings was based on the acquisition costs of ceftazidime and the acquisition costs of antimicrobial agents substituted for ceftazidime. Hidden costs of agents requiring monitoring, consumables and staff time were not added in so this could well have changed the cost avoidance figure (Ehrenkranz, 1989, Plumridge, 1990,). The authors still felt however, that the results of this study

justified the cost of a full time clinical pharmacist to function as a quality assurance coordinator, the annual salary for this post was not given but it is likely that the salary is less than the annual savings of \$114,000 (12 x \$9,500).

Few studies have included the costs of implementing control measures but those that have consider implementation to be cost-effective. In Australia a commercial advertising agency was used to change the prescribing of iv amoxycillin in primary pneumonia to iv benzylpenicillin. A course of iv amoxycillin averaged 37 Australian dollars compared with 7.30 Australian dollars for a course of iv benzylpenicillin. After the campaign 91% of patients were receiving benzylpenicillin as compared with 44% of patients before the campaign. However, the proportion had dropped to 68% 18 months after completion of the campaign. This figure of 68% was still significantly higher than the proportion of patients who were treated with benzylpenicillin before the advertising campaign. The campaign costs of 10,000 Australian dollars were recouped within 12 months by savings on drug costs (Harvey *et al* 1986). One American hospital (Coleman *et al* 1991) found that limiting formularies, restricting the usage of new expensive antibiotics and promoting the use of selected antibiotics achieved only a limited success in controlling the costs of parenteral antibiotics. This Hospital introduced a scheme whereby the infectious disease service (IDS) team reviewed the need for restricted antibiotics prior to prescription, introduced broad based dosage restrictions, prospectively and continuously reviewed antibiotic usage with authority to discontinue selected antibiotics upon receipt of culture results, or on clinical evaluation of the patient. Fine detail costs are labour intensive to determine, so these workers used the crude measure of average antibiotic cost per admission in order to assess the financial reductions achieved with the additional personal intervention techniques. The average monthly antibiotic costs during the 26 month post policy period were \$7,600 less than during the 16 month pre policy period resulting in an average yearly drug cost reduction of \$91,200. A pharmacist was added as a permanent member of the IDS team by the medical centers administration after the realisation that the 23% reduction in drug acquisition costs during the first 4 months after policy initiation was twice the salary expense for the position.

The costs of drug education can be justified by the savings that result from improved drug use but this education must be of a continuous nature as shown by the Coleman study (1991), to maintain the change in prescribing habits effected. Removal of a restriction policy for antimicrobials has been shown by Himmelberg *et al* (1991) to result in an increase in the inappropriate use of these agents and total expenditure to increase by 103%.

#### 4.7 Summary

The reasons why antimicrobials in the secondary care setting should be subject to economic evaluation are:-

- Antibiotics are the largest single group of drugs used in hospitals in the UK.
- Inappropriate antibiotic usage centres around:
  - (i) increased antibiotic resistance with consequent loss of efficacy.
  - (ii) unnecessary exposure to toxic side-effects.
  - (iii) financial waste.
- Antibiotic cost-containment, within the confines of the overall drug budget can be achieved by formularies and supplemental measures.
- Antibiotic cost-containment measures used to date may be at the expense of patient outcome and may transfer costs elsewhere.
- Opportunities exist to improve both resource utilisation and outcome.

The economics of antibiotic utilisation is a complex interplay of many factors which include why the antibiotic is being used, which agent is selected, how it is being administered, what adverse effects the agent causes or can cause and what the final outcome of its use is. An important issue which deserves much closer scrutiny is the economic impact of bacterial resistance.

Many institutions, to varying degrees, have made an attempt to control antimicrobial use, primarily in the form of formularies and policies. However, all too frequently, drug selection for formulary inclusion has tended to focus on acquisition cost alone, resulting in a cost-containment exercise for the pharmacy budget. There have been reports of hidden costs, such as administration,

monitoring and toxicity being taken into account during the decision-making process but the wider issue of opportunity cost does not seem to have been weighted with any importance. For example, decreased frequency of administration of antibiotics (which by definition preselects certain antibiotics) on the neonatal unit which reported bacterial resistance problems due to work overload (Isaacs *et al*, 1988) may well have avoided the problem by allowing enough time for standard infection control procedures to be observed.

Broad variation in current clinical practice is widely recognised (Davey *et al*, 1992). One reason put forward for this is the weakness of the scientific evidence underlying medical practice, it has been estimated that only 15% of medical interventions are supported by solid scientific evidence (Smith, 1991). It is not unreasonable, therefore, to state that prevailing treatments as well as new treatments, should be evaluated for cost-effectiveness. Without some form of structured approach in the selection and use of antibiotics, the financial penalties will, and have been shown to be exceedingly high.

Opportunities to improve both resource utilisation and outcome have been identified. Evidence exists, for example, that the use of oral antibiotics in preference to their iv administration could be increased without compromising clinical outcome. In the UK the possibility that NIPIV care may prove a cost-effective option for treatment of serious infection needs to be evaluated within the context of the NHS financing structure.

The amount of pharmacoeconomic data on antibiotics generated through research is increasing but most is just drug cost containment. An issue which needs addressing because it has a direct impact on any antibiotic pharmacoeconomic evaluation is what form of outcome measurement should be used in an analysis as this can radically alter the conclusion drawn. A full discussion of the issues surrounding outcome measurement and the impact it has on the pharmacoeconomic evaluation of antimicrobial use is given in the following chapter.

## Chapter 5

### 5. The economic issues of antibiotic use: part II - Outcome Measurement

Without some form of systematic quantification the consequences and usefulness of an action cannot be assessed. Knowledge of the effects of care on the health status of a patient therefore demands some form of outcome measure i.e. a health status index, that quantifies the impact of the treatment or intervention. Outcome measurement is intrinsic to economic appraisal of healthcare programmes but is in itself a contentious topic as will be discussed further in this chapter.

One of the major issues with the economic literature on antibiotic evaluation has been the focus on cost containment practices and to a much smaller extent, hospital length of stay. Assessment of antimicrobial treatment outcome, to date, has tended to focus on eradication of bacteria and the duration of treatment required to obtain eradication. Beyond this assessment little is known of what happens to a patient once discharged from the hospital. This deficit of knowledge has been shown in other areas of medical care to lead to misjudgement of outcome. Lack of follow-up of surgical patients after discharge results in a substantial underestimation of wound infection rate (Brown *et al*, 1987, Esuvaranathan *et al*, 1992, Bailey *et al*, 1992, Lynch *et al*, 1992). It is reasonable to assume therefore that assessment of antibiotic treatment failure rate in hospital alone may represent the tip of an iceberg. Consequently, there is an urgent need to determine an adequate duration of post-discharge follow-up for patients who have received antimicrobial therapy so that this can be integrated into the overall evaluation of outcome. The practicalities of how this can be achieved also needs to be determined. An antibiotic economic appraisal which does not include some form of follow-up must be considered incomplete.

In the US measures of outcome have been added to the standards set by the regulatory bodies that health care institutions must adhere to so that they can gain accreditation (O'Leary, 1987). However, because assessment of outcome is far from simple a US initiative was launched to develop these measures, by 1990 over \$30 million was allocated for research into this area (Epstein, 1990). The

assumption was that analysis of routine observational data held in computer banks (Medicare, insurance companies, hospitals) could give information on what the best treatments were. By 1994, the conclusion reached was that this assumption was wrong, it was not possible to identify outcome measures in this manner that would assist in valuing different treatments and the initiative research teams were disbanded (Sheldon, 1994).

### So what is needed from a quality outcome measure?

Basically, a quality outcome measure needs to be meaningful, relevant and fulfil the criteria given in table 5.1.

**Table 5.1 Quality Determinants for Outcome Measures**

<b>Reliable:</b>	reproducible and consistent
<b>Valid:</b>	accurately measures what it is intended to measure
<b>Responsive:</b>	able to detect a clinically important change

The varying characteristics of outcome measurement and types of measure which have been used in antibiotic evaluation are now discussed.

#### 5.1 Direct vs surrogate measures

An outcome measure can be classified as direct or surrogate. A direct outcome measure is one which measures an endpoint shown to have an effect on health related quality of life such as morbidity, disability or mortality. A surrogate outcome measure tends to monitor changes in physiological measures and *assumes* this affects health related quality of life, for example, laboratory values or functional tests (Editorial, 1990), however, this assumption may well be erroneous. Direct measures have a greater validity than surrogate measures. In a review of proxy measures of arthritis Fries (1983) highlighted how poor surrogate measures of actual disease status could be. Two frequently used surrogate measures for progression of rheumatoid arthritis are erythrocyte sedimentation rate and DNA latex fixation titer yet neither correlate particularly well with ultimate outcome. In addition to this lack of validity and responsiveness, Fries (1983) showed these measures to be poorly reproducible. Conversely, Fries (1983) showed other surrogate measures (patient and physician global assessment) to have good correlation to ultimate outcome and to be sensitive to change, reproducibility was not assessed so it is not possible to determine whether these

are reliable measures. Before a surrogate measure is employed it is important to assess the quality of the measure for reliability, validity and responsiveness otherwise the relevance of the measure chosen may well be nil.

To a large extent the type of measure used is a function of the time available for assessment. Therapeutic outcome of antimicrobial therapy is soon known i.e. bad outcomes happen quite quickly, because of this it is possible to readily employ direct measures. Those used to date have traditionally been of a physiological and unidimensional nature (Coleman *et al*, 1991, O'Hanley *et al*, 1989, Suwangool *et al*, 1991, Bates *et al*, 1995). Although therapeutic outcome is soon known it is important to determine when the episode is over as this can vary dependent on the treatment under evaluation. For example, as discussed earlier, lack of follow-up of surgical patients into the community results in an underestimation of wound infection rate.

Despite the amenability of antimicrobial evaluation to direct outcome measurement, assessment of therapy has largely focused on process outcome i.e. how the antibiotics are being used, for example, adherence of prescribing to antibiotic policies, frequency and timing of therapeutic monitoring of potentially toxic agents etc. Process outcome is important in its own right to ensure that antimicrobials are being correctly employed, but, process outcome results have frequently been extrapolated as a surrogate marker for patient outcome. This extrapolation may well be erroneous and lead to cost-containment practices which do not maximise beneficial patient outcome (Noel *et al*, 1978, Phelps *et al*, 1978, Hampson *et al*, 1988, Wyatt *et al*, 1992, Horn *et al*, 1992, Morgan *et al*, 1992). Table 5.2 lists examples of direct and surrogate outcome measures that have been used in antimicrobial treatment evaluation.

**Table 5.2 Outcome measures used in antimicrobial evaluation**

<b>Direct</b>	<b>Surrogate</b>
Mortality	Policy prescribing adherence
Morbidity	Therapeutic drug monitoring
	Timing of drug administration
	Recurrence of infection
	Reduced complications
	Side effects of therapy
	Pathogen presence

### 5.2 Objective vs subjective measures

Outcome measures can also be classified as objective or subjective. Objectivity implies that a quantification process is reproducible and consistent by the nature of its impartiality, a patient is not seen as an individual but as part of an aggregated norm. Objective outcome measures used in health care assessment are intended to measure impairment i.e. abnormal anatomical, physiological or psychological structure or function e.g. FEV1, ESR etc. The measure of impairment is then intended to be used to indicate the level of disability or handicap brought to total body function by this impairment. Objective measures have the least meaning to patients. Conversely, subjective measures are not impartial in that they are a personal rating by an individual or group of individuals. An example of a subjective measure would be the amount of pain said to be experienced by a patient with a given clinical condition, obviously this will vary depending on the pain threshold of each individual. Subjective measures are of most meaning to patients in that they can indicate at a personal level the degree of handicap or disability brought to them by their impairment of normal body function.

Although there can be inherent problems with subjective measures in terms of reproducibility, they can provide an additional perspective which cannot be gained by an objective measure alone. Objective and subjective measures are frequently used in the therapeutic assessment of patients with infection, for example

temperature measurement coupled to clinical impression is often used to ascertain whether an antibiotic regimen is effectively treating the illness. A published example of an objective measure being combined with patient subjective impression is a study by Hodson *et al* (1987). These authors compared the efficacy of conventional intravenous (iv) antibiotic therapy with oral ciprofloxacin in the treatment of acute exacerbations of pseudomonal chest infection in cystic fibrosis patients. Both groups of patients i.e. those treated intravenously and those treated orally showed equivalent improvement, however, the study also included a patient preference component in that the patients who received oral ciprofloxacin were asked whether they preferred oral treatment to iv treatment if they had received iv treatment in the past. Of the 20 patients, 17 said they preferred oral treatment to previous iv therapy (1 had no preference, 1 had not had previously received iv treatment, and 1 patient did not answer). It can be seen therefore that, all other things being equal, incorporation of patient preference data with efficacy outcome data in this instance would weight a decision to use oral ciprofloxacin rather than conventional iv treatment i.e. use of a subjective measure brought out something which otherwise would not have been observed with objective measures alone. To quote Fries (1983) '*outcome must reflect the values of patients*'.

Objective and subjective measures are suited to different research and practical applications and as such the purpose of an investigation has to be defined before the right outcome measure can be chosen, for example, an objective measure would be more suited to evaluating a treatment outcome for a given population whereas a subjective measure may be more helpful in helping set priorities for treatment.

### **5.3                    Continuous vs discontinuous measures**

Outcome measures can also be categorised into continuous or discontinuous. A continuous or longitudinal outcome measure is sensitive to gradational changes and can be used, for example, to give an indication of severity of disease. A discontinuous measure is of the yes/no type, for example, infection/no infection, it does not allow for any gradation. Traditional outcome measures used in the assessment of antibiotic treatment have tended to be of a discontinuous nature, for

example, mortality, appropriate/inappropriate prescribing, success/failure of therapy. Although a discontinuous measure may adequately assess some aspects of antimicrobial treatment it may be too crude to adequately evaluate others. Mortality can be used to determine whether an agent prevents death and some measure of cost-effectiveness can be interpreted from this but it is not as sensitive as the continuing measure, cost per life year saved (LYS), i.e. knowledge of the length of time that a particular drug extends life allows a more sensitive evaluation of the cost-effectiveness of alternative agents. It would depend on what is being measured as to which measure is the most appropriate i.e. although the cost per death prevented is quite crude it is a reasonable indicator to use for different treatments within the same population, however it is not as good as cost per LYS when examining different treatments in different populations e.g. comparison of treatments between 20 year olds and 80 year olds. The limitations of this measure (LYS) is that no consideration is given to the quality of life within the extended life years saved. The sequential extension to the life year saved is the quality adjusted life year (QALY), it has to be noted though that methodological problems still exist with its application. Quality adjusted life expectancy is life expectancy combined with a measure of disability and distress. The changes in quality of life are calculated from the concept 'utility'. Utility is a value judgement which can vary widely depending on the individuals perspective. Even when a group of individuals who would be expected to have a similar perspective, for example, when a cohort of physicians trained in the same speciality, are canvassed on the utility they would assign to the quality of life in a specific health state, wide variations are elicited. A study which highlights this problem was carried out by Weeks *et al* (1991). This study was examining the cost effectiveness of prophylactic intravenous immune globulin in chronic lymphocytic leukaemia. The workers used decision analysis techniques to determine whether prophylactic intravenous immune globulin was likely to result in an overall clinical benefit to patients receiving this treatment. Health outcomes were measured in terms of gains in quality-adjusted life expectancy, with 'utility' weights used to adjust life expectancy downward for decreases in the quality of life associated with a given clinical state. Utility estimates, used as weights in the calculation of quality

adjusted life expectancy, were obtained from a sample of 10 practising oncologists experienced in the care of patients with chronic lymphocytic leukaemia. The estimates were based on the physicians assessments of the quality of life in various health states experienced by patients and were derived using the reference gamble approach. In the reference gamble approach the respondent is asked to choose between life in a given clinical state and a gamble between death (assigned a value of 0) and perfect health (assigned a value of 1). The reference gamble elicits a measure of the respondent's assessment of the relative quality of life in that state, ranging from 0 to 1. The results from the 10 oncologists are shown in table 5.3.

**Table 5.3 Utility estimates of 10 expert physicians of the quality of life in a given clinical state**

<b>Clinical state</b>	<b>Low</b>	<b>High</b>	<b>Mean</b>
CLL without infection	0.50	0.999	0.87
CLL with a trivial infection	0.50	0.999	0.86
CLL with a moderate infection	0.50	0.99	0.81
CLL with a major infection	0.20	0.90	0.46

CLL = Chronic Lymphocytic Leukaemia

It can be seen from the range of values in the table just how much variation can be obtained even from experts within the same field and averaging the values can be almost meaningless as a wide variation can be hidden. This wide variation in clinical assessment of the same data set has been demonstrated by others (Chaput de Saintonge, 1988).

A moot point about the assigning of utility is who should be making the judgement. Given that outcome should be reflecting the values of patients and of society, using third parties, albeit experts within medical care, can lead to a situation whereby the values of patients are not adequately weighted. A study which highlights this was carried out by Chaput de Saintonge (1988), 48 rheumatologists were asked to weight 10 commonly measured clinical variables and to then judge the change in disease activity for 30 patients using these variables. Their judgement policies were then modelled. It was found that

although the expressed weighting given to patients global assessment was ranked third, it only achieved a ranking of 9 in the regression model, i.e. the weight the doctors believed they attached to this variable was not followed through in their actions.

The purpose of an outcome measure such as the QALY is that comparisons can be made between interventions that may be widely dissimilar, yet the very fact that consensus is difficult to obtain within a speciality questions the validity of using this for comparison between specialities at the present time. Even if the ideal situation existed whereby patients assigned utility values, consideration would have to be given to the effect that socio-economic, cultural and ethnic background may cause on the assigning of values. Consensus problems in all clinical areas are well recognised (Smith, 1991), in a recent editorial (Mckee *et al*, 1994) it was stated that *'There is a strong case for clinicians to come together, locally or nationally, to develop and disseminate agreed definitions of the most important diagnoses, procedures, and complications so that, when information is produced, everyone speaks the same language'*. This is an apparently simple statement but it is not just the clinicians who need to come together it is the patients and other health care professionals also, such that the *'language'* spoken includes everything that is important.

At present, the QALY does not appear to be an outcome measure that can be routinely applied to antimicrobial treatment. However, academic exercises using the QALY as an indicator of cost-effectiveness in antimicrobial treatment have been carried out. Tsevat *et al* (1989) used decision analysis and probability modelling to perform an economic analysis to evaluate whether patients with artificial joints should take prophylaxis before dental procedures. Using sensitivity analyses to vary the assumptions within the overall analysis it was calculated that the marginal cost-effectiveness of erythromycin prophylaxis compared to no prophylaxis ranged between \$1,300 (probability of infection 25/100,000) and \$393,600 (probability of infection 1/100,000) per QALY. The impact the utilities assigned have on the cost per resulting QALY can be dealt with by performing a sensitivity analysis, what does cause a problem is lack of scientific evidence for clinical assumptions. Central to the analysis by Tsevat *et al* (1989) was the

**assumption** that a transient bacteraemia during a routine dental procedure can cause an infection of a prosthetic joint. At the moment no evidence exists one way or another as to whether a transient bacteraemia during a routine dental procedure can cause an infection of a prosthetic joint.

Two quite different studies which highlight the additional value of continuous outcome measurement over discontinuous measurement in antibiotic treatment were carried out by Davey *et al* (1988) and Dunagan *et al* (1991). Davey *et al* (1988) evaluated antibiotic prophylaxis in both vaginal and abdominal hysterectomy. Using the traditional outcome measure of presence or absence of infection it was concluded that the prophylaxis was more effective in vaginal hysterectomy as pelvic infection was reduced from 20% to 2% whereas wound or pelvic infection after abdominal hysterectomy was only reduced from 18% to 10%. However when an economic analysis was carried out using the sum cost of treatment and prophylaxis as the outcome measure in addition to a patient recovery score, the opposite conclusion was supported. Antibiotic prophylaxis for vaginal hysterectomy increased the overall antibiotic bill with minimal symptomatic benefit to the patients or community health services, conversely antibiotic prophylaxis for abdominal hysterectomy saved hospital and community resources, and resulted in measurable benefits to the patients. Two important points are illustrated in this study, firstly there is no real basis for equating pelvic infections after vaginal hysterectomy with wound or pelvic infections after abdominal hysterectomy. The definition of pelvic infection after vaginal hysterectomy included patients who had a purulent vaginal discharge, but this event had no measurable effect on either their treatment or speed of recovery. In contrast, wound or pelvic infection after abdominal hysterectomy were associated with increased prescribing of antibiotics in hospital and after discharge from hospital, as well as measurably slower speed of recovery. The second point is that the use of continuous variables (costs of antibiotic treatment and recovery scores) are preferable for measurement of outcome rather than the discontinuous variable (infection/no infection) as this gives an indication of gradation of severity of infection.

Another example of a discontinuous outcome measure routinely used in antibiotic prescribing is that of 'appropriateness of prescribing'. Several papers (Achong *et al*, 1977, Jogerst *et al*, 1981, Swindell *et al*, 1983, Jewesson *et al*, 1985, Suwangool *et al*, 1991) have reported results for full courses of treatment which have been graded as either appropriate or inappropriate, yet it is virtually impossible to validly grade an individual's overall treatment in this way (Davey *et al*, 1995). The argument against this 'yes/no' approach is that the amount of information available at any one time which assists in the rational choice of an antibiotic can change during the treatment period. An antibiotic prescribed on initial clinical presentation may no longer be considered to be appropriate when bacteriology results become known. The appropriate/inappropriate approach does not allow for any grading within the treatment period. Dunagan *et al* (1991) overcame this problem by grading each **day** of treatment as appropriate or inappropriate which reflected the informational sources available, as such a **profile** of the appropriateness of each antibiotic course was established.

#### 5.4 Unidimensional vs Multidimensional

An outcome measure can be unidimensional i.e. an isolated endpoint, or multidimensional i.e. composite. A composite measure provides a wider perspective as more than one endpoint is being considered. A study of competing asthma treatments by Sculpher & Buxton (1993) depicts how using a composite measure, i.e. an episode free day (EFD), is more sensitive to changes in patients' health status than is the conventional unidimensional clinical parameter, FEV<sub>1</sub>, which is routinely used to assess the effectiveness of asthma therapies. The competing treatments were a short acting agent which needed to be administered four times daily versus a long acting agent which only required to be administered twice daily. The composite measure was constructed from individual patients daily record of personal events including occurrence of any asthma attack, sleep disturbance, need for rescue therapy, adverse events and peak expiry flow rate data. An EFD was any day the patient was not subject to any of these events. Total daily cost was taken as including the drug acquisition costs, rescue medication and the costs of treating adverse events. All costs were expressed in 1991 Canadian

dollars (\$Can). It was calculated that the incremental cost-effectiveness ratio was \$Can7.29 per additional EFD for the longer acting agent. A weakness of this composite measure is the lack of sensitivity within the variables comprising the measure because of the lack of gradational changes i.e. 1 asthma episode or 1 adverse event during a given day results in the loss of 1 EFD regardless of the severity of the individual event. However, the measure still provides a valuable descriptive picture which is sensitive to changes in patients' health status that are not detected by the clinical single point measurement of FEV1.

Composite measures have also been shown to be of more use than unidimensional measures in the evaluation of antibiotic therapy (Davey *et al* 1988). Davey *et al* (1988) compared conventional outcome measurement with less traditional measurements in the evaluation of prophylaxis for vaginal and abdominal hysterectomy. These workers combined a patient perspective recovery score with the costs of prophylaxis and treatment of infection that occurred despite prophylaxis. In doing so it was demonstrated that prophylaxis is more cost-effective for abdominal hysterectomy than for vaginal hysterectomy. These findings are diametrically opposed to findings which use the conventional outcome measure of reduction in infection rate alone.

Table 5.4 lists a few examples of unidimensional and composite outcome measures.

**Table 5.4 Unidimensional & Multidimensional Outcome Measures**

<b>Unidimensional</b>
Mortality
Recurrence of infection
Side effects of therapy
Patient mobility
Symptomatic relief
<b>Composite</b>
Episode free day
Quality adjusted life expectancy
Repeat consultations

### **5.5 Specific measures vs generic measures**

Outcome measures can also be described as specific or generic. A disease or treatment specific outcome measure is literally an outcome measure which is specific to one disease or treatment i.e. it has been designed to detect changes in that particular disease activity. A disease specific outcome measure can only usefully be used to compare the outcome of treatments or interventions directed at that one disease or treatment unless the dimensions examined within the measure are of the same relevance to other diseases/treatments. The outcome measure instrument emphasises particular parameters of significance to the disease under study, for example, the Arthritis Impact Measurement Scale (AIMS) or the Living with Asthma Questionnaire (Hyland *et al*, 1991). A generic outcome measure by comparison is designed to broadly apply across types and severities of diseases, across different medical interventions and to be applicable to a wide variety of patients or populations. It is intended to be used to compare treatments or interventions used in a wide spectrum of diseases and describes the impact of the treatment/intervention on the patient rather than provide a clinical assessment of disease status. These instruments can also be biased though depending on how they are constructed and which aspects of health assessment they explore.

Examples of generic outcome instruments include the Nottingham Health Profile (NHP) and the Medical Outcomes Study Short Form (SF-36) (Ware *et al*, 1992). Although disease specific measures are initially designed for comparison of outcome within the disease they are addressing, they are considered to be more sensitive to changes in outcome for particular patient populations than are generic measures (Hyland, 1992). The reason for this is that general instruments may include items irrelevant to a specific disease and omit others that are relevant. For example, the SF36 includes items that measure pain, which is not relevant to asthma, but does not include items that measure sleep, which is relevant to asthma. There is an issue of bias in both specific and generic measures, currently the most that can probably be gathered from these instruments is that one persons quality of life is better than another persons. It will only be if bias can be eradicated from these instruments that the degree of how much better can be determined. The issue of bias however, will almost certainly never be resolved because of the incorporation of value judgements. At the present time it would appear that both types of measure should be used in tandem so that relevant comparative data are available from both perspectives (Hyland, 1994).

The development of outcome measure instruments be they specific or generic, have largely focused and been devised around chronic long term illnesses. As such they are constructed to examine changes in health states over prolonged periods of time. Particularly in the area of disability, these measures are relatively insensitive to short term change, but effectively measure long term trends. The necessity for long term measures is obvious since there are many clinical examples of short term tactics that are deleterious over a prolonged period. Fries (1983) used the indiscriminate use of corticosteroids in rheumatoid arthritis (RA) as a prime example of this. In the short term, daily prednisone in RA is clinically and statistically superior to placebo in reducing synovitis, decreasing morning stiffness, increasing walking speed, decreasing the number of tender joints and improving grip strength. However, in the long term, daily prednisone, as compared with non-steroid treatment, leads to increased mortality, increased rate of development of disability, increased symptoms due to long term side-effects, more hospitalisation, and increased direct and indirect costs of disease (Fries,

1983). This example further illustrates how the use of short term surrogate measures are not necessarily valid measures of final outcome.

The relevance and validity of existing outcome measure instruments to acute conditions such as infectious diseases which require short term intervention has not been tested. This is a formidable area of research which would need to be carried out before application of these instruments to acute conditions such as infectious diseases could be reliably employed.

### **5.6 Other aspects of outcome measurement**

Having considered the various characteristics that an outcome measure can display there is another aspect that can alter the validity of a measure i.e. the setting in which the outcome is measured. The environment in which the measure is applied can artificially weight the results. For example, US Hospitals have learned that adequate assessment of the outcomes of inpatient care also involves consideration of what happens to patients after they have left the hospital (Vladeck, 1988). A classic example of this is wound infection rate after surgery. It has been shown that failure to pursue surgical patients after discharge results in a substantial underestimation of true wound infection rate. Law *et al* (1990) demonstrated the importance of community surveillance of postoperative wounds. These authors found that of all patients whose wounds became infected, 41% of cases were diagnosed in hospital and 59% were diagnosed in the community. Others have reported similar findings. Lynch *et al* (1992) in a trial of preoperative whole body disinfection in postoperative wound infection prophylaxis found that 61% of wound infections were diagnosed after hospital discharge. Esuvaranathan *et al* (1992) and Brown *et al* (1987) also found surgical wound infection rate to be double when patients were followed into the community. Bailey *et al* (1992) not only found gross underestimation of wound infections following hernia surgery when only hospital documented infections were used to determine wound infection rate but also the wound complication rate was grossly underestimated. These authors found the wound infection rate recorded in hospital notes to be 3% compared with 9% when additional information was obtained from community surveillance. Wound complications were detected in 28% of patients by

community surveillance compared with a complication rate of 7% in the case records for the same patients. Hardwick *et al* (1992) in the assessment of outcome data accuracy described similar findings for wound infections post emergency appendicectomy. Davey *et al* (1988) in a cost-benefit analysis of antibiotic prophylaxis for abdominal and vaginal hysterectomy also found infection rate to be greater when community surveillance data were included.

### 5.7 Summary

In summary 'outcome' is a general term consisting of several separate dimensions. Outcome should collectively include all those variables, patient values included, which have an impact on the disease under study, but as discussed, this is a very difficult area. It is an area where assumptions cannot be made. The use of surrogate measures can only be considered valid where they have been demonstrated to be a marker for outcome.

What has been used in the evaluation of antibiotic treatment is a wide variety of narrow spectrum measures with a large emphasis on process outcome i.e. examination of the standard of delivery of care. Measures used have tended to evaluate only one dimension of outcome yet it is possible to have dimensions within one episode care that go in opposite directions, for example, it is possible to effect a clinical cure without eradicating bacteria. The level of complexity of outcome measure used in an evaluation and the environment in which it is made will radically alter the inferences and conclusions that can be drawn i.e. composite outcome indices and continuous variable indices will provide greater information than the traditional unidimensional measures. What is ideally required is a single measurement for overall outcome incorporating quality of life, which is responsive to how effective a treatment is i.e. a multidimensional global outcome measure. For example, construction of a 'Pneumonia Outcome Scale' should be able to differentiate between the myriad of treatments available for this condition. Dimensions within the scale could include items such as resolution of primary infection, recurrent infection, occurrence of superinfection, other adverse outcomes etc. Each of these items are important but then the problem exists of how could they be weighted. Each individual piece of information would need to

be assessed and then pulled together into 1 final measure so that comparison between treatments could be made. Much research remains to be carried out in this area but what can we do at the present time? As demonstrated by Davey *et al* (1988) the use of multidimensional measures including monetary consumption, although not aggregated into 1 final index, promises to be of greater use than traditional unidimensional measures, in determining the cost-effective allocation of resources.

In the next two chapters, two aspects of antimicrobial treatment are evaluated in terms of multidimensional outcome, both traditional and continuous variable indices are used. The first study focuses on the use of the aminoglycosides but also examines the general antibiotic management of Gram-negative bacteraemia. This study uses observational data which has been collected in a systematic manner. It assesses appropriateness of practice and identifies outcome measures indicative of adverse outcome. Areas of resource wastage are identified and clinical practice changes are suggested which may lead to more effective resource allocation. The second study focuses on the development and feasibility of a novel (for the UK) health care delivery system for antibiotics i.e. non-inpatient intravenous care. Costs and preferences for care in a different setting were examined.

## Chapter 6

### 6. Drug utilisation study as a vehicle for economic analysis: What are the opportunity costs? - Aminoglycoside/Bacteraemia study

#### 6.1. Introduction - Aminoglycoside usage and Gram-negative bacteraemia

Despite 40 years of clinical use and the advent of pharmacokinetic monitoring, major problems still exist with the prescribing of the aminoglycosides. These problems range from the intrinsic oto- and nephrotoxicity of these agents through to the failure of therapy due to the fear of inducing dose-dependent toxicity. Even so, aminoglycosides continue to be used on a daily basis for those patients either suspected or proven to have a Gram-negative infection because they are incorrectly perceived as effective, low treatment cost agents.

Gram-negative sepsis continues to have a high mortality rate. Survival in Gram-negative septicaemia is reported to depend upon the extent of underlying disease, neutrophil count and early use of appropriate antibiotics (Kreger *et al*, 1980). Using the aminoglycosides in the currently recommended dosage regimens leads to gross underdosing (Zaske *et al.*, 1980, Summer *et al.*, 1983, Li *et al.*, 1989). Given that approximately half of all fatalities occur during the first 24 hours it is not surprising that underdosing is associated with treatment failure (Moore *et al.*, 1987). Therapeutic drug monitoring (TDM) is ostensibly used to maximise therapeutic aminoglycoside serum levels and to minimise toxic serum levels yet optimisation of levels is frequently elusive. Evidence in support of this statement are the results of a prospective audit of drug assay services and therapeutic drug use in a general hospital by Guest *et al* (1980). These workers found that only 10% of gentamicin assays were within therapeutic range. Based on these results therapeutic monitoring services were introduced to educate and advise on the rational and appropriate prescribing of the aminoglycosides (Eckert *et al*, 1991). Despite these measures an audit of aminoglycoside usage 9 years later did not find improved usage and that over 10% of measured peak concentrations for 179 patient courses were below 4mg/l (Li *et al*, 1989).

Many studies have been carried out to determine the most effective method for influencing the clinical practice of drug prescribing (Wilson *et al* 1991, Evans *et al* 1986, Rubinstein *et al*, 1988, Coleman *et al* 1991, McDonald, 1976, Sutters, 1989, Landgren *et al* 1988, Dannenhoffer *et al* 1989, Manning *et al*, 1986, Riley *et al*, 1991, Friis *et al*, 1991, Eckert *et al*, 1991). Evidence suggests that no single intervention is wholly effective but rather that a combination of methods has the greatest impact for change. This is endorsed by Robertson *et al* (1996) who discussed further that selection of an effective strategy is dependent on knowing the obstacles which prevent change. These authors suggest a psychological framework which can be used to select an appropriate strategy when change has been resisted. MuirGray (1986) considered that three criteria should be fulfilled for an educational strategy to be effective in changing clinical behaviour, these are:-

- (i) the education should be based on the doctors own work as well as on research findings
- (ii) the doctor should be helped to assess his/her work and to compare it with that of others, and
- (iii) that the whole team should be involved where teamwork is necessary for good quality care.

Not only does feedback of information about clinical practice have to be active and continuous to maintain change (Mugford *et al* 1991), the perceived position of the person providing the information is also important (Friis *et al*, 1991).

Several studies have documented the hidden costs of aminoglycoside therapy including costs of preparation, administration, monitoring and toxicity (Eisenberg *et al*, 1987, Davey *et al*, 1990, Plumridge, 1990, Wright, 1991, Malek *et al*, 1992, Kerr *et al*, 1993) but there is a paucity of information about the consequences of failed treatment for the patient or the health services. The potential importance of this omission is illustrated by a trial comparing cefazolin with cefamandole as prophylaxis for cardiac surgery. The difference in drug acquisition cost (\$82 per patient in favour of cefazolin) was more than offset by the cost of additional infections in the cefazolin group (average excess cost \$401 per patient receiving

cefazolin) (Roach *et al*, 1990). These excess costs were mainly attributable to readmissions for sternal wound infection.

It is proposed that heightening clinicians awareness to the overall costs of aminoglycoside treatment in both monetary and outcome terms would lead to a more efficient allocation of resources. The objectives of this study were:-

- To determine the general antibiotic therapy of Gram-negative bacteraemia and the indications which stimulate the initiation of aminoglycoside therapy.
- To produce a costing analysis of aminoglycoside treatment in general and in reference to Gram-negative bacteraemia with a focus on patient outcome.
- To determine the opportunity costs of aminoglycoside treatment.
- To identify measures of outcome which can be used to value different antibiotic treatments.
- To assess the predictive power of a previously published sepsis score to forecast potential cost and outcome.
- To propose methods for improving aspects of antibiotic usage and to evaluate the effectiveness of written and personal contact for modifying prescribing practice.

The study was carried out in two phases, Phase I dealt with the identification and quantification of the problems associated with aminoglycoside usage and the treatment of gram-negative septicaemia. Phase II was an attempt to modify clinicians prescribing practice by feedback of data from Phase I. Evaluation of change effected was carried out by measuring prescribing practice immediately before and after feedback intervention. The time schedule of the various steps in each phase are summarised below:-

## Summary of time schedule for Phases I & II

<b><u>Phase I</u></b>	
Aminoglycoside and septicaemia data collection	August 1990 - January 1991
Data analysis	January 1991
<b><u>Phase II</u></b>	
Baseline prescribing practice data collection	mid January 1991 - end February 1991 (6 weeks in total)
Drug Information (DI) note produced	February 1991
Circulation of DI note to clinicians	early March 1991 (one week prior to seminar presentations)
Individualised seminar presentations	mid March 1991
Prescribing practice data collection (post DI note and seminar presentations)	End March 1991 - mid May 1991 (6 weeks in total)

### **Study Funding and Medical Ethics Committee Approval**

The funding of this study was provided by Bayer UK. Data collection and computer entry was subject to quality control by a member of Bayer UK staff. Approval for this was obtained from the Medical Ethics Committee of Dundee Acute Hospitals.

Within the sponsorship contract a clause existed stating that all data remained the academic property including publication rights, of those person(s) carrying out the study and that Bayer UK had no rights to veto data publication or presentation.

A full description of the execution, results and discussion of Phase I followed by the same for Phase II is presented below.

## **6.2 Phase I**

A prospective utilisation audit of aminoglycoside prescribing and the general antibiotic management of Gram-negative septicaemia within Dundee Acute

Hospitals (now Dundee Teaching Hospitals trust) was carried out during the time period August 1990 to January 1991. At the time of the study there were 1231 acute beds on three sites (Ninewells Hospital, Kings Cross Hospital and Dundee Royal Infirmary).

## **Methods**

### **6.2.1 Study Population (Phase I)**

The study population, 301 adult patient episodes in total, consisted of all those patients prescribed an aminoglycoside or who had a proven Gram-negative bacteraemia within the aforementioned time period. In 9 instances a patient entered the study more than once because of either a readmittance to hospital (8/9) during the data collection period or a recurrent septicaemia prior to discharge (1/9). Of the 8 patients who were readmitted, 7 were readmitted once and 1 was readmitted twice. Hence 9 patients accounted for 19 patient episodes.

The date of entry onto the study was taken as the day the patient was prescribed a therapeutic course of an aminoglycoside for those patients in the aminoglycoside group, these patients may have previously received other antibiotics for the same infection.

For the bacteraemic patient episodes, the date of entry onto the study was taken as the first day they received any antibiotic for the presenting symptoms of the bacteraemia.

### **6.2.2 Data Collection (Phase I)**

Prospective patient specific data were collected by a pharmacist by means of a standardised clinical record form (see appendix A) for each patient episode. Sources used for data assimilation were medical case notes, drug kardexes, TPR charts, biochemical reports, microbiological reports, personal interview of medical staff, fluid charts, theatre sheets and nursing notes.

### **6.2.3 Follow-Up (Phase I)**

The hospital treatment of study subjects was monitored on a daily basis until the individual died or was discharged from the admitting hospital.

All patients discharged alive were subject to a three month follow up post discharge.

The General Practitioners of individual patients were contacted by mail (see appendix B for pro-forma) requesting details of any antibiotic prescription(s) supplied to the patient, with the reason for the prescription, within the three month period post discharge. If the GP had not replied within two weeks of pro-forma issue, a second request form was despatched.

Hospital re-admittance within the three month follow up period was determined from computerised records held by Tayside Health Board.

#### **6.2.4 Data Analysis (Phase I)**

The data from this first phase of the study was analysed in terms of antibiotic combinations used, route and frequency of administration, reasons for change in antibiotic therapy, clinical indication initiating antibiotic prescription, result and outcome of therapeutic drug monitoring, total costs of antibiotic treatment (inclusive of drug cost, consumables and staff time required for preparation and administration and any TDM undertaken), ultimate patient episodes outcome and an assessment of any iatrogenic events. This analysed patient data was used in phase II of this study.

Further analysis of this data was in terms of a previously published sepsis score (Cooke *et al*, 1993), patient follow up data was also used to determine whether further antibiotic treatment/hospital readmission suggested failure of initial antibiotic treatment. These details were not used for presentation purposes in phase II of this study.

#### **Equipment and Database Packages (Phase I)**

All data were stored and analysed in DBase IV (Ashton & Tate, Berks., UK) using a spreadsheet (Borland QuattroPro) and statistical software (Minitab 8.0) on an Opus 386SX microcomputer.

#### **Costs (Phase I)**

Drug costs were taken from Medical Index of Medical Specialities (MIMS) May 1991.

The cost of gentamicin assays was provided by the Department of Medical Microbiology, Ninewells hospital, Dundee.

Equipment costs are taken from Davey *et al* (1990) based on an average cost of £0.85 for a bolus injection and £2.23 for an infusion.

Staff costs are taken from Davey *et al* (1990) based on £8.56 per hour, with the time of 5 minutes per IV

### **Quality Control (Phase I)**

Data collection was subject to quality control by a clinical research associate (CRA) from Bayer, UK.

Twenty medical case records were selected at random by the Bayer CRA and all aspects of data collection were cross checked with the exception of data obtained by personal interview with medical staff.

Computer data entry was also subject to quality control by a similar method. The Bayer CRA selected at random twenty of the standardised clinical record forms and cross checked computer data entry of these records.

Clinical records for patients who died in hospital were reviewed jointly by an infectious disease consultant, clinical microbiologist and pharmacist to determine whether the treatment was appropriate. The assessment was based on the clinical condition of the patient and the spectrum of cover provided by the antibiotic(s) used. It did not take account of the antibiotic dosage.

### **Definitions:**

#### **Infections**

The site of infection was established from the case records and by personal interview with the medical staff. Presenting complaints were divided into the infection categories of pulmonary, urinary tract, abdominal, epididymo-orchitis, skin/soft tissue, blood and other as determined by individual patient's physicians. Patients with pyrexias of unknown origin, postoperative pyrexias or general malaise without the clinical signs of septicaemia were categorised as blood infections.

#### **Sepsis scores** (see appendix C)

Patients with clinical or microbiological evidence of urinary tract infection score one point unless the clinical event was postoperative (defined as occurring within

48h of surgery) which scored four points. It was not possible to define upper urinary tract infection from the information that was available, therefore this score was omitted. For respiratory infections patients were scored either two points (bronchitis or bronchiectasis) or four points if there was radiological evidence of pneumonia. Additional points were not scored for 'hospital acquired pneumonia' because it was difficult to determine the true date of onset of pneumonia from the clinical notes. Under 'septicaemia' patients were included if they had a confirmed bacteraemia or had clinically suspected septicaemia. For both groups patients scored one point unless the clinical event occurred within 48h of an invasive procedure (catheterisation, endoscopy etc.) or surgery, in which case the score was two or three points, respectively. Patients with confirmed bacteraemia who had a primary site of infection in the urinary or respiratory tract were scored additionally for these sites.

Pre-existing diabetes was defined as any treatment for diabetes mellitus. Renal disease was defined as patients receiving chronic dialysis. Hepatic disease was defined as biopsy proven cirrhosis and documented portal hypertension, episodes of past upper GI bleeding attributed to portal hypertension, or prior episodes of hepatic failure/encephalopathy/coma.

#### **Outcome Measures (Phase I):**

##### **Inappropriate intravenous (iv) therapy/ Suitability for oral treatment**

Inappropriate iv days were defined as those days a patient was capable of taking oral antibiotics i.e. they were receiving other oral medicines or were taking food or on at least 25ml sips of water.

The criteria used in the assessment of patients suitable for treatment by the oral route but who were actually receiving iv therapy included:-

Temperature <37.5 and >36.5

Pulse <100

MAP\* >69 and <109

No operation within 48 hours

No specimen sent for C&S or a negative culture

\* MAP - Mean arterial pressure is the product of systolic pressure minus diastolic divided by three and added to diastolic pressure

In addition to these criteria it was considered that:-

- 1) Intravenous (iv) therapy was appropriate for the first 24 hours postoperatively other than Urology patients who were frequently prescribed oral antibiotics postoperatively.
- 2) Those patients whose putative diagnosis was possible septicaemia were considered to be appropriately treated via the iv route for the first 24 hours.
- 3) All iv treatment of gut related problems (e.g. bowel obstruction, cholecystitis etc.) was considered appropriate.
- 4) Patients receiving concurrent iv antibiotics inappropriately were evaluated as if only one antibiotic had been administered (e.g. if a patient received the combination of cefuroxime, gentamicin and metronidazole inappropriately for one day then this was counted as 1 day of inappropriate treatment not as 3 antibiotic days).

#### **Appropriate/Inappropriate antibiotic therapy**

Assessment of whether a patient who died had received appropriate or inappropriate antibiotic therapy related to the spectrum of cover provided by the antibiotic selected for treatment and whether the clinical signs and symptoms necessitated antibiotic commencement. It did not relate to the actual dosage or frequency of usage of the antibiotic.

#### **Classification of the role of infection in readmissions**

Readmissions were classified by inspection of the case notes. Patients with clinical evidence of infection at the time of readmission were further classified into those whom infection appeared to be the primary cause of readmission (readmission definitely infection related) and those in whom readmission may have been caused by some other aspect of the patient's condition (readmission possibly infection related).

### 6.3. Results - Phase I

The study population consisted of **301** patient episodes, 120 females (39.9%) and 181 (60.1%) males.

Patient ages ranged from 15-92 years; the average age was 62 and the median age 65.

Patients were located in various specialist units. The largest number of study patient episodes came from the Urology department (95 patient episodes, 31.6% of total), followed by 61 patient episodes (20.3% of total) from Surgery. The medical department contributed 34 patient episodes (11.3%), the remainder were located in the following disciplines :- Intensive care, Respiratory medicine, Geriatric medicine, Haematology, Orthopaedics, Ophthalmology.

The study group was divided into two main subpopulations, those who received an aminoglycoside (**255** episodes in total) and those who had a documented gram-negative bacteraemia (**86** episodes in total). There was some overlap between the two subgroups, in that **40** of the aminoglycoside patient episodes also had a gram-negative bacteraemia. Of the remaining **46** gram-negative bacteraemic patients, **1** patient did not receive any antimicrobial therapy and **45** received antibiotic(s) other than an aminoglycoside.

The number of patients who died whilst receiving antibiotic treatment was **36**, **14** of these patients had a documented gram-negative bacteraemia. Of this subgroup **7** received an aminoglycoside containing regimen, the remainder received other antibiotic combinations. The remaining **21** deaths occurred in patients who were receiving an aminoglycoside containing regimen for various infective foci other than gram-negative bacteraemia.

Of the total study population **28** patient episodes were granulocytopenic, this group merits further discussion as a prescribing policy was in force at the time of the study. The standard policy therapy for granulocytopenic patients on presentation of fever was a combination of gentamicin and piperacillin, if an adequate clinical response did not occur within 48 hours patients were changed onto second line antibiotics. However, the policy was not adhered to for **3**

granulocytopenic patients who were bacteraemic consequently they did not receive an aminoglycoside. These 3 patients were included in the bacteraemic group.

Phase I results are further discussed in the following individual sections:-

Section 1 - Aminoglycoside data analysis

Section 2 - Bacteraemia data analysis

Section 3 - Outcome of therapy including community surveillance

Section 4 - Quality Control And Care Issues

#### 6.4. Section 1 - Aminoglycoside Data Analysis

Aminoglycoside therapy was commenced in over 50% of cases (132 of 255 patient episodes) due to a suspected blood infection based on presenting signs suggestive of septicaemia. Typically these included rigors, alteration in consciousness, peripheral pallor or abnormal sweating. However, other patient episodes with suspected blood infection had pyrexias of unknown origin, general malaise or postoperative pyrexias without clinical signs of septicaemia. Only 40 of these patient episodes had a documented Gram-negative bacteraemia.

Other presenting complaints were divided into the infection categories of pulmonary, urinary tract, abdominal, epididymo-orchitis, skin/soft tissue and other. Table 6.1/1 shows the number of patients for each category.

Of the 255 patient episodes who received an aminoglycoside, 231 received gentamicin, 15 received netilmicin and 9 were initially commenced on gentamicin then transferred over to netilmicin because of increased age or decreased renal function.

Rarely was an aminoglycoside used alone (18 of 255 patient episodes, 7.1%) but rather in combination with one or more antibiotics. The most frequently used combination was that of gentamicin with augmentin (53 of 255 patient episodes, 20.8%) followed by gentamicin, cefuroxime and metronidazole (44 of 255 patient episodes, 17.2%). Table 6.1/2 gives a full breakdown of all the aminoglycoside antibiotic combinations used.

The Tayside antibiotic formulary in place at the time of this study recommended gentamicin or in certain circumstances netilmicin in combination with another antibiotic for the following indications only; cellulitis, post-operative wound infections associated with gastro-intestinal surgery or surgery of the female genital tract, septicaemia or suspected septicaemia and for specified types of surgical prophylaxis i.e. abdominal surgery or abdominal or vaginal hysterectomy.

At the time of the study only one clinical unit had its own individual antibiotic policy in place. The policy was for pyrexia of unknown origin in haematology-oncology patients and consisted of piperacillin and gentamicin as first-line therapy. Piperacillin was found to be combined with an aminoglycoside for 44 of

255 patient episodes (17.2%) over half (25 of 44; 56.8%) of these were haematology-oncology patients.

Aminoglycosides were rarely prescribed as part of an initial antibiotic regimen i.e. only 88 of 255 patient episodes (34.5%) were prescribed an aminoglycoside as first line therapy. The remaining 167 patient episodes had already received antibiotic treatment before an aminoglycoside was prescribed.

Duration of therapy with an aminoglycoside ranged from 1 to 33 days, with a mean of 5 days and a median of 2.5 days.

An intrinsic problem of aminoglycoside usage is that of nephrotoxicity. Dose adjustment based on serum aminoglycoside levels limits dose-dependent damage and allows for therapeutic levels to be achieved. In this study only 187 patient episodes received therapeutic drug monitoring (TDM) with a range of 1-11 assays/patient episode/course (for a more detailed breakdown of assay utilisation refer to Table 6.4/1 in section 4).

Within the study group 11 patients experienced a 50% increase in serum creatinine indicating a degree of nephrotoxicity. Five of these patients did not have elevated pre- or postdose levels and 6 did. Elevated serum levels refers to  $>2\text{mg/l}$  for a pre-dose level and  $>10\text{mg/l}$  for a post-dose level for multiple daily aminoglycoside administration. One of the patients with a 50% increase in serum creatinine had in fact been treated with grossly suboptimal aminoglycoside levels, post-dose= $2.4\text{ mg/l}$ , for the duration of treatment. Despite this the patient recovered from a gram-negative bacteraemia, the isolate of which was suggestive of bowel contamination. The antibiotics used in combination with the gentamicin were cefuroxime and metronidazole to which the isolate was sensitive.

Aminoglycoside therapy was initiated in 13 cases when the patients serum creatinine was above normal limits ( $150\text{ micromoles/l}$ ) indicating a pre-existing impaired renal function. Use of the aminoglycosides in this type of patient may be particularly hazardous and brings into question the suitability of these patients for this type of treatment.

Almost 80% (203/255) of patient episodes prescribed an aminoglycoside were either taking oral medications or were able to do so, only 52/255 patient episodes (20.39%) were orally compromised at initiation of therapy i.e. were on nil by

mouth orders, had had an operation within the preceding 24 hours, had significant ileus, had manifestations of gut ischaemia and/or gross electrolyte disturbances or were vomiting. All aminoglycoside courses were administered by the intravenous route with two notable exceptions, one patient was given a nebulised aminoglycoside for a chest infection and one patient received the aminoglycoside in the dialysate of a CAPD bag for acute CAPD related peritonitis.

Whilst in hospital the ultimate response to therapy for all diagnoses was success for 172/255 (67.5%) patient episodes and failure for 55/255 (21.6%), a further 28/255 (11%) patient episodes were unassessable. Excluding gram-negative bacteraemias the success rate was 70% (151/215 patient episodes), the failure rate 20% (43/215 patient episodes) with 10% (22/215 patient episodes) unassessable. The criteria used to define these outcomes are shown in Table 6.1/3 along with the number of patient episodes in each outcome category.

Only the direct costs have been measured in monetary terms in this study. The costs of using aminoglycoside treatment for proven bacteraemic episodes have been considered separately from aminoglycoside usage in other indications so that this can be compared with the non-aminoglycoside treatment of proven bacteraemia. The costs of treating a neutropenic study patient episode with an aminoglycoside have also been considered separately from other aminoglycoside patient episodes as this group received an aminoglycoside as part of a written policy including other relatively expensive drugs such as piperacillin. In addition ICU patients receiving an aminoglycoside were examined separately as it was felt that these patients have a tendency to high resource usage because of their critical condition. Costs of antimicrobial agents, assays, equipment and staff time were all found to be markedly higher in the neutropenic patients (median total treatment cost £599) and ICU patients (£471) when compared to other aminoglycoside patients. As a subgroup of the remaining aminoglycoside patients those with a bacteraemia were also found to have higher costs (£278) than those with another indication (£185). Table 6.1/4a gives the median and 95% confidence intervals (CI) for the component costings of each of the subgroups considered.

Treatment costs were related to outcome. Compared with patients who had a successful outcome, treatment costs were an average of £357 per patient higher in

those who died (95% CI £31-682) and an average of £418 higher in patients who failed to respond to initial therapy (95% CI £89-747). Removal of patients with Gram-negative bacteraemia from the analysis had little impact on these results; treatment costs were £431 per patient higher in the non-bacteraemic patients who did not respond to initial treatment (95% CI £61-802).

## 6.5. Section 2 - Bacteraemia Data Analysis

During the six month study period there were 86 patient episodes with at least one positive blood culture for a Gram-negative organism. Although the age range for these patients was between 15 and 91 years the average age was 69 with a median age of 71.5 years.

The most common infecting organism was *E.coli* (45/86 cases, 52%) followed by *Klebsiella* species (10/86 cases, 11.6%), all infecting organisms are listed in Table 6.2/1.

Of the 86 patient episodes 30 had another focus of infection. For 16 cases the organism isolated was the same as that causing the bacteraemia suggesting that this may have been the primary site of infection however further typing of the organisms was not carried out so it is not possible to make a categorical statement. Table 6.2/2 lists the other sites of infection and the time at which associated specimens were collected in relation to the blood culture specimen.

Although only 8/86 (9.4%) patient cases were initially orally compromised intravenous therapy was favoured at initiation of the treatment period for 72/86 patient cases, 13/86 patient cases received oral therapy alone and 1 of the 86 patient cases did not receive any antibiotic therapy. The purpose of this section of the study was to examine the antibiotic treatment of Gram-negative bacteraemia therefore the patient who did not receive antibiotic therapy is excluded from the following analysis, therefore only 85 patient cases are now examined.

There appeared to be little consensus of agreement about the initial treatment of a bacteraemia, the most frequently employed combination was gentamicin and augmentin but this only accounted for 16.5% (14/85) of cases. Gentamicin containing regimens accounted for 35.3% (30/85) of cases in total but there was a wide variation in the combination antibiotic(s) used. No patient received an aminoglycoside alone. An aminoglycoside was added into the antibiotic regimen for a further 10/85 patient episodes before the end of the treatment period. Table 6.2/3 gives a detailed breakdown of all antibiotic combinations at initiation of therapy.

Whilst in hospital the ultimate response to therapy for all bacteraemic patient episodes was success for 46/85, failure for 28/85 and 12/85 were unassessable. Table 6.2\4 shows the criteria used to define these outcomes and the number of patient episodes in each outcome category.

In total 40/85 bacteraemic patient episodes were treated with an aminoglycoside containing regimen, median direct costs £278 (95% CI £191-507). The mortality in this subgroup was 17.5% (7/40 patients), death was thought to be directly related to the gram-negative bacteraemic episode for 5/40 of these patients (10%) and not directly related for 2/40 (one death was due to a rampant fungaemia secondary to granulocytopenia and the other was due to a gram-positive and Mycoplasma pneumoniae bacteraemia secondary to granulocytopenia). The remaining 45/85 patient episodes were treated with a non-aminoglycoside containing antibiotic regimen, median direct costs £97 (95% CI £ 69-143), Table 6.1/4b shows the component costings for this group of patients, all of which were lower than those bacteraemic patients treated with an aminoglycoside containing regimen. The mortality of this subgroup was 15.6% (7/45 patients), death was thought to be directly related to the bacteraemic episode for 6/45 of the patients (13.3%) and not directly related for 1/45 (this patient died of pulmonary oedema and CCF).

## **6.6. Section 3 - Outcome of therapy including community surveillance:**

### **6.6.1 Ultimate response to therapy in Hospital**

The ultimate response to therapy whilst in hospital for the aminoglycoside subpopulation in terms of success, failure and unassessability and the criteria used to determine these are given in Table 6.1/3. The ultimate response to therapy whilst in hospital for the bacteraemic subpopulation again in terms of success, failure and unassessability and the criteria used to determine these are given in Table 6.2/4 section 2.

Calculated sepsis scores and their relation to the above hospital outcome measures and median treatment costs are given separately in Table 6.3/1 for the non-bacteraemic aminoglycoside patients, the bacteraemic aminoglycoside patients and the non-aminoglycoside bacteraemic patients. From this table it can be seen that the distribution of sepsis scores are very similar in the bacteraemic patients who did or did not receive an aminoglycoside. Sepsis scores were higher in the bacteraemic patients; greater than 70% had a sepsis score 5 and above compared to only 43% of the non-bacteraemic patients (see Figure 6.2a). In the bacteraemic patients there was also a marked increase in mortality with ascending sepsis score (Figure 6.2b), in survivors there was also a relationship between sepsis score and initial treatment failure (figure 6.2c). The median sepsis scores were 10 for patients who died in hospital, 6.5 for patients with treatment failure and 5 for survivors with full response to treatment. In the aminoglycoside group mortality was 10/40 (25%) and 7/30 (23%) had an adverse outcome. In the non-aminoglycoside group mortality was 7/45 (16%) and 7/38 (18%) had an adverse outcome. The relationship between sepsis scores and outcome was not so clear in the non-bacteraemic patients (see figures 6.2b & 6.2c). Median sepsis scores were 4 in survivors, 5 in patients who died in hospital and 6 in patients with initial treatment failure.

For all subgroups as the sepsis score increased so did the median cost of treatment. Although the distribution of sepsis scores were very similar between the bacteraemic patients who received an aminoglycoside and those that did not, the

median treatment costs were quite dis-similar (Table 6.3/1). The median treatment cost of a bacteraemic patient treated with an aminoglycoside containing regimen was at least double that of a bacteraemic patient treated with a non-aminoglycoside containing regimen.

Within the aminoglycoside group i.e. both bacteraemic and non-bacteraemic patients, treatment costs were related to outcome. Compared with patients who had a successful outcome, treatment costs were an average of £357 per patient higher in those who died (95% CI £31-682) and an average of £418 higher in patients who failed to respond to initial therapy (95% CI 89-747). Removal of patients with Gram-negative bacteraemia from the analysis had little impact on these results; treatment costs were £431 per patient higher in the non-bacteraemic patients who did not respond to initial treatment (95%CI £61-802).

Of the 215 non-bacteraemic aminoglycoside patients, 20 (9.3%) had zero sepsis scores indicating little clinical evidence of infection. None of these patients died yet median treatment costs were £123 per patient (range £14-701, avg £209 per patient). The diagnostic group with the lowest sepsis score was epididymo-orchitis (median 0; range 0-5). There were no deaths in this group yet the median treatment cost was £112 per patient (range £51-651; avg £150). Analysis of variance showed a weak relationship between sepsis scores and treatment cost in the aminoglycoside group, so that sepsis score only accounted for a maximum of 2.6% of the variance in treatment costs.

### **6.6.2 Further antibiotic treatment in the community**

Three month follow up questionnaires were circulated to GPs for 245 patients. Although 266 patients were discharged alive, 21 patients were known to have died or been readmitted to hospital at the time the questionnaires were sent out. Questionnaires were returned for 225 (92%) of the 245 patients. In addition to completing the questionnaire, two GPs noted that the hospital discharge letter had not mentioned that their patient had received aminoglycoside therapy. Of 84 patients who were discharged home to continue on oral antibiotic treatment, this was not continued by the GP on eight occasions. A further 63 patients received new antibiotic prescriptions within two months of discharge for further symptoms

of infection which may have been related to the original infection. Of this 63, seven had also received a second therapeutic course whilst remaining in hospital and prior to discharge.

### **6.6.3 Readmission to hospital**

It was determined from the health board computer that 69 patients were readmitted within three months of discharge. These records were accessed to determine whether their readmission was related to their previous infective episode. It was possible to access 64 case notes but 5 were untraceable.

From the information available in the case notes it was considered that 26 patients were readmitted due to infections related to their primary infective episode whereas 38 cases were either, emergency admissions, elective admissions or out-patient appointments not related to the primary infective episode. Table 6.3\2 A gives detailed information about the 38 patients readmitted for reasons other than recurrence of their infective episode. Table 6.3\2B shows the number of patients from each original infection category readmitted with signs suggestive of recurrence of infection.

### **6.6.4 Death and appropriateness of therapy**

Of the 301 study patient episodes, 36 patients died whilst receiving their initial antibiotic treatment. A further 29 died after completing antibiotic treatment but during the three month follow up period. Table 6.3/3 summarises the appropriateness of therapy and whether the patient had underlying pathology. Appropriateness was based on whether the clinical signs and symptoms necessitated antibiotic commencement and if so, the spectrum of antimicrobial cover provided by the initial antibiotic. Seven patients (19.4% of all deaths) were considered to have received inappropriate treatment and did not have underlying pathology which could have contributed to their death as determined from the medical case notes. However, a note of caution is that the Post Mortem (PM) report from one of the patients who appeared to have no underlying pathology according to the medical case notes was found to have widespread metastases due to an unknown primary at necropsy. This highlights that data on the majority of

patients, who did not have a PM, must be regarded as incomplete when considering underlying pathology.

Of the 14 patients with bacteraemia who died, death was considered to be directly related to the initial septic episode for 11 and not directly related for 3. Two of the three patients had rapidly fatal underlying pathology (one death due to a rampant fungaemia secondary to granulocytopenia and the other due to a gram-positive and Mycoplasma pneumoniae bacteraemia secondary to granulocytopenia), the third patient died of pulmonary oedema and CCF.

Of the 71 bacteraemic patients who survived the initial treatment period 4 died whilst still in hospital but for reasons not directly related to the septic episode. Of the 68 discharged alive a further 7 died in the three month follow up period.

## **6.7 Section 4 - Quality Control And Care Issues**

### **6.7.1 Therapeutic Drug Monitoring (TDM)**

At the time of this study in Dundee acute units, the aminoglycosides were almost without exception administered as an iv bolus. Recommendations were in place stating that therapeutic drug monitoring of paired blood samples be taken (i.e. to measure trough and peak levels) for patients in receipt of aminoglycoside treatment. The recommendations stated that trough levels be taken immediately before administration of an aminoglycoside and peak serum levels be measured 30 minutes after administration unless indicated otherwise, dosage adjustments being based on this premise.

Of the 255 patient cases who received an aminoglycoside during the study period only 187 (73.3%) received any form of therapeutic drug monitoring (TDM). For these patients the range of assays/patient episode/course varied from 1 to 11. However only sufficient data were available to interpret assays for 173 patient cases. Table 6.4/1 summarises the assay results. Only 15% (48/321) of interpretable assays had a trough and corresponding peak level within the recommended therapeutic range. Underdosing (70%, 224/321) was more common than overdosing (23%, 74/321). However, overdosing was more frequently corrected by dose adjustment: 49/74 (66%; 95% CI 55-77%) vs 95/224 (42%; 95% CI 36-49%).

#### **6.7.1.1 TDM and mortality outcome in hospital**

Of the sixteen patients who died (Table 6.3/3) whilst receiving 'appropriate' aminoglycoside therapy, 3 (18.7%) did not receive any TDM. For the 13 patients who did receive TDM, initial aminoglycoside levels were above the recommended range for 1 patient, subtherapeutic for 8 (61.5%) and uninterpretable for 2 (12.5%).

#### **6.7.1.2 Relationship of drug monitoring costs to overall treatment costs**

As a proportion of overall treatment cost TDM contributed an average of 12.5% (median 9.9%). To some extent the proportional contribution made by TDM was

dependent on the combination antibiotics used with the aminoglycoside. However, the shorter the course of antibiotic treatment, the more sensitive the total treatment cost was to the monitoring costs (Table 6.4/2). Drug monitoring costs accounted for greater than 20% of the total treatment costs in 17% of patients receiving TDM.

### 6.7.2 Management errors

In addition to the 68 patient cases who did not receive any TDM a set of recurring management errors came to light which included:-

#### 1) Failure to adjust doses for baseline serum creatinine

(13 instances)

**Case example:-** A 77 year old, 60kg woman with a serum creatinine of 247umols/l (calculated creatinine clearance 16ml/min) was commenced on Gentamicin 100mg three times daily.

A more appropriate dose would have been 120mg every 48 hours assuming stable renal function.

#### 2) Inappropriate administration times i.e. upto 4 hours

late (10 instances)

**Case example:-** The highest trough occurred in Case 1 above. The 2pm dose was missed and administered at 6pm, the next dose was then given at 10pm. Serum levels the following day revealed a trough level of 6.3mg/l and a peak of 11.4mg/l. The effects of the inappropriate dosing times were almost certainly compounded by the failure to adjust the dose for the baseline serum creatinine.

#### 3) Administration of additional doses due to non-recording of the first administered dose

(9 instances)

**Case example:-** A patient prepared for theatre was given the prescribed prophylactic 140mg gentamicin bolus, however the dose was not recorded on the kardex. On receiving the patient in theatre the anaesthetist noticed the omission on the kardex and administered a further 140mg gentamicin to the patient. The double dosing was not discovered until some hours later when the anaesthetist

requested that the house officer ensure all patients receive prescribed prophylactic antibiotics.

#### 4) Failure to use assay results (38 instances)

**Case example:-** A 70 year old woman with a klebsiella bacteraemia was treated from Days 1-3 with gentamicin 120mg bd. As her pyrexia persisted the gentamicin dose was increased empirically to 160mg bd for Days 4-9. Serum levels on Day 5 revealed a trough of 0.8mg/l and a peak of 4.5mg/l despite this the dosage was not increased further.

**Case example:-** An 83 year old woman was treated initially with cefuroxime for a suspected chest infection, it was then determined that she had a positive gram-negative blood culture. Gentamicin 40mg tid was then commenced in addition to the cefuroxime for seven days despite serum levels on day 3 showing a trough of 1.4mg/l and a peak of 2.4mg/l.

#### 5) Ad hoc dosage reductions by inexperienced house officers leading to suboptimal treatment (3 instances)

**Case example:-** a 77 year old woman had a gentamicin dosage adjusted on the basis of serum levels to 160mg bd. The on-duty house officer covering this ward for the weekend had not observed this dosage before and so decided it was incorrect, the house officer proceeded to change the dose back to 80mg tid for the duration of the weekend period because 'that was the dosage stated in the data sheet'.

### **6.7.3 Missed doses**

The number of patient cases who had at least one missed or non-recorded dose during therapy was **134**. The total number of missed/non-recorded doses was **620**, with a range of **1-35** per treatment course. The reasons for these missed/non recorded doses and the number of doses in each category are given in Table 6.4/3. It can be seen that for almost 65% (402 instances) of the non recorded doses it was not possible to elucidate whether the dose had been administered. Figure 6.1 shows the percentage of missed/non-recorded doses per treatment per patient.

Twenty five patients 'missed' more than 10% of their prescribed treatment and 1 patient 'missed' almost 92% of the prescribed therapy.

#### **6.7.4 Lack of documented information**

For the purposes of audit medical staff were interviewed to determine the reasons for change in antibiotic agent, dose, frequency or route of administration. For 301 study patient episodes, 49 had at least one change in therapy for which no clear reason could be defined, i.e. the medical staff present did not know the reason for change and there was no documentation in the medical notes explaining the reason for change. A further 10 patients had a change in therapy by mistake.

#### **6.7.5 Inappropriate intravenous (iv) treatment**

As only 52 of 255 (20.4%) patient cases receiving an aminoglycoside were orally compromised it was considered that there must have been a proportion of patients unnecessarily treated by the iv route. Application of objective pre-defined criteria to the study population (301 patient cases) selected out 26 patients who appeared to be have been ideally suited to receive oral treatment. Review of these patients' case notes showed that 23 patients had received iv therapy unnecessarily, 3 of these patients had not required any form of antibiotic treatment and the remaining 20 patients would definitely have been suitable for treatment by the oral route. Half of these patients had a diagnosis of epididymo-orchitis. The remaining 3 patients however, had a serious clinical condition which necessitated treatment by the iv route. Using the set criteria alone to determine which route a patient should be treated by would have allowed these patients to fall through the 'catch net'. The clinical diagnoses of those patients selected by the objective criteria as having received unnecessary iv treatment and verification of this by the medical case notes are given in Table 6.4/4.

#### **6.7.6 Antibiotic Failure Rate**

In this study 19 patients of 265 survivor episodes (36 patients died) required further antibiotic treatment whilst in hospital, 15/19 of these cases were for the same indication as the initial antibiotic course. This gives a treatment failure rate of 5.7% (15/265) for surviving patient cases.

At 3 month follow up with the patients GP, 63 had been prescribed an antibiotic whilst in the community (this does not include continuation antibiotics from the hospital).

Twenty six patients were re-admitted to hospital with signs and symptoms suggestive of recurrence of infection, 6/26 (23%) were readmitted within 7 days of discharge.

Recalculation of the antibiotic treatment failure rate using information from community surveillance shows how the rate more than doubles from 5.7% to 15.5% ( $15/265 + 26/265$ ) by incorporating only those cases readmitted to hospital. If all patients who received an antibiotic from the GP (63/265) are also included in the calculation the failure rate rises to 35.5% ( $15/265 + 26/265 + 53/265^*$ ) \*(of the 63 patients receiving antibiotics from the GP 10 were readmitted).

During the study 36 deaths occurred whilst patients were receiving antibiotic therapy. For 32 the deaths were considered to be directly related to the initial infective episode. If these deaths are incorporated into the estimation of antibiotic treatment failure calculated for surviving patients (range 5.6% - 35.5%), the overall treatment failure rate for the whole study population ranges from 15.6% to 38.5% ( $15+32/301 - 15+16+53+32/301$ ) depending on whether community surveillance is included.

## 6.8 Discussion - Phase I

In a cost comparison of intravenous antibiotic administration based on direct costs alone, Plumridge (1990) demonstrated that the acquisition cost of an antibiotic is a poor predictor of total daily treatment cost particularly for those antibiotics with a relatively low acquisition cost. A group of antibiotics which have generally been perceived to be very effective and inexpensive to use because of their low acquisition cost are the aminoglycosides. This observational clinical practice study provides strong evidence, in the form of overall direct treatment costs **and** outcome data, to challenge this perception. In this study, utilisation of the aminoglycosides were found to be fraught with management problems, treatment failure was not an uncommon occurrence, treatment costs escalated with adverse outcome and the costs of treating a gram-negative bacteraemia were high when compared to alternative therapies. Three readily measurable indicators of outcome were identified which can be used to value different antibiotic treatments. Further discussion of these findings follows.

In Dundee Acute Units the aminoglycosides were found to be used for a wide range of indications (table 6.1/1). The predominant indication being suspected or proven bacteraemia. Selection of use was primarily as a second line agent i.e. 65% of the 255 study patients had already received another antibiotic before the aminoglycoside was prescribed. This may well have been a reflection of concern about their dose related toxicity. In addition to the aminoglycoside, 93% of patients were receiving concurrent antimicrobials with a similar spectra of activity. Both of these factors make it difficult to assess the precise role of aminoglycoside treatment in the final outcome, however the study findings will be compared and discussed in relation to previously published standards. Almost equal numbers of proven gram-negative bacteraemias were treated with aminoglycoside (n=40) and non-aminoglycoside (n=45) containing treatment regimens.

Whilst in hospital antibiotic treatment failure rate was 5.7% for survivors, incorporation of those patients whose death was considered to be directly related to the infective episode and therefore to treatment failure increased this rate to 15.6%. This was further increased to 38.5% when community surveillance i.e.

additional antibiotics prescribed by the GP and readmission to hospital with signs and symptoms suggestive of recurrence of infection, were included. There appear to be no published data on long-term follow up of patients in the community who have received therapeutic courses of antibiotics in hospital. Davey *et al* (1991) in a discussion of the human and non-financial costs of hospital-acquired infection stated that a full assessment of morbidity can only be accomplished by home follow up. Recent studies have shown that failure to pursue surgical patients after discharge results in a substantial underestimation of true wound infection rate (Reimer *et al*, 1987, Davey *et al*, 1988, Law *et al*, 1990, Lynch *et al*, 1992, Esuvaranathan *et al*, 1992, Bailey *et al* 1992). This study suggests that there is a high probability that the detectable failure rate in hospital of antibiotic treatment is an underestimation of the true failure rate. Obviously these data are flawed in that all subsequent infections cannot definitely be related to the initial infective episode without full typing of bacterial isolates and this information was not available. However, the point is made that the treatment failure rate of 5.7% for surviving patients, determined by need for further antibiotic therapy whilst in hospital, has a high probability of being an underestimate of the true failure rate which may be as high as 38.5%.

Community surveillance of antibiotic treatment rarely addresses antibiotic toxicity. The bilateral vestibular damage caused by aminoglycosides may not become manifest until a patient is discharged home. This type of damage is distressing to the patient causing a peculiar form of dysequilibrium associated with a hallucination of vertical movement of the surroundings. The damage is irreversible and has been termed 'bobbing oscillopsia'. Cases of 'bobbing oscillopsia' caused by aminoglycoside toxicity continue to be reported in the medical literature (Ramsden *et al*, 1982, Brahams, 1986, Duncan *et al*, 1987). Two GP's indicated on the community surveillance proforma's that they had been unaware from their patient's hospital discharge letter of the aminoglycoside treatment. This has ramifications in that should a patient present to the GP with signs and symptoms of aminoglycoside toxicity the physician does not have the background information on which to base a diagnosis.

Long term community surveillance is time consuming and demanding of resources but total lack of surveillance appears to lead to a gross underestimation of treatment failure. A two week period of observation would have picked up almost 50% (11/26) of readmissions in this study which were primarily due to infection and would also have minimised the number of readmissions which were due to other reasons. However, even within this two week period there were 5 readmissions which were not due to infection, so that tracking readmissions from computerised data (Chambers *et al*, 1990, Milne *et al*, 1990, Colledge *et al*, 1994) may give a falsely high estimate of adverse outcomes unless individual patient records are checked. Unfortunately, case note review may not always be ideal because of lack of documentation. Taylor *et al* (1990) in a study to determine the impact of surgeon's diagnosis on surgical wound infection rates found that the reason for the postoperative prescription of antibiotics was often missing from clinical case records. Bailey *et al* (1992) found in their study of community surveillance of complications after hernia surgery, that many wound complications were not recorded in the hospital records and therefore could not be audited by case note review. In the present study 49 patient cases had at least one change in therapy for which no clear reason could be defined, i.e. documentation in the medical case notes explaining the reason for change was absent.

In terms of process outcome it was found that there was frequent underdosing of the aminoglycosides, lack of adequate dosage adjustment, overuse of the intravenous route, other adverse events due to human error and a recurring lack of documentation. In the review of individual patient records it was virtually impossible to grade overall treatment as appropriate or inappropriate because of the multiplicity of changes that were made within any one treatment period. This problem has been recognised in another audit of aminoglycoside treatment and management of bacteraemia (Dunagan *et al*, 1989) which concluded that it was only possible to grade each day of treatment as appropriate or inappropriate. However, one of the reasons for treatment failure in the present study could be underdosing. The recommended dosage of 2-5mg/kg/day of an aminoglycoside agent (gentamicin, netilmicin, tobramycin) is frequently associated with subtherapeutic serum levels. Flint *et al* (1985) in their study of 68 critically ill

patients with nosocomial pneumonia, reported that only 19% of patients treated with an aminoglycoside were considered to have therapeutic levels (peak serum level of 8-10mg/l) from the outset, compared with 58% of patients who were considered to be subtherapeutic. These findings of subtherapeutic aminoglycoside levels are similar to others (Anderson *et al*, 1976, Guest *et al*, 1980, 1980, Summer *et al*, 1983, Sculier *et al*, 1984, Li *et al*, 1989, Hickling *et al*, 1989, Zeitany *et al*, 1990). The pharmacokinetics of aminoglycosides in critically ill patients are extremely variable, and dosage requirements vary widely even in patients with normal renal function. In one large study (Zaske *et al*) the half-life of gentamicin varied from 0.4-7.6 hours in those with a normal estimated creatinine clearance, the daily dose requirement ranged from 0.7-25.8mg/kg/day. Moore *et al* (1984), by multivariate analysis, found the most important factor in the treatment of Gram-negative pneumonia with aminoglycosides to be adequate peak concentrations and further demonstrated (1987) that a determinant of the clinical therapeutic response to aminoglycoside treatment is the peak concentration achieved i.e. the greater the maximum peak to MIC ratio, the greater the clinical response rate. It can be seen therefore, that the dosage of aminoglycoside selected for treatment is critical. Failure to achieve adequate peak aminoglycoside concentrations early in the course of treatment must contribute to an increased morbidity and mortality.

A large proportion of patients in the present study receiving aminoglycoside therapy were grossly underdosed and a significant proportion, (26.7%), did not receive any therapeutic drug monitoring, (TDM). Cumulative assay results (see Table 6.4/1) demonstrated the need for serum assaying early in the treatment course to provide information for dosage adjustment. Unfortunately, intervention aimed at optimisation of the antibiotic dosage was required but not executed in all cases. Although underdosing was three times more frequent than overdosing, it was overdosing which was more frequently corrected. This may well have been a reflection of concerns about dose-related toxicity which has been described by others (Noone *et al*, 1974). Sixteen patients died who were considered to have no underlying pathology and to have received appropriate aminoglycoside therapy (table 6.3/3), 8 of these patients were known to have subtherapeutic levels, it could

be argued therefore that the suboptimal drug levels contributed in part to their mortality. As discussed extensively by Parker *et al* (1993) a method to overcome underdosing is aminoglycoside administration once daily. The practical advantages of this being; a straightforward dosage calculation, a guaranteed peak serum concentration in the therapeutic range, a potential reduction in treatment period, easier quality control of preparation and administration, a decrease in personnel time, fewer assays are required and consumable costs are lower.

A set of recurring management errors described by many other workers (Davey *et al*, 1983, Clark *et al*, 1986, Cousins *et al*, 1989, Li *et al*, 1989, Davey *et al*, 1990, Lesar *et al*, 1990, Dunagan *et al*, 1991, Leape *et al*, 1991) were observed in this study. These included failure to adjust doses for baseline serum creatinine, inappropriate administration times i.e. up to 4 hours late, administration of additional doses due to non-recording of the first administered dose, transcription errors between kardexes, failure to use assay results, ad hoc dosage reductions and missed doses. Any or all of these errors may have contributed in part to an adverse patient outcome.

Almost 80% of study patients receiving intravenous (iv) antibiotics were found to be capable of taking oral medication, indicating an overusage of the intravenous route of administration. Using highly selective criteria (see 6.7 section 4), 26 patients were considered to have been suitable for oral treatment from the outset. Case note review confirmed that the vast majority of these patients had received iv therapy unnecessarily. However, 3 patients of the original 26 were in a serious clinical condition requiring intravenous treatment. Using the objective selection criteria alone to determine which route a patient should be treated by would have allowed these patients to fall through the 'catch net' and underlines the necessity for 'clinical judgement' to be exercised when using guidelines of this nature. In a discussion of the pharmacoeconomics of iv drug administration Parker *et al* (1992) concluded that the disadvantages of the iv route far outweighed the advantages and where feasible should be avoided. These authors further stated that maximisation of valuable resources would be achieved by the increased use of the oral route. The economic advantage of expediting antibiotic therapy from the iv route to the oral route was first discussed by Quintilliani *et al* (1987). These

workers as late as 1987 pointed out that although a number of antibiotics with pharmacokinetic and microbiologic activity suitable for treating serious infections existed, clinical experience was limited. Since then, several programs (Grasela *et al*, 1991, Allen *et al*, 1992, Frighetto *et al*, 1992, Solomkin *et al*, 1996) have demonstrated that it is possible to substitute oral therapy for iv therapy without compromising outcome but in order to maintain change intervention needs to be prospective. As already discussed in Chapter 4, it will be necessary to remove the 'worry' from doctors that oral is not quite as good as iv therapy before oral therapy in serious infection is fully accepted. Seto *et al* (1996) has reported minimum net monthly savings of HK\$26,000 from an ongoing iv to oral switch campaign. Unfortunately, this campaign has focused on process outcome alone and has not included any form of patient outcome. Another similar study (O'Brien *et al*, 1996) carried out in the UK estimated savings of £1,000 over a four week period if patients inappropriately treated by the iv route were changed to oral therapy. Allen *et al* (1992) identified that there are no agreed guidelines for the appropriate time to change from iv to oral therapy, however the criteria used by these workers to determine when a patient was suitable for oral therapy were similar to those used in this current study.

Drug cost accounted for the majority of the total treatment cost for all patients (tables 6.1/4 a&b). Not surprisingly drug costs were proportionally higher for the neutropenic patients who received an increased number of expensive concurrent 'policy' antibiotics. For the aminoglycoside patients, proportional drug monitoring costs (average 12.5%, median 9.9%) were lower than reported by others (Plumridge, 1990, Malek, 1992). This study was purely observational in approach and reflects the 'real' costs of treating a population with aminoglycosides and not the idealised 'controlled study' situation whereby all patients who should receive therapeutic drug monitoring (TDM) in fact do. Only 73% of the study population were subject to monitoring, consequently the proportional costs of serum assaying for the aminoglycoside population as a whole are lower than the proportional costs would be for any individual patient who did receive TDM. However, it was shown that the shorter the course of antibiotic treatment, the more sensitive total

treatment cost was to monitoring cost (table 6.4/2). Total monitoring costs for 187 patients were £6,264.

Aminoglycoside treatment costs were related to outcome, being substantially higher in those who died and who failed to respond to initial therapy irrespective of their presenting diagnosis. Only initial treatment costs were evaluated in this study, costs in the community and from readmission were not included in the total treatment cost because it was not always transparent that the two episodes were directly related. However, one clear example in which readmission was, without dispute, related to the initial infective episode illustrates the potential magnitude of the costs of inadequate antibiotic treatment. Total treatment cost for the first admission was £186. The patient was readmitted two days after discharge with gross suppuration of the wound and the total treatment cost for the second admission was £1757 (antibiotics, equipment, staff time).

Overall treatment costs varied markedly between the two groups of bacteraemic patients, with those having received an aminoglycoside being substantially higher, median overall treatment cost £278, than those not receiving an aminoglycoside containing regimen, median overall treatment cost £97. It could be argued that the difference in treatment cost was related to seriousness of infection but calculated sepsis score and hospital outcome was very similar between the two groups (table 6.3/1).

The opportunity costs associated with aminoglycoside therapy revolve around the monitoring, toxicity and failure of these agents. In this study the costs of monitoring were £6,264 for 187 patients and the associated staff time involved in sample taking. Had alternative agents been used then this money and staff time would have been released for use elsewhere. There has been no attempt in this study to attach a monetary value to any toxicity resulting from the use of the aminoglycosides. However, Eisenberg *et al* (1987) found that 7.3% of patients treated with an aminoglycoside at 6 Philadelphia area hospitals developed aminoglycoside-associated nephrotoxicity. The additional cost per case of nephrotoxicity was \$US446 for ancillary services, \$US825 for additional routine days and \$US1152 for intensive care days. Additional consultations were \$US78 per patient. Therefore the mean total additional cost was \$US2501. The

occurrence of this toxicity is not certain for any particular patient but is a probability. Therefore the cost of treating this toxicity has to be divided between all patients receiving aminoglycoside treatment. Eisenberg calculated that the average additional cost per patient receiving aminoglycoside therapy was \$US183, i.e. this is the 'risk' cost of developing renal toxicity. This is an opportunity cost to the institution in that should an alternative agent to the aminoglycosides be used the cost of toxicity would not have to be met.

The opportunity costs of antibiotic failure are the resources consumed in retreatment which could be used in some other programme. The bearer of the opportunity costs of antibiotic failure is dependent on when and where treatment failure is manifest. Obviously it is the hospital if the treatment failure occurs prior to patient discharge but if treatment failure occurs after discharge either all of these costs or a proportion of these costs are transferred out to the community. If the infection is not serious enough to warrant re-admission to hospital then all of the costs are borne by the community, for example, GP time, antibiotic costs, consumable costs (wound dressings etc.), community nursing time. In the present study 63 patients received further antibiotics from their GP within two months of hospital discharge. If the infection is serious enough to require re-admission to hospital then a proportion of the costs are still borne by the community in that the GP is involved in the re-admission procedure which is demanding of their time and also perhaps in initially attempting to treat the infection. In the present study 26 patients were readmitted with infections considered to be related to their primary infective episode. Once re-admitted the hospital is then responsible for further costs incurred by the infection which includes bed residency in addition to the direct costs of retreatment. No attempt was made in this study to evaluate in total monetary terms the opportunity cost of failed aminoglycoside treatment for the study population, however, a case example which shows how costs can escalate is the patient who consumed a further £1757 in direct retreatment costs after readmission following failed aminoglycoside therapy.

Even if clinicians remain unconvinced that aminoglycosides should be used rarely, it is still possible to minimise the opportunity costs of treatment by changing from multiple daily administration to single daily administration (Parker *et al*, 1995).

One of the aims of this study was to evaluate the predictive power of a sepsis score (Cooke *et al*, 1993) to forecast potential cost and outcome of treatment. The scoring system had evolved from earlier scores targeted at patients with surgical sepsis with the intention that it should be based on information readily available in any hospital unit. Although the investigations required to complete the score are simple in comparison with the APACHE score, these simple investigations were performed inconsistently in practice and even the clinical information required to complete the score was often not in the patient records. Most of the deficiencies could be addressed prospectively but would cause a problem for application of the score retrospectively. In addition to this problem of availability of data for the sepsis score there were some problems with definition. The recently published definitions for hospital-acquired infection (Ayliffe *et al*, 1993) will help to achieve consistency and could reasonably be used as the standards for the sepsis score. The terms 'post-procedural' and 'post-operative' require better definition, both in terms of the procedures to be included and the interval before scoring which is considered relevant. The sepsis score includes three points for 'septicaemia' which is postoperative. In this observational study the majority of the patients in the postoperative category (operation within 48 hours) had transient pyrexia without other signs of sepsis yet four of 11 patients who had been operated on within the previous week died and all 11 patients had a hypotensive episode. This indicates that it would be preferable to distinguish between suspected infection and suspected sepsis, defined by evidence of infection plus physiological criteria of inflammatory response, additionally, the period of time defined by 'post-operative' needs to be clarified. Despite these problems there appeared to be a relationship between ascending sepsis score and increased morbidity and mortality for bacteraemic patients, the relationship was somewhat equivocal for non-bacteraemic patients. As the sepsis score increased so did the cost of treatment, the score therefore appears to be a potentially useful method not only for objective assessment of disease severity but also as a predictor of potential cost. Such a measure would help to identify patients with low scores who may be suitable for less aggressive treatment, as well as alerting clinicians to patients who may require more intensive care. The majority of patients were capable of taking oral

treatment, yet even patients with zero sepsis scores continued to receive expensive iv therapy. A recent UK audit used the sepsis score to match pairs and compare outcome of patients who received oral versus parenteral treatment, this showed similar outcomes even though the patients who received oral treatment had sepsis scores ranging from 1 to 13 (Cooke *et al*, 1993).

## 6.9 Phase II

Analysis of the data from Phase I showed that the indications for initiation of aminoglycoside treatment, the suitability of particular patients for this form of therapy, the dosages used and all aspects of therapeutic drug monitoring utilisation were quite poor. Additionally when all direct treatment costs (drug, equipment, staff, monitoring) were taken into account aminoglycoside usage was found to be an expensive form of therapy that was not always associated with a successful outcome. In addition an overall recurring problem was that of over-reliance on the iv route for antibiotic administration.

By feeding this data back to clinicians and therefore heightening awareness to these problems of use and the costs associated with aminoglycoside usage, an attempt was made to modify prescribing practice. Data feedback was achieved by written (Drug Information note) and oral presentation.

### Methods

#### 6.9.1 Study population (Phase II)

The clinician groups selected for data feedback were urological, surgical and medical (clinical pharmacologists) staffs. These clinicians were responsible for the care of 63% of patients who constituted the study population in Phase I. The remaining patients in Phase I were cared for by a diverse group of clinicians ranging from Intensive Care through to Ophthalmology. Within the time limitation of the study it was not logistically possible to target this diverse group of clinicians for data feedback.

#### 6.9.2 Baseline prescribing practice data collection (Phase II - part 1, mid-January 1991 to end February 1991)

For each of the clinician groups constituting the study population, baseline antibiotic prescribing habit data were collected from the wards serviced by these clinicians for six weeks using an abbreviated form of the clinical record form used in Phase I (see appendix F). This data included the number of patients receiving antibiotics, indication for antibiotic, type of antibiotic used, route of administration, length of treatment, change of treatment etc. A quick analysis of

this data to identify any other antibiotic prescribing problems peculiar to individual clinician groups was used to supplement data from Phase 1 of the study which was destined for feedback to these clinicians.

### **6.9.3 Drug Information (DI) Note production and circulation (Phase II, February 1991)**

Data from Phase I of the study (mismanagement of aminoglycoside usage, treatment costs, inappropriate usage of the iv route etc.) were used to produce a drug information note entitled 'Rational Antibiotic Prescribing: The Relative Role of Intravenous and Oral Therapy' (see Appendix D).

The drug information note was circulated to the study population one week prior to their oral data presentations.

### **6.9.4 Individualised seminar presentations (Phase II - mid March 1991)**

Seminars were held with each of the study population clinician groups to present data from Phase I of the study augmented with baseline antibiotic prescribing data collected in Phase II, part1.

#### **6.9.4.1 Data presentation to Clinical Pharmacologists**

It was necessary to analyse baseline prescribing data for presentation as the data was being collected, therefore not all data were included. In this preliminary analysis 50 baseline patient records of the final 71 were used. The additional data used to supplement the general findings of phase 1 are shown in Table 6.5/1. Case examples of the patients treated by the iv route were used to highlight how costs are escalated not only by use of the iv route instead of the oral route but also by such things as incorrect frequency of dosing and prolongation of use of the iv route.

#### **6.9.4.2 Data presentation to Surgeons**

As with the medical unit it was necessary to analyse baseline prescribing data for presentation as the data were being collected, therefore not all data were included. In this preliminary analysis 54 records of the final 57 were used.

A recurring problem was related to the licensed indications for usage of drug prescribed. Of 25 patients who had received iv cefuroxime 10 had been changed to oral cephalexin, this change was inappropriate in 7 instances. The 7 cases of

inappropriate usage was because this group had an intra-abdominal related infection, cephalexin does not have a Product Licence for this type of infection. The point was made that in addition to expediting the change from the iv route of administration to the oral route attention to the Product Licence of the oral antibiotic selected also has to be given. Prophylactic antibiotics prescribed at the time of operation were also found to be continued for no apparent reason in a number of patients.

#### **6.9.4.3 Data presentation to Urologists**

Data from Phase 1 of the study highlighted a subpopulation of patients with epididymo-orchitis whose treatment schedule was less than optimal. Table 6.5/2 summarises this data. The seminar presentation to the Urologists focused on the treatment of this infection in addition to the general study findings.

The infecting organisms associated with epididymo-orchitis are usually chlamydia or gram-negative bacilli, a differential determination of the infecting organism can only be carried out by obtaining a sample for culture by prostatic massage. There were no prostatic massage samples collected for any of the Phase I patients so knowledge of the infecting pathogen(s) was unknown. Based on this and the knowledge that the aminoglycosides penetrate prostatic tissue poorly an alternative treatment strategy was proposed. This consisted of a two week course of oral ciprofloxacin 500mg twice daily to cover potential infection with gram-negative organisms, moderate coverage being given to chlamydia. Because chlamydia are slow growing organisms it was considered that the ciprofloxacin alone would not provide adequate coverage to a chlamydial infection so at the end of the ciprofloxacin treatment it was suggested that a two week course of once daily doxycycline at a dose of 200mg (tetracycline is the drug of choice for chlamydial infections) should then be employed to complete the treatment course. This treatment protocol would therefore provide coverage to both groups of frequent pathogens responsible for epididymo-orchitis. The perceived benefits of this strategy were reduced costs, £55.05 (MIMS, Feb.1992) for one months oral treatment, and improved outcome as compared with an average iv treatment cost of £150 shown to have been associated with treatment failure. In addition it was

thought that these patients would have an earlier discharge because oral therapy can be taken at home.

At the end of each presentation, physicians were requested to complete a questionnaire (see Appendix E) which had been 'tailored' to their particular seminar.

#### **6.9.5 Prescribing practice data collection, post seminar presentations (Phase II - part 2, end March 1991 - mid May 1991)**

Following the seminar presentations, six weeks of antibiotic prescribing data were collected in the same manner as was used for the baseline antibiotic prescribing data (Phase II - part1).

#### **6.9.6 Data Analysis (Phase II)**

Comparison of the two sets of prescribing practice data collected in parts 1 and 2 were intended to allow an evaluation of any prescribing behaviour modification brought about by the information feedback sessions.

#### **Equipment and Database Packages (Phase II)**

All data were stored and analysed in DBase IV (Ashton & Tate, Berks., UK) using spreadsheet (Borland QuattroPro) and statistical software (Minitab 8.0) on an Opus 386SX microcomputer.

#### **Costs (PhaseII)**

Drug costs for Phase II were taken from MIMS February 1992.

#### **Tests of Significance**

The tests of significance applied to changes in prescribing behaviour between parts 1 and 2 of Phase II were the Chisquare test of significance with Yates correction for small numbers and determination of confidence intervals using the method for proportions.

#### **Outcome Measures (Phase II):**

##### **Inappropriate intravenous (iv) therapy/ Suitability for oral treatment**

Inappropriate iv days were defined as those days a patient was capable of taking oral antibiotics i.e. they were receiving other oral medicines or were taking food or on at least 25ml sips of water.

The criteria used in the assessment of patients suitable for treatment by the oral route but who were actually receiving iv therapy included:-

Temperature  $<37.5$  and  $>36.5$

Pulse  $<100$

MAP\*  $>69$  and  $<109$

No operation within 48 hours

No specimen sent for C&S or a negative culture

\* MAP - Mean arterial pressure is the product of systolic pressure minus diastolic divided by three and added to diastolic pressure

In addition to these criteria it was considered that:-

- 1) Intravenous (iv) therapy was appropriate for the first 24 hours postoperatively other than Urology patients who were frequently prescribed oral antibiotics postoperatively.
- 2) Those patients whose putative diagnosis was possible septicaemia were considered to be appropriately treated via the iv route for the first 24 hours.
- 3) All iv treatment of gut related problems (e.g. bowel obstruction, cholecystitis etc.) was considered appropriate.
- 4) Patients receiving concurrent iv antibiotics inappropriately were evaluated as if only one antibiotic had been administered (e.g. if a patient received the combination of cefuroxime, gentamicin and metronidazole inappropriately for one day then this was counted as 1 day of inappropriate treatment not as 3 antibiotic days).

### **6.9.7 Results Phase II**

General demographic details of patients recruited in both parts of Phase II are shown in Table 6.5/3. It can be seen that there were substantially fewer patients receiving antibiotics in the second part of Phase II i.e. 140 vs 218. The actual case mix appears to be different between the two parts of Phase II. In part 1 27% of antibiotic prescriptions were for either a suspected or proven chest infection

compared to only 17% in part 2. This may have been due to some extent to seasonal variation as part 1 was undertaken during the winter whereas part 2 was carried out during the spring.

Over 50% of patients prescribed antibiotics both in parts 1 and 2 of Phase II received them via the oral route. The proportion of patients receiving a course of antibiotics initially by the intravenous (iv) route followed by oral administration was relatively constant between the two parts also, 18% in part 1 and 20% in part 2. However the time to change (measured in days) from iv to oral appeared to decrease in part 2 i.e. only 49% of patients were changed from iv to oral within 2 days in part 1 as opposed to 65% who were changed to the oral route within 2 days in part 2. This difference is not statistically significant. What appears to be statistically significant is the change in number of inappropriate iv days. Over three quarters of total iv days were considered to be inappropriate in part 1 whereas less than 50% were considered so in part 2. Table 6.5/4 provides a breakdown of the number of inappropriate iv days and the statistical significance between parts 1 and 2 for observed differences overall and also by speciality.

During the presentations to the various speciality groups it was suggested that oral ciprofloxacin would be a suitable substitute for an aminoglycoside. The proportion of patients prescribed ciprofloxacin increased from 10% in part 1 to 27% in part 2. From the questionnaires (see appendix E) circulated to the physician groups the speciality specific data and cost data generated the most interest. Without exception all physicians felt that this type of audit should be repeated on a regular basis. Table 6.5/5 summarises the responses received from the questionnaires.

### **6.9.8 Changes in prescribing behaviour by speciality**

#### **Clinical Pharmacology**

The largest change in prescribing habit was apparently seen with this group. The proportion of inappropriate iv days in part 1 was 80%, reduced to just over 24% in part 2 with a P value <0.001.

From the questionnaires issued at the end of the seminar 8 of 11 physicians had answered that they thought their prescribing practice would be changed as a result of the information supplied to them (see table 6.5/5).

## **Surgery**

Five of seven surgeons thought their prescribing practice would change as a result of the seminar (see table 6.5/5). This translated to an apparent change of inappropriate iv days of 68.2% in part 1 to just over 47% in part 2, statistical significance  $P < 0.01$ .

## **Urology**

All of the urologists present (8) thought their prescribing practice would change (see table 6.5/5). Yet an analysis of the overall prescribing of iv antibiotic therapy did not show statistically significant changes, the proportion of inappropriate iv days in part 1 was 85.4% and 74.5% in part 2. However, when the antibiotic treatment of those patients with epididymo-orchitis admitted after the seminar presentation was examined, almost all (11 of 13) were prescribed the treatment protocol suggested, although one of these patients also received three days of iv gentamicin concurrently with the oral ciprofloxacin for reasons unknown. One patient received oral ciprofloxacin in combination with metronidazole prior to an orchidectomy and the diagnosis of epididymo-orchitis was unsure in the thirteenth patient and was potentially considered to be a cellulitis of the scrotum, this patient was prescribed 2 days of gentamicin in combination with 2 days of iv augmentin and the course of treatment completed with oral augmentin. There was a fourteenth patient who received the new treatment protocol for epididymo-orchitis but this patient was located on a surgical ward in Ninewells hospital. The registrar treating this patient had previously been employed in the urology department and had become aware of the recommendations for treatment of epididymo-orchitis.

To determine whether the new treatment protocol suggested at seminar prevented recurrent infection, all patients admitted in the post-seminar data collection period with a diagnosis of epididymo-orchitis were followed for three months after their hospital discharge (see Table 6.5/6). For these patients the new treatment protocol appeared to be associated with a high degree of success and an average direct marginal cost saving of £95 per patient.

## 6.10 Discussion - Phase II

Feedback of study findings fulfilled the three criteria MuirGray (1986) considered important for an educational strategy to be effective in modifying clinical behaviour. Subjectively, clinicians appeared to have a high degree of interest in the findings and in particular were sensitive to cost data (table 6.5/5). A large proportion considered that their prescribing practice would be modified by the informational feedback. However, as demonstrated by Chaput de Saintonge *et al* (1988), what doctors think they do and what they do in practice can be quite diverse events. In the first instance for the study population as a whole, it appeared that prescribing practice was modified with a statistically significant decreased usage of the iv route, inappropriate iv antibiotic days decreased from 75.9% to 46.3% ( $P < 0.001$ ), (table 6.5/4). As a group the Clinical Pharmacologists appeared to show the greatest change overall from 80% down to 24.3% ( $P < 0.001$ ), however, the Urologists showed little statistical change in general iv antibiotic usage (85.4% to 74.5%,  $P > 0.10$ ).

In retrospect, however, the methodology for this phase of the study was less than robust. Although it appeared that a statistically significant change in prescribing practice for iv antibiotics occurred, it was not possible to attribute the change to the intervention for more than one reason. Firstly, an oversight occurred relating to the timing of data collection. The intention of this phase of the study was to compare prescribing practice behaviour, pre and post intervention for a static study population. The collection of the baseline prescribing data i.e. pre-intervention, commenced in mid-January and continued for the following 6 weeks. Unfortunately there was a changeover in junior house staff at the beginning of February. The ramification of this being that the study population pre-intervention was somewhat different to that post-intervention. Given that the junior house staff carry out the largest proportion of prescribing albeit under the auspices of their seniors, an uncontrolled variable had been introduced into the data collected.

Secondly, only half of the staff from the surgical group attended their intervention seminar. Consequently the non-attenders would only have received the printed information (DI note) as feedback.

Thirdly, it is highly probable that the case-mix of patients for whom antibiotics were prescribed, changed between the pre-intervention and post-intervention data collection periods. It can be seen from table 6.5/3 that there was a higher proportion of patients in the pre-intervention period with a chest infection i.e. 27% vs 17%. It is highly possible that the patients in the post-intervention period were not as ill as those in the pre-intervention period and therefore were not perceived to need iv antibiotics for as prolonged a time span as those in the pre-intervention period.

These three variables alone, dynamic study population, incomplete delivery of feedback and change in case-mix, considerably weakens the inference that the intervention used was the cause of an observed reduction of iv antibiotic prescribing. In addition to these variables there may well have been other unknown variables which may have explained the change seen. It is for these types of reasons that Brennan *et al* (1994) argue strongly that tests of statistical significance should not be used as evidence for the validity of observational results.

Although the methodology used in this phase of the study was flawed and overall it was not possible to determine whether the informational feedback did have any effect on prescribers behaviour, a dedicated change in the treatment of epididymo-orchitis did take place after the intervention, i.e. a clinically significant change occurred (O'Brien *et al*, 1994). It can be argued that this particular change in prescribing behaviour was as a direct result of the informational feedback because the treatment protocol proposed at feedback was both more effective and less expensive than that used historically. Consequently it would have been very difficult for the Urologists to justify the continuation of historical prescribing behaviour in this instance.

### **6.11 Summary Discussion for Phases I and II**

In conclusion, unlike the failed US patient outcome research initiative (Sheldon, 1994) which used computerised non-systematic observational data, the first part of this study has shown that observational data collected with a systematic approach can be used to identify meaningful outcome measures. By focusing on both

process and patient outcome, this current study has demonstrated that although aminoglycosides are ubiquitous in use, their management is poor and they are not low treatment cost agents. In fact, the aminoglycosides are associated with several opportunity costs; monitoring, toxicity and treatment failure. In addition to death in hospital, three readily measurable indicators of adverse outcome of hospital antibiotic therapy associated with marked increases in hospital treatment costs were identified. These were:- change to an alternative iv drug regimen; retreatment with antibiotics in hospital; and readmission with infection. A further element of resource wastage was also identified in that a high proportion of patients capable of receiving oral therapy were being treated with intravenous antibiotics.

The study also tested the predictive power of a sepsis score (Cooke *et al*, 1993) to forecast potential cost and outcome of treatment. Evidence to support the score as a method of stratifying bacteraemic patients for risk was produced provided the data for the score was collected prospectively. As the sepsis score increased so did the cost of treatment, the score therefore appears to be a potentially useful method not only for objective assessment of disease severity but also as a predictor of potential cost. Such a measure would help to identify patients with low scores who may be suitable for less aggressive treatment, as well as alerting clinicians to patients who may require more intensive care. Evidence to support the predictive power of the score for non-bacteraemic patients was lacking.

The intention of Phase II was to measure the effect that feedback of cost and antibiotic management data from Phase I had on clinicians antibiotic prescribing behaviour. Unfortunately, the methodology used in the second phase of the study was found to be poor in design. The prescribing behaviour data collected, both before and after feedback, were found to possess more than one known confounding variable, dynamic study population, incomplete delivery of feedback and a change in case-mix. The lack of a control group further exacerbated these problems. Although a statistically significant difference in prescribing behaviour was observed between the two data collection periods, the presence of these confounding variables invalidated the statistical analysis. As a consequence it was not possible to determine whether informational feedback had altered general

antibiotic prescribing practice. The presence of these confounding variables serve to highlight the important issue discussed by Brennan *et al* (1994) that extreme caution is required when applying statistical tests to observational data.

Despite the lack of evidence to suggest that feedback had had any effect on general antibiotic prescribing, the treatment of epididymo-orchitis did appear to have been influenced in a positive manner. A dedicated change in the treatment of epididymo-orchitis did take place after the intervention, i.e. a clinically significant change occurred (O'Brien *et al*, 1994). It can be argued that this particular change in prescribing behaviour was as a direct result of the informational feedback because the treatment protocol proposed at feedback was both more effective and less expensive than that used historically. Consequently it would have been very difficult for the Urologists to justify the continuation of historical prescribing behaviour in this instance.

#### **How has this study affected current practice?**

The findings of this study have led to several local initiatives which have minimised the opportunity costs identified. Local initiatives include;

- The development of a policy for once daily administration of aminoglycosides published in the antibiotic formulary of Dundee Teaching Hospitals NHS Trust.
- Publication and dissemination of treatment guidelines for suspected sepsis and consultant review of patients with bacteraemia in the Directorates of Medicine and Surgery. Early in 1993 a sepsis protocol to be used by junior doctors in the empirical management of sepsis was established after consultation of a multidisciplinary group. The protocol was produced on a single sheet and was also made available in poster form on all relevant wards. It was aimed at best guess therapy pending the results of culture and other investigation. In addition, an unsolicited bed side consultation has been made by an Infectious Diseases (ID) consultant to all patients with a documented bacteraemia in the above Directorates. Diagnosis and suggested changes to therapy are made by the consultant to the patient's clinician. It has been estimated that the total cost of running this service, including full audit and feedback of results, is about £6,500 per year (Nathwani *et al*, 1996). Although the cost is not fully offset by

savings in antibiotic costs, it is felt that the quality of care given to patients is much higher and therefore the service continues to operate.

- Strategic changes in the location of patients with epididymo-orchitis from an acute surgical bed in the Urology unit to an acute medical care bed in the Infectious Diseases unit (following the results of the study routine treatment of these patients is now by the oral route).
- Implementation of guidelines and standards for the use of parenteral and oral antibiotics in the Directorate of Medicine. A further full scale audit has shown compliance with standards for initiation of parenteral treatment to be 99% and a lower compliance of 82% with the timing of switch from parenteral to oral treatment. A process of continuing education and training for all staff involved in prescribing, administering and monitoring antimicrobial therapy is ongoing.

#### **Implications for practice and for future research**

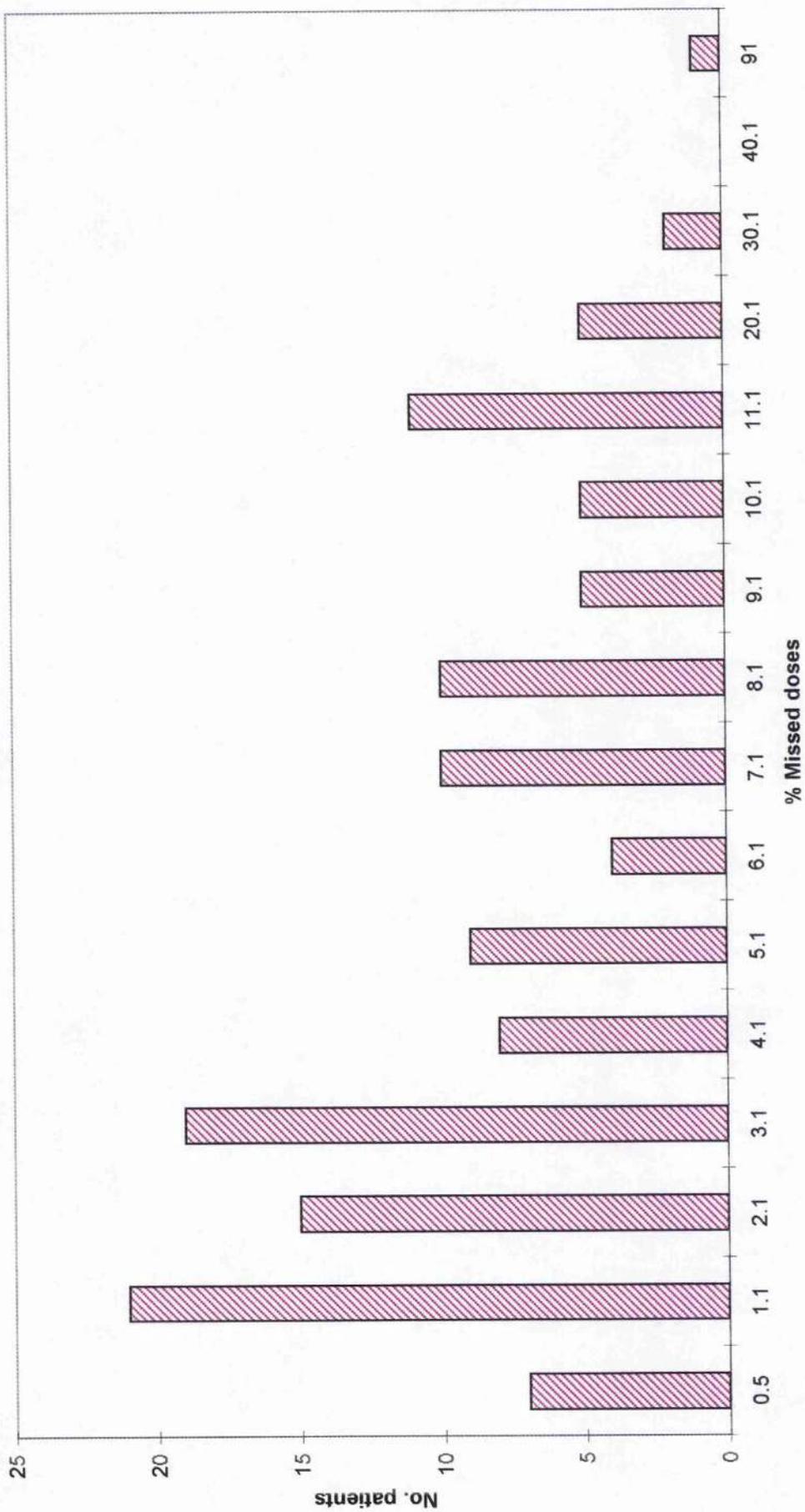
This study has shown that current clinical practice is not always ideal and can be associated with many opportunity costs. Although time and effort is involved in determining simple and meaningful patient outcome measures, this investment will need to be continued if we are to move away from narrow cost-containment practices which may be increasing resource use elsewhere. Heightening clinicians awareness to the costs of treatment coupled to measures of outcome can be successful in modifying clinical behaviour to more efficient practices (re: epididymo-orchitis). However, as highlighted by the deficiencies of this study, if changes in clinical behaviour are to be measured in a significant manner the mechanism used will require careful design. Documentation needs to be improved otherwise any form of meaningful retrospective evaluation will be difficult to undertake. Post-discharge follow-up must be included in patient outcome in future studies of antibiotic therapy. Even if the follow-up period is limited to the first two weeks post-discharge, with an acknowledgement that some failures will still be missed, it will at least give an indicator of failure rate without which no reasonable estimate can be made.

With particular reference to aminoglycoside usage, it is believed that the work and findings of this study have contributed to the ongoing debate about once daily

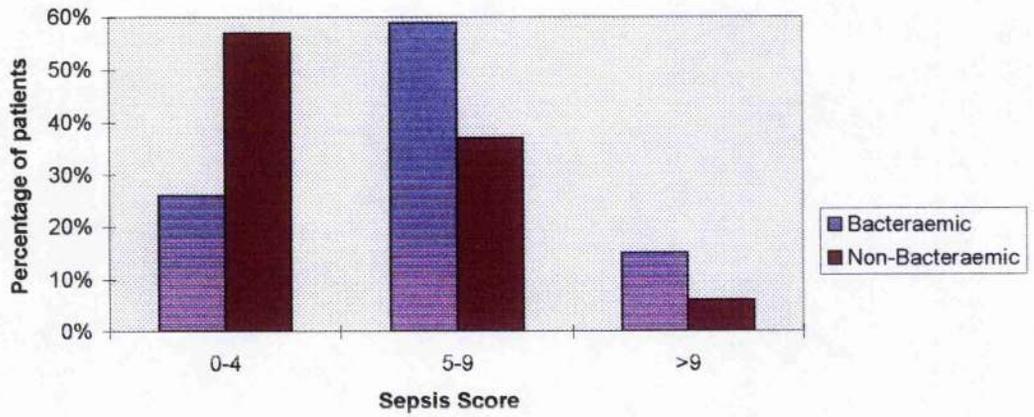
aminoglycoside dosing (Parker *et al* ,1993, O'Shaughnessy *et al*, 1994, Parker *et al* ,1994, Parker *et al* ,1995, Freeman *et al*, 1997).

## **Figures and tables for Chapter 6**

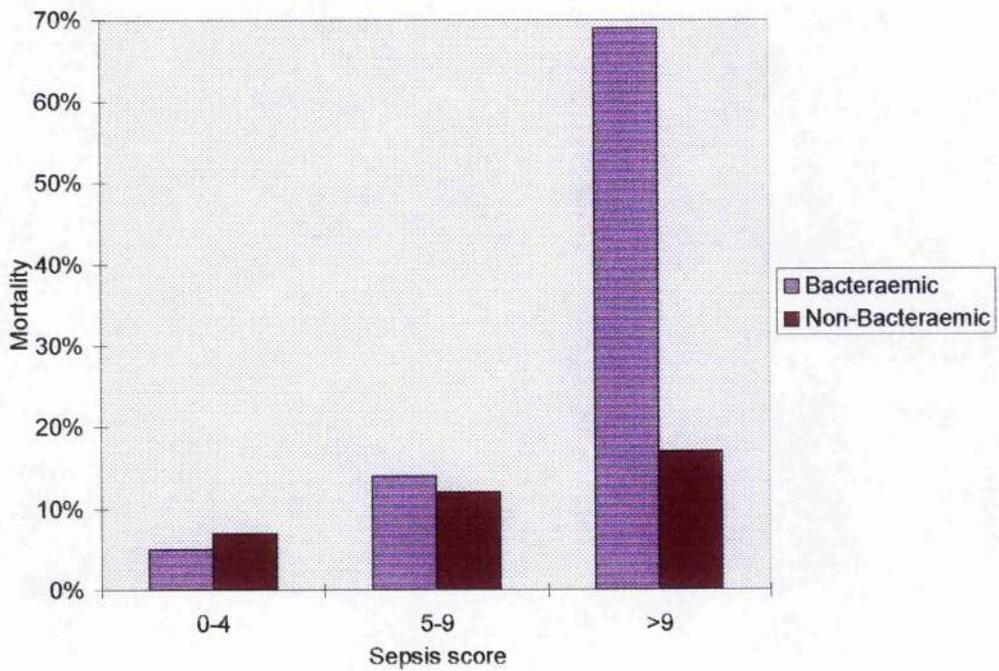
Figure 6.1 % Missed doses per treatment



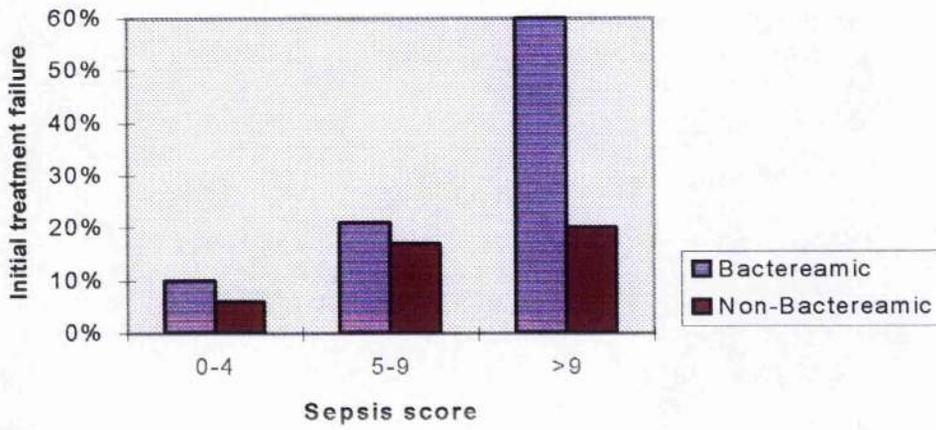
**Figure 6.2a** Distribution of sepsis scores for all bacteraemic patients (n=85) and non-bacteraemic aminoglycoside (n=215)



**Figure 6.2b** Mortality by sepsis score in all bacteraemic patients (n=85) and non-bacteraemic (n=215) patients



**Figure 6.2c** Rate of treatment failure for all surviving bacteraemic patients (n=68) and for surviving, non-bacteraemic, aminoglycoside (n=194) patients



**Table 6.1/1 Presenting Complaint For Initiation Of Aminoglycoside Therapy**

<b>Infection Category</b>	<b>Patient Episodes</b>	<b>% of Total</b>
Blood	132	51.8
Pulmonary	20	7.8
Urinary Tract	22	8.6
Abdominal	30	11.8
Epididymo-orchitis	14	5.5
Skin/Soft Tissue	12	4.7
Other	25	9.8

**Table 6.1/2 Antibiotic Combinations On Initiation Of Aminoglycoside Therapy.**

<b>Combination</b>	<b>Patient Episodes</b>	<b>% Of Total</b>
Gentamicin alone	18	7.1
Gentamicin + Augmentin	53	20.8
Gentamicin + Augmentin + Metronidazole	28	11.0
Gentamicin + Cefuroxime + Metronidazole	44	17.2
Gentamicin + Piperacillin	30	11.8
Gentamicin + Piperacillin + Metronidazole	6	2.4
Gentamicin + Metronidazole	19	7.4
Other combinations (<5 patient episodes each)	57	22.3
(including netilmicin, amoxicillin, penicillin, ampicillin, ceftazidime, fusidic acid, flucloxacillin, vancomycin, ciprofloxacin, erythromycin, cephalixin, trimethoprim, cefuroxime, piperacillin)		

**Table 6.1/3 Ultimate Response To Therapy For The Aminoglycoside Group In Hospital\***

**i) For all diagnoses**

<b>Success</b>	<b>Patient episodes</b>	<b>(%)</b>
Resolved on original treatment	53	20.8
Resolved on iv therapy followed by po treatment	118	46.3
Resolved but therapy stopped due to Adverse Drug Reaction	1	>0.5
	<b>Total 172</b>	<b>67.5</b>
<b>Failure</b>		
Died #	28	11
Changed to alternative iv antibiotic with subsequent resolution	18	7.1
Antibiotic recommenced for same indication because of recurrent symptoms	9	3.5
	<b>Total 55</b>	<b>21.6</b>
<b>Unassessable</b>		
iv therapy changed to po treatment then back to iv therapy	7	2.7
Further antibiotics for another infection	5	2.0
Other ~	16	6.3
	<b>Total 28</b>	<b>11.0</b>
	<b>Overall Total 255</b>	

**cont Table 6.1/3 Ultimate Response To Therapy For The Aminoglycoside Group In Hospital\***

**ii) For all diagnoses minus proven gram-negative bacteraemics**

<b>Success</b>	<b>Patient episodes</b>	<b>(%)</b>
Resolved on original treatment	47	21.9
Resolved on iv therapy followed by po treatment	104	48.4
	<b>Total 151</b>	<b>70.0</b>
<b>Failure</b>		
Died	22	10.2
Changed to alternative iv antibiotic with subsequent resolution	15	7.0
Antibiotic recommenced for same indication because of recurrent symptoms	6	2.8
	<b>Total 43</b>	<b>20.0</b>
<b>Unassessable</b>		
iv therapy changed to po treatment then back to iv therapy	6	2.8
Further antibiotics for another infection	4	1.9
Other ~	12	5.6
	<b>Total 22</b>	<b>10.0</b>
<b>Overall Total 215</b>		

\* Some people were readmitted to hospital within a short time period following discharge with a recurrence of their original infection.

# died three weeks after discontinuation of antibiotics

~ Dehiscd wound, died after discharge to another hospital, longterm antibiotics for unknown septic focus, for leg amputation, for organ transplantation, self discharge, self discontinuation etc.

Table 6.1/4a Component costings (drug, assay, equipment and staff time) for aminoglycoside patients

	Aminoglycoside: not bacteraemic, neutropenic or in ICU (n=177)		Aminoglycoside: neutropenic but not bacteraemic (n=19)		Aminoglycoside: intensive care but not bacteraemic (n=19)		Aminoglycoside: bacteraemic (n=40)	
	Median	95% CI	Median	95% CI	Median	95% CI	Median	95% CI
Drug	£114	£98-144	£462	£317-679	£270	£173-501	£177	£118-349
Assay	£18	£14-18	£32	£18-45	£54	£34-68	£23	£18-27
Equipment	£33	£28-39	£75	£54-105	£82	£54-120	£49	£34-77
Staff Time	£20	£17-22	£30	£22-42	£42	£28-56	£28	£21-41
Total cost	£185	£162-214	£599	£429-871	£471	£317-760	£278	£191-507

**Table 6.1/4b Component costings (drug, equipment and staff time) for bacteraemic patients treated with a non-aminoglycoside antibiotic regimen (n=45)**

	<b>Median</b>	<b>95% CI</b>
<b>Drug</b>	<b>£68</b>	<b>£48-96</b>
<b>Equipment</b>	<b>£17</b>	<b>£9-24</b>
<b>Staff Time</b>	<b>£9</b>	<b>£6-12</b>
<b>Total cost</b>	<b>£97</b>	<b>£69-143</b>

**Table 6.2/1 Frequency Of Infecting Organism Causing Bacteraemia**

<u>Organism</u>	<u>Patient Episodes</u>	<u>(%)</u>
E.coli	45	52.3
Klebsiella	10	11.6
Pseudomonas spp	6	7.0
Salmonella	4	4.7
Proteus	4	4.7
Enterobacter	4	4.7
B.fragilis	3	3.5
N.meningitidis	2	2.3
Acinetobacter	1	1.2
coliforms	2	2.3
Mixed (1x E.coli+ Klebsiella+ Strep.spp, 1x E.coli+ Proteus, 1x E.coli+ Klebsiella+ Strep.faecalis+ Clostridia spp., 1xPseudomonas spp + Staph.epidermidis, 1x Haem.influenzae+ Staph.epidermidis)	5	5.8

**Table 6.2/2 Type And Time Of Specimen In Relation To The Initial Blood Culture Specimen For Those Bacteraemic Patient Episodes With Another Focus Of Infection**

Focus of infection and specimen		No of episodes with same organism	No of episodes with different organism
<b><u>Urinary tract</u></b>			
Urine	same day	6	1
	1-7 days earlier		1
	16 days earlier		1
	1-7 days later	1	2
Dipslide	same day	4	1
	1-7 days earlier	2	
	subtotal	13	6
<b><u>Abdominal</u></b>			
Wound swab	1-7 days earlier	1	
	1-7 days later		2
	subtotal	1	2
<b><u>Pulmonary</u></b>			
ET Aspirate	same day		1
	1-10 days earlier	1	1
Sputum	1 day later		1
	subtotal	1	3
<b><u>Other</u></b>			
Mouth swab			1
Faeces		1	1
Skin swab			1
	subtotal	1	3
	<b>Overall total</b>	<b>16</b>	<b>14</b>

**Table 6.2\3 Initial antibiotic treatment of Bacteraemic patients**

<b>Antibiotic</b>	<b>No patient episodes</b>	<b>% of total</b>
Gentamicin + Augmentin	14	16.5
Cefuroxime + Metronidazole	9	10.6
Augmentin	9	10.6
Ciprofloxacin	8	9.4
Amoxycillin	7	8.2
Cefuroxime	6	8.1
Gentamicin + Piperacillin	5	7.1
Gentamicin + Cefuroxime + Metronidazole	3	3.5
Gentamicin + Metronidazole	2	2.4
Ciprofloxacin + Metronidazole	2	2.4
Penicillin	1	1.2
Penicillin + Chloramphenicol	1	1.2
Cephalexin	1	1.2
Flucloxacillin	1	1.2
Co-trimoxazole	1	1.2
Amoxycillin + Ciprofloxacin	1	1.2
Vancomycin	1	1.2
Amoxycillin + Ceftazidime	1	1.2
Gentamicin + Cefuroxime	1	1.2
Trimethoprim	1	1.2
Gentamicin + Cefuroxime + Flucloxacillin	1	1.2
<b>Total</b>	<b>85*</b>	

\* nb 1 patient with bacteraemia did not receive any antibiotic therapy

**Table 6.2\4 Ultimate response to therapy for bacteraemic patient episodes**

	No. patient episodes	% of total
<b><u>Success</u></b>		
Resolved on original treatment	19	22.1
Resolved on iv therapy followed by po therapy	26	30.2
Resolved but therapy stopped due to adverse drug reaction	1	1.1
<b>Subtotal</b>	<b>46</b>	<b>53.5</b>
<b><u>Failure</u></b>		
Died	14	16.3
Changed to alternative iv antibiotic and resolved	5	5.8
Antibiotics recommenced for same indication because of recurrent symptoms	9	10.5
<b>Subtotal</b>	<b>28</b>	<b>32.6</b>
<b><u>Unassessable</u></b>		
IV therapy changed to po therapy then back to iv therapy	1	1.1
Further antibiotics for another indication	4	4.7
Other*	6	8.1
<b>Subtotal</b>	<b>11</b>	<b>14</b>
<b>Overall total</b>	<b>85</b>	

\* self discharge, po treatment to iv then back to po, died after transfer to another hospital, query need for antibiotics as query significance of bacteraemia, long term antibiotics for unknown septic foci etc.

Table 6.3/1 Sepsis scores, hospital outcome and cost of treatment

Sepsis score	Non-bacteraemic aminoglycoside patients n=215			Bacteraemic aminoglycoside patients n=40			Non-aminoglycoside patients n=45			bacteraemic		
	No patients (% total)	Cost of treatment	Outcome (% sepsis group)	No patients (% total)	Cost of treatment	Outcome (% sepsis group)	No patients (% total)	Cost of treatment	Outcome (% sepsis group)	No patients (% total)	Cost of treatment	Outcome (% sepsis group)
0-4	122 (57%)	Range £10-2233 Average £275 Median £172	Success=90 (73.7%) Fail=7 (5.7%) Death=9 (7.3%) Unass=15 (12.3%)	9 (22.5%)	Range £60-1068 Average £347 Median £250	Success=7 (78%) Fail=1 (11%) Death=1 (11%) Unass=0 (0%)	13 (29%)	Range £6-303 Average £89 Median £46	Success=5 (38%) Fail=1 (8%) Death=0 (0%) Unass=7 (54%)			
5-9	81 (38%)	Range £18-2440 Average £353 Median £222	Success=54 (66.7%) Fail=12 (14.8%) Death=10 (12.3%) Unass=5 (6.2%)	25 (62.5%)	Range £49-2856 Average £453 Median £233	Success=11 (44%) Fail=5 (20%) Death=2 (8%) Unass=7 (28%)	25 (55.5%)	Range £1-480 Average £139 Median £118	Success=6 (24%) Fail=4 (16%) Death=3 (12%) Unass=12 (48%)			

cont Table 6.3/1

Sepsis scores, hospital outcome and cost of treatment

Sepsis score	Non-bacteraemic patients n=215		aminoglycoside		Bacteraemic patients n=40		aminoglycoside patients		Non-aminoglycoside patients n=45		bacteraemic
	12 (6%)	Range £42-4944 Average £872 Median £481	Success=6 (50%) Fail=2 (16.6%) Death=2 (16.6%) Unass=2 (16.6%)	Range £13-4032 Average £957 Median £374	6 (15%)	Success=0 (0%) Fail=1 (16.5%) Death=4 (67%) Unass=1 (16.5%)	7 (15.5%)	Range £7-232 Average £110 Median £138	Success=0 (0%) Fail=2 (29%) Death=4 (57%) Unass=1 (14%)		
>9											

**Table 6.3/2 Patients readmitted to hospital within three months of hospital discharge n=69**

Notes untraceable n=5

**A) Readmitted but reason not related to original infection n=38**

<b>Reason for readmittance</b>	<b>No of patients</b>
Arranged admission for investigative procedure eg. cystoscopy, colonoscopy	5
Outpatient clinic review	8
Admission for unrelated problem eg. pain management, convalescence, haematemesis, radiotherapy etc.	15
Arranged admission for elective surgery	10

**B) Readmission considered to be related to original infection n=26**

**Initial foci of infection and time to readmittance from original discharge**      **No of patients**

<b>Blood:</b>	1-7 days	3
	15-21 days	5
	22-28 days	2
	>28 days	2
<b>Respiratory:</b>	1-7 days	2
	8-14 days	1
	>28 days	1
<b>Urinary:</b>	8-14 days	2
	22-28 days	2
	>28 days	1
<b>Epididymo-orchitis:</b>	1-7 days	1
	>28 days	1
<b>Other</b>	8-14 days	2
	>28 days	1

**Table 6.3/3 Death whilst receiving initial treatment, underlying pathology and appropriateness of therapy**

	<u>No of deaths</u>
<u>Non-bacteraemic receiving aminoglycoside therapy</u>	
Appropriate treatment + underlying pathology	4
Appropriate treatment + no underlying pathology	12
Inappropriate treatment + no underlying pathology	6
<u>Bacteraemic receiving aminoglycoside therapy</u>	
Appropriate treatment + underlying pathology	3
Appropriate treatment + no underlying pathology	4
<u>Bacteraemic not receiving aminoglycoside therapy</u>	
Appropriate treatment + underlying pathology	3
Appropriate treatment + no underlying pathology	3
Inappropriate treatment + no underlying pathology	1

**Table 6.4/1 Aminoglycoside assay results for patients receiving Therapeutic Drug Monitoring**

	No of Assays (No of patients)
<b>Uninterpretable assays (Lack of data on sampling times)</b>	<b>50 (42)</b>
<b>Interpretable assays</b>	<b>321 (173)</b>
<b>Assays within recommended range</b>	<b>48 (33)</b>
<b>Overdose</b>	
postdose >10mg/l	27 (26)
postdose <10mg/l but trough >2mg/l	47 (36)
total overdose	74 (62)
<b>Underdose</b>	<b>224 (139)</b>
postdose <8mg/l	
<b>Dose adjustment</b>	
decreased dose due to high serum concentrations	49/74 (66%) (62)
increased dose due to low serum concentrations	95/224 (42%) (139)

At the time of this study the Tayside recommended therapeutic ranges for gentamicin and netilmicin were :-  
 predose level <2mg/l  
 postdose level > or = 8mg/l but < or = 10mg/l.

Table 6.4/2 Relationship of Therapeutic Drug Monitoring (TDM) costs to length of antibiotic treatment and overall treatment costs for those patients receiving TDM n=187

TDM costs as a % of overall treatment cost	Treatment cost range (median cost)	No of patient episodes	Length of treatment of all antibiotics in days (median)	Length of treatment of aminoglycoside in days (median)
1-10%	£104-4944 (£409)	96	1-70 (7)	1-31 (6)
10.1-20%	£92-1757 (£186)	59	1-18 (5)	1-18 (4)
20.1%-30%	£68-301 (£88)	22	1-33 (6)	1-33 (4.5)
>30%	£25-145 (£73)	10	1-6 (3)	1-6 (3)

**Table 6.4/3 Reasons for missed antibiotic doses**

<b>Reason for non-administered or non recorded dose</b>	<b>No. of doses</b>
Not recorded on Kardex therefore no evidence of administration	402
Not recorded on Kardex but on fluid chart	90
Nil by Mouth orders	37
Reasoned missed dose *	29
Nil in Stock	16
Dose changed due to misunderstanding	8
Misunderstanding between med. & nursing staff	7
Venflon tissue or no iv access	7
Patient absent	7
Patient non compliance	2
Other	15

\*Examples of reasons include:-

- 1) preceding dose given late therefore prescribed dose not given
- 2) in transit to ICU
- 3) at theatre
- 4) problems with giving set
- 5) unable to swallow, vomiting

**Table 6.4/4 Clinical condition of patients deemed to have received iv treatment unnecessarily by pre-defined selection criteria and verification by case-note review n=26**

<b>Necessity of iv treatment determined by case note examination</b>	<b>Clinical diagnosis (No. patients)</b>
No therapy required	Ureteric colic (1) Cerebrovascular accident (1) Chronic obstructive aiways disease with no indication of infection (1)
Suitable for oral therapy	Epididymo-orchitis (10) Chest infection (4) Urinary tract infection (3) Cellulitis (1) Renal colic (1) Swinging pyrexia (1)
Intravenous treatment necessary	Subacute bacterial endocarditis (1) Chronic obstructive aiways disease with infection (1) Osteomyelitis (1)

**Table 6.5/1 Additional baseline data used to supplement findings from Phase I presented to Clinical Pharmacologists**

<b>Baseline audit of all patients receiving antibiotic therapy (13/1/92-25/2/92) on two medical wards</b>	<b>No of patients n=50</b>
<b>Indication for antibiotic treatment</b>	
<b>Proven or suspected chest infection</b>	<b>33</b>
<b>Urinary tract infection</b>	<b>8</b>
<b>Assorted other infections</b>	<b>9</b>
<b>Unable to take oral medication</b>	<b>2</b>
<b>Treated by the oral route only</b>	<b>42</b>
<b>Total direct costs of treatment</b>	<b>£415</b>
<b>Treated by the intravenous route</b>	<b>8</b>
<b>Total direct costs of treatment</b>	<b>£921</b>

**Table 6.5/2 Epididymo-orchitis patient data from Phase I presented to Urologists**

<b>Patients with epididymo-orchitis</b>	<b>No of patients</b>
<b>Treated with an aminoglycoside containing regimen</b>	<b>16</b>
<b>Unable to take oral therapy</b>	<b>0</b>
<b>Suitable for oral therapy at initiation of treatment determined by selection criteria and case-note review</b>	<b>10</b>
<b>Total direct cost of these cases</b>	<b>£2517</b>
<b>Average cost per patient</b>	<b>£150</b>
<b>Median cost per patient</b>	<b>£112</b>
<b>Underwent Therapeutic Drug Monitoring</b>	<b>7</b>
<b>Subtherapeutic</b>	<b>6</b>
<b>Overdose</b>	<b>1</b>
<b>GP antibiotic prescription for recurrent infection</b>	<b>4</b>
<b>Hospital readmission due to recurrent infection</b>	<b>2</b>

Table 6.5/3

Patient demographics for parts 1 & 2 of Phase II	
Part 1 13/1/92-25/2/92 (44 Days)	
Pre Printed Information and Seminars	
No of Patients	21-91
Age Range (Yrs)	No. Patient (% of total)
Sex	90 (64%)
Male	50 (36%)
Female	68 (48%)
Speciality Location	40 (28%)
Urology	32 (23%)
Clinical Pharmacology	25 (18%)
Surgery	39 (28%)
Unable for oral therapy	24 (17%)
Reason for Antibiotic	15 (11%)
UTI (Susp./prov)	13 (9%)
Chest Infection (Susp./prov)	49 (35%)
Prophy. postop	
Epididymo-orchitis	
Other	

cont Table 6.5/3		Patient demographics for parts 1 & 2 of Phase II	
Part 1		Part 2	
Pre Printed Information and Seminars		Post Printed Information and Seminars	
<u>Route of Admin</u>	<u>No. Patient (%)</u>	<u>No. Patient (%)</u>	<u>No. Patient (%)</u>
Oral only	133 (61%)	75 (54%)	
Intravenous (iv) only	23 (11%)	14 (10%)	
IV changed to oral	39 (18%)	28 (20%)	
Other	24 (11.5%)	23 (16%)	
<u>IV changed to oral</u>	39 (18% study population)	28 (20% study population)	
<u>Time of Change (Days)</u>	<u>No. Pat. (% of total iv changed to oral)</u>	<u>No. Pat. (% of total iv changed to oral)</u>	
1	8 (21)	10 (36)	
2	11 (28)	8 (29)	
3	9 (23)	3 (11)	
4	3 (8)	3 (11)	
<u>Notes untraceable</u>	16 (7%) 10 (7%)		
<u>Additional antibiotics</u>	19 (9%) 13 (9%)		
<u>Patients receiving Ciprofloxacin</u>	22 (10%)	38 (27%)	

**Table 6.5/4 Inappropriate iv days****All Phase II results, parts 1 & 2**

	<b>Part 1</b>	<b>Part 2</b>
Patients (no)	<b>215<sup>#</sup></b>	<b>132<sup>*</sup></b>
Total days (Oral and intravenous)	<b>1704</b>	<b>1350</b>
Intravenous (iv) days	<b>261</b>	<b>214</b>
% of total days	15.3%	15.9%
Inappropriate iv days	<b>198</b>	<b>99</b>
(% of iv days)	75.9%	46.3%
95% CI	70.7-81.1	39.6-52.9
Difference		29.6%
95%CI of diff		21.1-38.1
Chisquare with Yates correction	42.71 with 1d.f P<0.001	

**By speciality****Urology**

Patients (no)	<b>89</b>	<b>62</b>
Total days (Oral and iv)	<b>738</b>	<b>739</b>
No.iv days	<b>82</b>	<b>55</b>
% of total (oral & iv)	11.1%	7.5%
Inappropriate iv days	<b>70</b>	<b>41</b>
(% of iv days)	85.4%	74.5%
95%CI	77.7-93.0	63.0-86.1
Difference		10.8%
95%CI of diff		-3.0-24.6
Chisquare with Yates correction	1.85 with 1d.f. 0.50>P>0.10	

cont Table 6.5/4

**Inappropriate iv days**

**Clinical Pharmacology**

	<b>Part 1</b>	<b>Part2</b>
Patients (no)	<b>69</b>	<b>38</b>
Total days (Oral and iv)	<b>554</b>	<b>371</b>
No.iv days	<b>50</b>	<b>74</b>
% of total (oral & iv)	9.1%	19.9%
Inappropriate iv days	<b>40</b>	<b>18</b>
(% of iv days)	80%	24.3%
95% CI	68.9-91.1	14.5-34.1
Difference		55.7%
95%CI of diff		40.9-70.5
Chisquare with Yates correction	34.94 with 1d.f. P<0.001	

**Surgery**

Patients (no)	<b>57</b>	<b>32</b>
Total days (Oral and iv)	<b>412</b>	<b>240</b>
No.iv days	<b>129</b>	<b>85</b>
% of total (oral & iv)	31.3%	35.4
Inappropriate iv days	<b>88</b>	<b>40</b>
(% of iv days)	68.2%	47.1%
95% CI	60.2-76.3	36.4-57.7
Difference		21.2%
95%CI of diff		7.8-34.5
Chisquare with Yates correction	7.51 with 1d.f. 0.01>P>0.001	

# The population of patients in this part was 218, however 3 patients were unevaluable for inappropriate iv days, 1 patient was on longterm antibiotic therapy for osteomyelitis and bacterial endocarditis with many confounding factors such as changes in therapy due to deteriorating renal function, 3 patients case notes were untraceable and it was not possible to determine length of treatment.

\* The population of patients in this part was 140, however 8 patients were unevaluable for inappropriate iv days, 1 patient was on longterm antibiotic therapy for osteomyelitis and bacterial endocarditis with many confounding factors such as changes in therapy due to deteriorating renal function, 7 patients case notes were untraceable and it was not possible to determine length of treatment.

Table 6.5/5 Summary of physician responses to end of presentation questionnaire

	Medical speciality		
	Surgery	Clinical Pharmacology	Urology
No of questionnaires returned/total staff in study group	7/14	11/11	8/8
Junior House Officer	4/6	4/4	2/2
Senior House Officer	1/2	2/2	1/1
Registrar	1/2	2/2	1/1
Senior Registrar	-/1	1/1	1/1
Consultant	1/3	2/2	3/3
General questions posed			
Which aspects of the presentation did you find of most interest?*			
All audit findings	2	4	5
Speciality specific data	6	7	6
Cost data		5	4
Other		1	
Did you read the Drug Information Note?	Yes 3 No 1	Yes 8 No 2	Yes 5 No 3
Having listened to the presentation do you think your prescribing practice will be affected?	Yes 5 No 1	Yes 8 No 3	Yes 8 No 3
Do you think this type of audit should be repeated on a regular basis?	Yes 7 No 1	Yes 11 No 1	Yes 8 No 1

\* more than one option could be selected

**Table 6.5/6 Community surveillance of patients admitted with epididymo-orchitis in the post-seminar data collection period (31/3/92-14/5/92)**

<b>Three month follow-up</b>	<b>No of patients</b>	<b>Comment</b>
<b>No further antibiotics</b>	<b>7</b>	
<b>Change of antibiotic at discharge</b>	<b>1</b>	<b>Vomiting due to doxycycline</b>
<b>Died</b>	<b>1</b>	<b>Due to ischaemic heart disease, not related to epididymo-orchitis episode</b>
<b>Further antibiotics</b>	<b>2</b>	<b>Haematuria following catheter change (1) Only received 1 day of 28 days initial treatment (1)</b>
<b>Surgical removal of testis</b>	<b>1</b>	
<b>No response from GP</b>	<b>2</b>	

## Chapter 7

### 7. **Feasibility of assessing the costs and benefits of a novel healthcare programme within a UK hospital.**

#### 7.1. **Introduction - Non-inpatient intravenous (NIPIV) antibiotic care versus Inpatient intravenous antibiotic care**

As discussed previously in chapter 5 (The economic issues of antibiotic use) a NIPIV service for the administration of antibiotics has been widely available to North American patients since the 1970's. Within the UK, provision of this type of service has been on an ad hoc basis and limited to a select population of hospital patients, primarily those suffering from cystic fibrosis with recurrent infection (Gilbert *et al*, 1988). Given that this type of service is considered cost-effective in the US setting for a myriad of conditions, a feasibility study designed to examine the logistics, costs and benefits of such a service for patients with acute infection was undertaken in the Infectious Diseases Unit (IDU) of Dundee Acute Hospitals NHS Trust, Tayside. Within the study, three perspectives were considered, that of the patients, the initial secondary care provider and that of other health care professionals who could possibly become involved in the provision of a NIPIV service.

The objectives of this study were:-

- To determine which patients are suitable for home or outpatient intravenous (iv) antibiotic care.
- To determine how practical provision of a home/outpatient iv antibiotic service is within Tayside.
- To quantify the costs and benefits of non-inpatient iv treatment versus outpatient iv treatment.
- To evaluate the perceptions of both study patients and Tayside General Practitioners (GPs) of this type of service.
- To assist in the production of a business plan for a NIPIV service.

### 7.1.1. Patients and Methods

From January 1994 through to November 1994 all patients admitted to the IDU of Dundee Acute Hospitals were considered for non-inpatient care. The unit is the regional unit for treating adults with infection and serves a population of approximately 400,000. The unit is comprised of 54 beds, 28 of these are devoted to orthopaedic patients who have an infective complication with the remainder devoted to patients with any other infection. The majority of admissions to the unit are direct referrals from GPs in the community but a significant number are referrals from other units within the Trust.

On admission, patient assessment was undertaken by a junior house officer and senior house officer/registrar, difficult cases being assessed by the on-call infectious diseases (ID) consultant. If antibiotics were considered appropriate, patients were commenced on a standard regimen identified by a unit protocol. The route of administration being determined by clinical need at the point of prescription. Patients receiving iv antibiotics for 24 hours were further evaluated by a senior member of the study team to determine whether a need existed to continue with the iv route and if so, whether the patient was a prospective candidate for the NIPIV programme. This required that the patient was medically stable, was expected to require the iv route of administration for at least 5 days and had an infection amenable to either ceftriaxone or teicoplanin<sup>1</sup>. If these criteria were met the patient was socially assessed through a personal, interactive, semi-structured interview. Encouragement was given to the patient to have a family member or friend present at the interview. Several hours prior to interview an information sheet (see appendix G), which explained the background and reasons to the study, was given to each of the patients such that they could discuss it with their family/friends if they so desired, it also gave them the opportunity to formulate any questions. At interview all aspects of the study were explained to the patient and the opportunity was given for the patient to ask as many questions as they wanted. Each interview took approximately 30 minutes to carry out. The social assessment included fully informing the patient of all aspects of the study,

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<sup>1</sup>These antibiotics were chosen because they only required administration once daily and therefore, from a patients perspective, preparation and administration requirements were relatively simple.

determining that the patient was motivated and willing to participate and that home circumstances were supportive for this form of therapy, for example, easy access to a telephone, suitable drug storage facilities etc. (full details of the social assessment screening questionnaire are given in the appendix G). On admission to the study each patient signed a consent form.

The study included an outpatient arm and a home care arm. Outpatient treatment necessitated attendance at the ward once a day for antibiotic administration and iv access assessment. Home treatment necessitated that the patient or a relative/carer be trained to prepare and administer the prescribed antibiotic at home. The patient was required to attend the ward twice weekly for iv access assessment. On entering a patient to the study a planned discharge to the home environment was carried out. This included the insertion of an appropriate iv line, and where necessary, instruction in aseptic technique and care of the iv line (see appendix G for patient guidelines and information pack). The two types of iv access used were a 21G venflon catheter or a peripherally inserted 'midline' (PIC line) catheter. Instruction in aseptic technique and iv access care continued until the patient felt comfortable and competent and the instructor equally considered the patient competent in their technique. At this point transport arrangements and review dates and times for return to the hospital were confirmed. Transport arrangements included a private facility (taxi) or reimbursement of travel costs, whichever the patient preferred. Additionally, the time arranged for attendance at the hospital was that which was convenient to the patient. This allowed those patients returning to work to attend either before or after the working day. Prior to discharge each patient was asked what they perceived the benefits and drawbacks of such a service to be, they were interviewed again at the end of their treatment to determine if their opinion had changed.

On discharge to the home environment each patient was supplied with all items they would require (drugs and all consumables they would require for preparation and administration and for care of their iv access), in addition a cascade 24 hour contact list (see appendix G) was supplied. Each patient had a final appointment with one of the infectious disease consultants to assess their response to treatment and whether any further therapy or investigation was required.

Even though clinical responsibility was maintained by the hospital for the patient during the study period, each patient's GP was contacted on the day of discharge to their home to give notification that the patient would be in the community with an iv access in situ. The GPs and members of the community nursing team were not asked to be directly involved in the study. Furthermore, no hospital based member of the team visited the patient at home although advice and support was available at all times.

Detailed financial accounting of all drugs and consumables used was recorded for each patient, this included those consumables used in providing an iv access. Note was also taken of the amount of staff time taken in patient continuing care. Total transportation costs or distance travelled, were recorded for each patient. In order to create a comparable costing for hospital based treatments two ID consultants independently made an estimate, based on the clinical history, of what therapy these patients would have reasonably received had they remained in hospital. Treatment was defined according to the written guidelines in the IDU. These guidelines specify the drug, dose, route of administration and duration of treatment. For example, guidelines for the management of cellulitis recommend iv treatment with flucloxacillin, 1gm, four times daily, in addition to benzylpenicillin, 1.2gms, four times daily, both for 48 hours, followed by a further 7 days of oral flucloxacillin, 0.5gm, four times daily. The consultants also estimated the length of patient stay. This allowed all direct costs (drugs, consumables, staff time) of study treatment to be compared and contrasted with the standard direct inpatient treatment costs had the patient remained as an inpatient.

A telephone survey of all Tayside GP teams was carried out to determine their attitude to the provision of a NIPIV service. This was achieved by initially contacting each practice by letter briefly explaining the reasons for and the purpose of a NIPIV service and providing a copy of the questions to be explored at interview (see appendix G). Contact was then made by telephone to arrange a suitable time to carry out the interview. Although only one partner per practice was interviewed, it was assumed (as requested) that the views expressed were a consensus of all the partners in the practice.

A focus group of study patients participated in a roundtable discussion with non-clinical marketing experts to further establish their views on the NIPIV scheme. Medical ethics committee approval was sought and obtained for this study.

#### **7.1.2. Equipment and Database Packages**

All data were stored and analysed using spreadsheet (Borland QuattroPro) software on a Toshiba 486 microcomputer.

#### **7.1.3. Source of costs**

All antibiotic drug costs were taken from MIMS July 1994.

Staff time was taken as the average cost of one hour's nursing time (£10/hour) in 1994 (Davey, 1996).

Consumable costs (syringes, needles, giving sets, sterets, vecafix, tegaderm etc.) were provided by central supplies dept, Dundee Acute Hospitals Unit, 1994.

Vygon Nutriline 'PIC' 300mm midline catheter kit - purchase cost from Vygon (UK) Ltd. 1994- £25/kit (each kit included all consumables required for aseptic insertion e.g. swabs, guide needle, syringe etc.).

Chest X-ray charge - £22 (calculated by Business Manager, Radiography dept., Kings Cross Hospital, 1994).

In the calculation of staff time for hypothetical inpatient costs, the preparation and administration of a bolus injection was taken as 10 minutes (Cousins *et al*, 1989).

#### **7.1.4 Calculation of treatment costs**

For those patients in the home iv arm the cost of treatment was inclusive of staff time taken to counsel and assess the patient, staff time taken to provide the iv access (i.e. insertion time etc.), cost of x-rays to determine appropriate location of access <sup>2</sup>, staff time taken for aseptic preparation and administration training, drugs and consumables used and the staff time taken for evaluation of the iv access site and of any remedial action required (e.g. replacement of access etc.).

The cost of treatment for patients in the outpatient arm included staff time taken to counsel and assess the patient, staff time taken to provide the iv access (i.e. insertion

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<sup>2</sup>Only those patients with a PIC line inserted required a chest x-ray.

time), cost of x-rays to determine appropriate location of access <sup>3</sup>, drugs and consumables used and staff time taken for preparation and administration of antibiotic and evaluation and care of the iv access site.

#### **7.1.5 Transportation costs**

Patients own travel was offered to be reimbursed at 26p/mile (this figure was calculated by the RAC, 1994, to cover car, average wear, tear and fuel costs - personal communication).

Taxi transportation charges as per contractor (approx. 75p/mile).

#### **7.1.6 Study Funding**

Monies were not readily available from within the NHS service to carry out this study therefore equal sponsorship was sought from the manufacturers of the antibiotics (ceftriaxone and teicoplanin) chosen for use, namely Roche and Marion Merrell Dow. Antibiotic selection preceded study funding.

Within the sponsorship contract entered into with each company a clause existed stating that all data remained the academic property including publication rights, of those person(s) carrying out the study and that neither company had the right to veto data publication or presentation.

### **7.2. Results**

#### **7.2.1 Study population characteristics**

During an 11 month period, 1,057 patients were admitted to the IDU. Less than 60% (559) were receiving antibiotics. More than 50% of these patients (304/559) received antibiotics by the oral route, leaving a subgroup of 255 (24% of original admission population) patients from which to recruit. From this subgroup 24 patients met the initial criteria and were socially suitable for entry into the study. Table 7.1 shows the reasons for non-recruitment of the other 231 patients, the main reasons were short term need of parenteral antibiotics and medical instability. However, social circumstances were a factor in 25 patients that may have been surmountable with

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<sup>3</sup>Only those patients with a PIC line inserted required a chest x-ray.

greater community support. A further 2 patients were recruited to the study from the ID outpatients clinic and another 3 were referred to the study from other units in the hospital giving a final total of 29 study patients. The reasons for iv treatment of the study patients in preference to oral therapy are given in Table 7.2.

Recruited patient age ranged from 17-75 years and the length of treatment ranged from 1-88 days. The longest length of treatment for the home arm was 69 days and 88 days for the outpatient arm. Figure 7.1 shows the distribution of length of treatment.

Table 7.3 shows the indication, location of treatment and antibiotic used. The major indication for NIPIV treatment was skin and soft tissue infection accounting for over 50% of patients, with the remainder of patients having a mixed bag of infections. A larger proportion of patients were treated as outpatients, 19, versus 10 patients in the home arm.

### **7.2.2 The costs of treatment**

The component costs of treating a patient on the NIPIV programme are given in table 7.4a. The consumable costs associated with the preparation and administration of the study drugs have been separated from the consumable costs associated with establishing and caring for the iv access. The rationale being that with any iv treatment, access is necessary, and will therefore be the same for all treatments and as such can be disregarded in comparisons between treatments. Consequently the following comparisons of study treatment costs with hypothetical inpatient costs exclude the iv access costs. Conversely, the consumables associated with drug preparation and administration will vary with the frequency and type of drug used. The iv access costs have been shown in table 7.4a for the sake of completeness, it can be seen from this table that on average, iv access costs account for less than 3% of the total treatment cost.

NIPIV study treatment costs (drug acquisition, consumables used, staff time) are compared and contrasted with the hypothetical direct inpatient treatment costs (as determined by ID consultant consensus) in table 7.4b. Hypothetical direct consumable and time costs are not given for patients 4 and 17 because it was decided (by the two ID consultants) that had they stayed in hospital it would have been possible to treat them orally because total compliance would be achieved which could not have been

guaranteed in the community, this being the rationale for iv treatment in the community. Both patients had osteomyelitis.

The average cost per NIPIV study patient was £665 compared with the average cost of £427 for inpatient treatment. This indicates average additional costs of £261 per patient for NIPIV therapy, however if orthopaedic cases are excluded (patients 4, 6, 16, 17 and 24), the additional cost of NIPIV treatment per patient reduces to £62 (see table 7.5a). Orthopaedic infections are associated with particularly high treatment costs because of their chronicity and therefore duration of treatment required. From table 7.5b it can be seen that the average cost of treating an orthopaedic patient was £2548 in the NIPIV programme compared to £1523 had the patient been treated as an inpatient, giving an additional cost of £1025 for the NIPIV programme.

Overall NIPIV costs for the 29 study patients exceeded the hypothetical inpatient treatment costs by just over £6,600. This was primarily brought about by the difference in drug acquisition costs. The acquisition costs of the drugs used in the study exceeded those that would have been used in the hospital by 70% (£17,219 cf £10,030), to a small extent this was offset by the NIPIV consumable costs being lower than those for inpatient treatment (£464 cf £1369).

The daily acquisition cost of teicoplanin was much greater than that of the daily acquisition cost of ceftriaxone (£52.10/400mg teicoplanin vs £11.46/1gm ceftriaxone). To observe how total treatment costs were affected by drug acquisition costs, a comparison has been made between actual NIPIV study treatment costs and what the costs would have been, calculated on the basis that patients were treated with ceftriaxone where possible. The vast majority of patients would have been suitable for ceftriaxone treatment with the exception of two individuals. One of whom had a macrolide/lincomycin/streptogramin resistant *Staphylococcus epidermidis* infection (patient 24) and another who had a *Staphylococcus epidermidis* infection (patient 17) resistant to both cefuroxime and augmentin. It can be seen from table 7.6 that preferential use of ceftriaxone rather than teicoplanin in the 13 patients identified as suitable, would have reduced their average treatment cost from £509 to £133 giving a cost difference of £376 per patient, in favour of ceftriaxone. Putting these treatment costs back into the NIPIV study population as a whole and comparing with the proposed hospital inpatient costs it can be seen (table 7.7) that the average NIPIV

treatment cost would be reduced to £486 with a cost difference of £59 per patient in excess of hospital inpatient treatment, this is however, without excluding the high cost orthopaedic infection patients. Examining the effect that the orthopaedic patients have in this scenario is shown in tables 7.8a and b. Excluding the orthopaedic patients, and using ceftriaxone where possible for the NIPIV patients, the average cost of treatment would have been reduced to £132 compared to £199 for hospital inpatient treatment giving a cost difference of £67, this time in favour of NIPIV treatment (see table 7.8a). However, the average cost of treating an orthopaedic infection patient still remained higher in the NIPIV setting (£2190) than in the hospital setting (£1522) (see table 7.8b) primarily because it was not possible to use ceftriaxone for two of the patients (17 & 24) for the reasons already discussed. In addition, another substantial component in the cost difference in this instance is that oral therapy could be used in the hospital as compliance would be guaranteed which it could not be in the community. What has to be remembered though is that these costs relate to the preparation and administration of drug alone and does not take into consideration the bed day costs of an orthopaedic patient which was on average 63 days. Table 7.9 summarises the various costing scenarios described above.

### **7.2.3 Impact of the NIPIV programme on utilisation of hospital bed days**

The total number of bed days saved by the 29 patients on the NIPIV programme totalled 532, representing an average of 18 bed days per patient. However this figure is skewed by the five orthopaedic patients who accounted for almost 60% (316) of these bed days. The average number of bed days saved per non-orthopaedic patient was 9 days with a median of 5.5 days which is in stark comparison to the average of 63 days and median of 62 days for an orthopaedic patient.

It can be seen from table 7.10 that the total bed day capacity of the ID unit was 19,710 and as a proportion the 532 days saved by those patients on the NIPIV programme represented only 2.7%. Capacity utilisation for the ID unit was assumed to be around 45% based on the preceding 3 years average, as such the 532 bed days saved still only represented 4% of 1994 expected actual bed day consumption.

At the time of this feasibility study the 'hotel cost' per bed day in the ID Unit was calculated to be £313 (Scottish Health Service Costs, 1994). It could be argued therefore that £166,516 ( $532 \times £313$ ) had been saved, however unless the savings could be made tangible by reducing fixed costs this argument would be flawed.

Considerable rationalisation of the ID service has taken place and in 1996 the number of inpatient beds has been reduced to 35, 22 on the Kings Cross site and 12 in a new Orthopaedic Infection Unit at Dundee Royal Infirmary. Nonetheless, at the level of 29 patients per year, NIPIV therapy would still have a minimal effect, even on this reduced bed capacity.

#### **7.2.4 Transportation costs**

Of the 29 patients, 14 requested or required the taxi transportation proffered, the remainder (15) chose to use their own transport. Although the patients using their own transport had the opportunity for travel reimbursement to the hospital not one patient decided to take advantage of this. Table 7.11 shows the individual mileage covered by patients and the costs of taxi transportation. Where taxi transportation was provided the average cost was £114 per patient. However, 4 of the patients were orthopaedic patients who received transportation for 28 days or longer, their average cost was £266 per patient, giving an average cost of £53 per patient for the remaining group.

#### **7.2.5 Patients perspective of NIPIV treatment who received this form of treatment**

As part of the initial screening process, patients were asked what their perceived benefits of home/outpatient iv treatment might be, these benefits fell into 1 of 5 categories and are summarised in table 7.12, it can be seen that the most frequently cited advantage is the freedom afforded of being at home. During the screening process patients were also asked whether they or their relatives had concerns of any nature regarding NIPIV treatment. Of the 29 patients, 26 had no personal concerns whatsoever, 3 had concerns which were of a low level nature in that the concerns did not deter the patient from participating in the programme. Sixteen patients had chosen to discuss entry into the programme with a close relative or friend and 13 had not. Of the 16 patients who did discuss the NIPIV programme with a relative or friend,

concerns were expressed by 4 relatives. The nature of the concerns expressed both by patients and relatives are given in table 7.13.

Of the 29 study patients, 26 completed the 'end of study' questionnaires, 1 patient did not return the questionnaire, 1 patient died and the remaining patient was removed from the study after their initial diagnosis was changed after 1 day on the NIPIV programme. The results from the questionnaire are summarised in tables 7.14 & 15. Of the 26 patients, 8 (33%) reported a problem but 75% (6) of these were of a quite minor nature (from a medical viewpoint that is, rather from the patients perspective) and were related to either the speed of injection or to the discomfort caused by the iv access. Two patients (7.7%), however, were considered to have experienced a problem of an important nature and were related to hypersensitivity type reactions. The experience of these two patients and the ramifications for a NIPIV service are discussed further in section 7.2.7 Safety of NIPIV care. The vast majority of patients, 92% (24), said they would repeat this form of therapy again, the reasons given by the two patients (8%) who said they wouldn't, considered that they would have had more rest had they remained in hospital. Five patients (19%) thought that NIPIV had caused them 'out of pocket' expenses but qualified this by stating that this was of their own choice. The perceived advantages of the patients prior to participating in the study were corroborated by the actual advantages experienced (table 7.15).

Nine of the patients who had been treated between January and August 1994 on the NIPIV programme were interviewed in a focus group discussion. The meeting was facilitated by Professor Stephen Parkinson and Daragh O'Reilly of Bradford Management Centre. A summary of the key points from this discussion are given in table 7.16. All patients participating in the discussion group stated they would repeat this form of therapy and felt the treatment at home improved their quality of life.

#### **7.2.6 GP perspective of NIPIV treatment**

A response to the summary letter circulated to 61 GP practices representing 295 individual GPs was obtained from 41 practices (representing 125 GPs). Not all practices responded to all questions.

Of the 41 practices surveyed, 22 estimated from previous experience that they would refer between 1-10 patients with infection to the IDU per annum, 10 thought they

referred between 11-20 patients annually and the remainder felt they couldn't give a realistic estimate. Of the practices who were able to give a rough referral estimate, the majority considered their referrals to be due to skin and soft tissue infections or chest infections.

When asked about the advantages/disadvantages of a NIPIV service to both themselves and to their patients, a large proportion (71%) saw no advantage to themselves and a substantial disadvantage (46%) in the form of an increased workload. When considering the patients potential benefits of a NIPIV service, the majority of GPs thought that the patients would gain from getting home quicker and being in their own environment. The disadvantages to the patients discussed by the GPs varied widely but all centred around the lack of experience of this type of therapy. All advantages and disadvantages discussed by the GPs are shown in table 7.17.

When the GPs were asked whether they would favour the availability of a NIPIV service, a larger proportion (24/39) said they would favour one than wouldn't (4/39). A further 11 practices felt that they would need more information before they could answer. The options presented to the GPs for how a NIPIV service could be organised and the GP responses to these options are given in table 7.18. It can be seen that majority support only remained for a NIPIV service when both funding and responsibility remained within the secondary care sector.

### **7.2.7 Safety of NIPIV care**

Eight patients (27.6% of study population) reported a medical related problem associated with their NIPIV care. The type of problem expressed by six patients was considered to be of a quite minor nature (from a medical viewpoint that is, rather from the patients perspective) and was related to either the speed of injection or to the discomfort (phlebitis) caused by the iv access. The problem experienced by the remaining two patients (6.9% of study population) was of a more serious nature. Both these patients displayed a hypersensitivity type reaction whilst receiving antibiotic treatment as outpatients. The first reaction followed administration of a second dose of teicoplanin which was being used to treat a right leg cellulitis. The antibiotic had been administered within the hospital with the patient then returning home. The onset of

symptoms (rigours, global piloerection, dry mouth, chest tightness and shortness of breath) occurred some 60 minutes post dose, the episode being of approximately 20 minutes duration. The patient contacted the hospital during the episode and although advised to return to the ward the patient declined but returned the following day. Treatment was changed to ceftriaxone, the patient continued on the programme and the infection was successfully treated. The second reaction was experienced by a patient being treated with ceftriaxone for osteomyelitis of the right temporal bone. The reaction was first experienced some 30 days after initial antibiotic commencement and took the form of a transient flushing sensation in the face and neck immediately following antibiotic administration. From this point forward the patient reported an increasing degree of transient flushing sensation on administration of ceftriaxone. An antihistamine (terfenadine, 60mg twice daily) was administered to try to ameliorate the problem but with little success. Antibiotic administration was stopped 26 days after the first report of 'flushing'. On follow-up the patient reported that the reaction had abated. During the antibiotic treatment, this patient was also taking medication (isosorbide mononitrate, glyceryl trinitrate, frusemide, aspirin, amlodipine, lisinopril) for underlying pathology of ischaemic heart and peripheral vascular disease. However, given the circumstantial evidence it was felt that the 'flushing' reaction was in fact due to the ceftriaxone rather than the other chronic medication.

### **7.3. Discussion**

The stimulus for this feasibility study was the consistent reports from the US on the cost effectiveness and patient popularity of NIPIV services. The experience encountered in this study reflects both similarities and dissimilarities with the US reports. The similarities centred around the workability and patient preference for such a service, the dissimilarities were of a fiscal nature and the reserved attitude of primary care physicians to their involvement in the provision of this type of service. As in the US, the study used a multidisciplinary health care team and successfully demonstrated that it is logistically feasible to select and treat patients with varied acute infection in the non-inpatient setting. However, the number of patients selected over the 11 month period was relatively small, this was due in the main to the selection

procedure which required that patients were perceived to require antibiotics for 5 or more days. Seventy three percent (186/255) of patients in the IDU receiving iv antibiotics did so for less than 5 days. Therefore the procedural criteria accounted for the low recruitment rate rather than medical instability which may have been expected to be more problematic i.e. less than 10% of patients (20/255) were unsuitable for reasons of medical instability. It is entirely possible, therefore, that the recruitment rate could have been substantially higher.

A surprising aspect from the patient social assessment interviews was that although NIPIV therapy was an entirely new concept, very few patients or relatives had concerns about participating in the programme. In fact at the end of treatment, patients expressed a consistent, distinct preference for this form of therapy when compared to the alternative of hospital inpatient care and this was independent of the length of time a patient spent in the programme. Most problems experienced by patients were of a minor nature and neither deterred the patient from continuing on the programme or from expressing their intention that they would readily participate again. Poretz (1993) reported that adverse drug reactions occur no more often in the NIPIV setting than in the hospital setting and that the incidence of phlebitis is actually lower than in the hospital. However, the issue of safety of NIPIV care was raised in this feasibility study by two patients (6.9%) experiencing an adverse event which was of a serious nature. The issue being that if an adverse event occurs within the confines of a hospital there are trained personnel on hand to deal with the problem. This catch net does not exist for patients in the home setting.

Given that NIPIV care originated in the US and the predisposition that North Americans have for litigation it would be reasonable to assume that a vast literature concerning safety and legal issues alone would exist, this doesn't appear to be so. Safety aspects are referred to in the literature but it is somewhat piecemeal. An explanation for this may lie with the way NIPIV care developed around the purpose of reducing the costs of treatment to patients. It would seem that North American patients have implicitly accepted the risk of an adverse event occurring at home for the benefits of convenience and lower care costs. From the information that is available it certainly appears that adverse reactions are no more frequent than those occurring in hospital, it is not unreasonable therefore, to assume that this has come to

be considered 'acceptable risk'. In one of the first reports of NIPIV care in 62 patients with cystic fibrosis, Rucker *et al* (1974) stated that no major complications were noted although mild phlebitis necessitating changing the iv line site was required after 7-8 days in some patients. The initial experience of Stiver *et al* (1978) with the NIPIV care of 23 patients concluded that side effects were no different from those in-hospital treated patients and that there was actually a decreased prevalence of phlebitis in patients treated at home. Four years and another 102 patient treatments later, these workers (Stiver *et al*, 1982) reported the continued acceptance of NIPIV care in that no side effects were experienced that necessitated discontinuation of home treatment or readmission to hospital. Others have also reported the safety of NIPIV care, Kind *et al* (1985) treated 315 patients over a 10 year period with no problems relating to the outpatient use of antibiotics. In a review of North American NIPIV literature Balinsky *et al* (1989) concluded '*there currently exists sufficient data to support both the safety and clinical effectiveness of outpatient parenteral antibiotic therapy*'. This conclusion has continued to be endorsed by others (Bernstein, 1991, Grizzard, 1991, Graham, 1991, Williams, 1993). However, the quantification of 'acceptable risk' from the existing literature is somewhat nebulous. The Manitoba home iv antibiotic program was reviewed after 12 years of operation (Cote *et al*, 1989), there had been 748 admissions to the program equating to 15,366 patient days. During this time phlebitis was occurring at a rate of 14.7% and there had been 7 penicillin induced allergic reactions, 1 reaction was severe leading to respiratory failure requiring resuscitation. Despite this the overall conclusion of the review was that the home iv program was safe and effective. Implicit in this conclusion therefore is that phlebitis occurring at 14.7% and 1 respiratory failure for 748 admissions constitutes 'acceptable risk' to this particular healthcare provider. In a different study (New *et al*, 1991) the complications observed and considered 'acceptable' were phlebitis occurring at a rate of 11.3% and aminoglycoside associated problems occurring at a rate of 2%. Adverse event rates vary between individual drugs and therefore, so will the 'acceptable' risk, for example, Tice (1991) considers ceftriaxone to have a 'good' safety profile for use in the outpatient setting with a 4% incidence of adverse effects, whereas Morales *et al* (1994) consider cefotaxime to be acceptable in a similar setting with an adverse event rate of 40%. The severity of an adverse event is obviously important in determining

'acceptability', those experienced by Morales *et al* (1994) with cefotaxime were largely considered mild.

Several models of home iv care now exist within North America (Tice, 1993) and it has been estimated that some 250,000 patients are treated annually (Rubinstein, 1993), consequently, basic safety standards have evolved that a service must meet in order to earn accreditation by the Joint Commission on Accreditation of Healthcare Organisations (Malloy, 1990). These include administration of the first dose and observation by a trained professional, adequate training and education of patients/carers in preparation and administration techniques, the ability of patients/carers to identify adverse events and the issue of anaphylaxis kits. In addition, patients should have access to a trained professional on a 24 hour basis.

If NIPIV care is to become as widely acceptable in the UK as it has in North America, then it will have to be considered safe by those using it. To this end two aspects will need to be made explicit. Firstly it will be important for a consensus to be reached between those receiving and providing the care as to what constitutes 'acceptable' risk and secondly, measures will need to be in place which minimize the risk of an adverse event occurring and ameliorate the situation should an adverse event occur.

There was a high correlation between perceived and actual advantages of NIPIV care expressed by the patients in this feasibility study. The most frequently cited benefit was that of having the freedom of being at home followed by the opportunity to return to work or deal with personal matters. This desire to return to a more normal lifestyle reflects the benefits expressed by patients in the US. Furthermore, to take advantage of an earlier discharge to the home environment, study patients were prepared to incur costs to themselves by providing their own transport. Patients' perspective should be considered in any service development as they are the end user. The type of qualitative interview approach used in this study, to elicit patients' perspective, has been found useful by others in the UK (Harries & Hill, 1994).

As previously mentioned, reports from the US consistently report cost savings associated with NIPIV services. The fiscal findings in this study were not as clear cut as the US reports, this is possibly due to two major differences that exist between the UK and US. Firstly, the reports from the US are from well established infrastructures designed to specifically provide a NIPIV service. This feasibility study did not have

an established infrastructure and sought to incorporate this type of service into an existing secondary care setting. Secondly, US patients and third party payers immediately realise cost savings from entry into a NIPIV programme as they no longer have to pay hospital 'hotel' costs. The payment for secondary care treatment is organised in an entirely different manner in the UK and cannot be directly compared with that of the US. The demand for the NIPIV programme generated by the feasibility study reduced bed day consumption by a negligible 4%. It is highly unlikely therefore that fixed costs (staffing levels, other overheads etc.) would be decreased because of this reduction, consequently the potential 'hotel cost savings' of £166,516 (see section 7.2.3) are illusory. Decreasing fixed costs appears to be quite a complex issue as highlighted by others (Stern *et al*, 1995). One study (Stern *et al*, 1995) demonstrated that although a 30% reduction in the average length-of-stay for knee arthroplasty patients could be achieved, the associated decrease in fixed costs was a more modest 13%. The examination of financial costs in this NIPIV feasibility study has therefore, focused on the direct, variable treatment costs, as these can be readily identified and valid comparisons made between alternative forms of treatment. An initial inspection of treatment costs in the feasibility study and assuming a payer perspective alone i.e. the hospital, could lead to the conclusion that provision of a NIPIV service is economically unattractive. Comparison of the direct, variable treatment costs between the study NIPIV care and hypothetical inpatient hospital care showed the average cost difference per patient (£228) to favour inpatient care. However, closer examination of these costs revealed more than one identifiable influence within the study which caused this preference, these were the existence of a high treatment cost subpopulation i.e. orthopaedic patients with an increased average cost of treatment of £1,025 for NIPIV care, and the unforced use of the high acquisition cost antibiotic, teicoplanin. This unforced use of teicoplanin reflects an important limitation of the study which was brought about by the sponsorship. The sponsors, Roche & Marion Merrell Dow, insisted that equal numbers of patients were treated with ceftriaxone or teicoplanin. Removal of these biases reversed the average cost difference per patient to £67 in favour of NIPIV care (see table 7.9).

Other costs to consider associated with this study of NIPIV provision, are those of transportation for those patients who were unable to provide their own. The average

cost in the study per orthopaedic patient was £266 and £53 per non-orthopaedic patient. From this closer examination of costs it appears that treatment of an orthopaedic patient on this type of NIPIV programme remains unattractive, however, this is not the case for the short duration treatment of non-orthopaedic patients, even when the costs of transportation (£53) are offset against the treatment cost gain of NIPIV (£67) therapy. The economic case disfavouring orthopaedic patients however, is not quite as clear cut as it would appear. The variation of clinical treatment for this group of patients is wide and although some are presently considered suitable for oral treatment in Dundee Teaching Hospitals Trust (DTHT), standard therapy in the US is iv treatment for six weeks as it is by others in the UK (Kalley *et al*, 1996). Should a change in treatment policy occur in DTHT then the current economic evaluation may well change.

Unlike their US counterparts, the GPs' approached in this study were somewhat reluctant to participate in the care of a patient in receipt of NIPIV therapy and were equally reluctant to fund this form of therapy. The consensus was that this type of service would involve an increase in workload with little benefit to the GPs'. Since the time of the GP survey, the government has issued a directive (NHSME EL(95)5) which is prescriptive about the way in which packages of care to patients at home initiated in the secondary care sector should be funded. Essentially, it can no longer be the responsibility of the GP to prescribe drugs etc. for specific 'packages of care' (e.g. NIPIV therapy) to patients at home. It is now the District Health Authorities (DHAs) (or their reorganisational successor (see chapter 2)) who have been charged with making financial arrangements for this type of patient. The DHA has to make the appropriate logistic arrangements and contract negotiation with whoever they deem fit to provide the 'package of care' service to the 'at home' patients. The service can be provided by contract with a Trust or directly with an NHS or commercial supplier. The directive, NHSME EL(95)5, has effectively excluded GPs from further participation in the **supply** of NIPIV care, so to some extent the negative perspective adopted by the GPs can be disregarded in future considerations of whether the further development of a NIPIV programme should be taken forward. However, fundholding GPs could possibly become **purchasers** of NIPIV care in a similar manner to the DHAs. The perspective fundholders may then adopt, could in all likelihood, be

different from those GPs primarily concerned about personal workload implications i.e. the cost-effectiveness of a NIPIV service would become an important issue for the fundholding budget.

In summary, the study objectives were achieved, NIPIV care is feasible. Appropriate selection criteria for patient recruitment to a NIPIV programme were developed, provision of a quality service was shown to be practical and examination of the costs and benefits highlighted segments of the market (within the parameters of the study) for which this type of service initially appears to be cost effective and not so cost-effective. Study patients expressed a high degree of preference for NIPIV care and were supportive for the continuation of this alternative form of therapy even though some costs were identifiably transferred to themselves, conversely the majority of GPs' were only supportive of the idea of such a service provided there were no financial or increased workload implications. The issue of 'safety' was raised by this feasibility study, as a result, the notion of 'acceptable risk' deserves exploration in the further development of NIPIV care.

The production of a business plan for a NIPIV service using the findings from this study is currently underway. In addition, suitable orthopaedic patients are currently being treated in this non-inpatient manner even though at a financial level it has initially appeared more costly. The driving force for this being the patient non-financial benefits accrued by avoiding long-term hospitalisation.

This study has also highlighted an important issue which needs to be borne in mind when interpreting results from this type of feasibility programme, that is, bias introduced by a conflict of interest. Resources were not available from public funds to carry out this study. It was only possible to readily, secure funding from pharmaceutical sponsors, consequently certain parameters had to be adhered to within the study i.e. funding was dependent on equal numbers of patients being treated with ceftriaxone and teicoplanin. Consequently a source of bias was introduced in the form of drug acquisition cost. It should become a prerequisite that the results from future studies are examined for sources of bias similar to that just described.

### **Implications of this study for future research**

It is to be hoped that facilitation of further service development will be aided by the publication of NHSME EL(95)5, as a source of funding for specific packages of care at home, has now been identified. The NIPIV programme just described was a **feasability** study, however, the programme has provided a base on which further developments could expand. For example, demand for the service could be increased by including those patients who require less than 5 days iv antibiotic treatment and by incorporating other conditions amenable to NIPIV therapy, such as congestive cardiac failure, peripheral vascular disease and some long term AIDS care.

In 1995, a multidisciplinary, expert workshop was convened to set out and discuss current views in the UK, on the pros and cons of non-inpatient parenteral antibiotic therapy (Non-inpatient use of parenteral antibiotics, 1995). This expert panel raised and ranked 16 issues which needed to be acted upon to ensure appropriate non-inpatient use of parenteral antibiotics. The Dundee feasibility study has addressed 7 of these issues comprehensively and a further 3 in part (see below), those issues which have only been addressed in part and the remaining 6 which have not been addressed at all will require future clarification if a NIPIV programme is to be established as a stand alone combined primary/secondary care service.

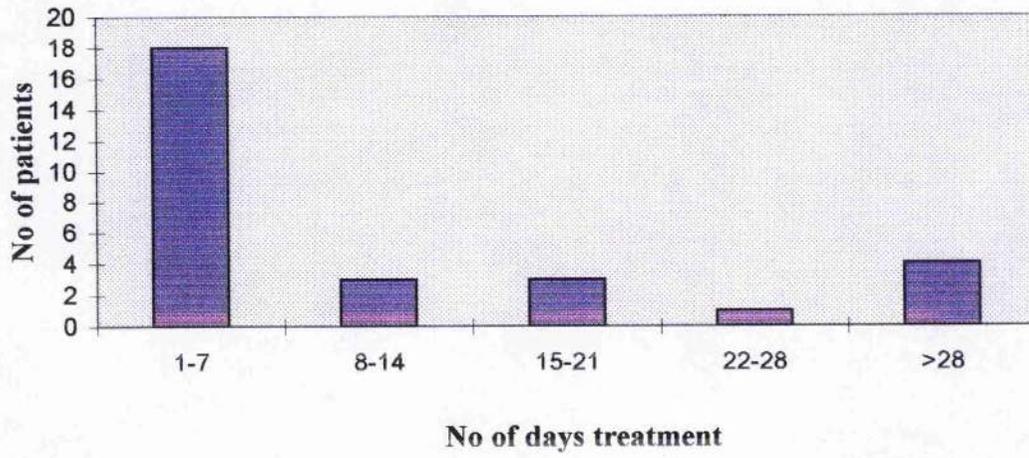
Issue and ranking	Action point	Addressed by Dundee study
Training/information 1=	Provide full information, training and assessment for carers, patients and staff.	Yes
Support/communication 1=	Provide 24-hour patient help-line and other lines of communication.	Yes
Patient selection 1=	Agree a protocol for selecting patients, including appropriateness of NIV therapy, suitability and safety of home environment, reliable diagnosis, patient co-operation, competence and willingness to go home.	Yes
Develop team structure 1=	Provide a dedicated service with community support services (e.g. district or practice nurses) and a multidisciplinary treatment team with a defined action plan and decision-making process; create a suitable infrastructure etc.	In part (only within the hospital)
Define team functions 5=		Further clarification required
Audit and quality 5=	Develop clear shared care guidelines and standard protocols; comply with good professional, legal and ethical standards; obtain feedback from all involved parties; identify important processes which relate to outcome; analyse/audit outcome, safety, costs and patient satisfaction.	In part (only within the hospital)
Funding/administration 7=	Define costing and calculate possible savings; attend to purchaser/provider considerations and reassure prescribers about costs; set up agreements on service level, and define who pay supplies and pays for drugs, patient travel, staff care and training.	Further clarification required
		No

Issue and ranking	Action point	Addressed by Dundee study
Clinical follow up 8	Establish an easy, regular fail-safe system for monitoring, follow-up and assessment of efficacy and toxicity, with the option to admit if necessary; prospectively identify unsuitable patients and possible complications; assess individual tolerability.	Yes
Accountability 9=	Consider indemnity; assess who does what and who is responsible and accountable for it.	No
Logistics 9=	Ensure that supplies of drugs, equipment, (from hospital pharmacy or specialist company) and patient home support are maintained.	Yes
Safety issues 11	Establish safe and secure intravenous access and maintain asepsis with excellent line care.	Yes
Research 12	Investigate and establish optimum treatment and discharge time, efficacy, patient benefit, risk/benefit (home vs hospital); establish what 'appropriate' treatment is, and, whether oral would be equivalent to iv treatment.	No
Promotion 13=	Establish a mechanism for GP liaison and sell the idea to the GP and practice staff by involvement and information to ensure their co-operation; sell the idea to patients/families by enthusiasm, education and reassurance.	In part (i.e. promoted to patients and families)  Promotion to primary care staff needs clarification.

Issue and ranking	Action point	Addressed by Dundee study
Drug selection 13=	Identify pathogens and their susceptibility; have suitable drugs available and choose the safest drug appropriate to the pathogen; decide on appropriate drug delivery.	Yes
Politics 15	Market the idea with a clear strategy for media relations, at conferences and through peer group pressure, and education of prescribers and their influences; reassure prescribers that beds will not be lost; publicise successes, consider whether GP should be involved etc.	No
Access 16	Create an infrastructure to cover admission, referral from hospitals and GPs, and rapid allocation of patients to non-inpatient treatment.	No

## **Figures and tables for Chapter 7**

**Figure 7.1**    **Distribution of length of treatment for patients on NIPIV program**



**Table 7.1 Reasons for non-recruitment of patients receiving iv antibiotics onto the NIPIV study**

Reasons for non-recruitment	No of patients
Short term iv antibiotics (<5 days)	186
Medically unstable	20
Socially not suitable (e.g. history of depression, too infirm, etc.)	19
Other (e.g. too far to travel, study antibiotic unsuitable)	6

**Table 7.2 Reasons for iv route of administration vs oral route**

<ul style="list-style-type: none"> <li>• Failure of oral therapy</li> <li>• Immunocompromised</li> <li>• Serious infection- need to ensure high serum levels</li> <li>• Underlying pathology e.g. diabetes</li> <li>• Ramadan</li> </ul>
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**Table 7.3 Indications and antibiotic used for treatment in study population**

Indication (% of study population)	Teicoplanin (no of patients)	Ceftriaxone (no of patients)
Cellulitis (51.7)	9	6
Osteomyelitis (10.3)	2	1
Other orthopaedic infection (6.9)	1	1
Line sepsis (6.9)	2	-
Pneumonia (10.3)	-	3
Lung abscess (3.4)	-	1
PUO (6.9)	-	2
?Tonsilitis (3.4)	1	-
<b>Location of treatment</b>		
Outpatient clinic	9	4
Home	6	10

Table 7.4a: All direct treatment costs of NIPiV study patients and percentage of all treatment cost represented by iv access cost

Patient ID	Drugacqiscost	Drugconsumcost	Ivaccessconsumcost	Stafftimecost	Alltreatcost	Treatcost-ivaccess	%ivaccessofalltreatcost
1	137.52	4.65	0.92	5.83	148.92	148	0.62
2	833.6	6.35	3.68	7.5	851.13	847.45	0.43
3	68.76	4.05	0.92	5.83	79.56	78.64	1.16
4	2019.96	274.67	119.4	459.82	2873.85	2754.45	4.15
5	364.7	3.83		2.5	371.03	371.03	0.00
6	2292.4	14.86	122.53	30.82	2460.61	2338.08	4.98
7	260.5	3.22	0.92	1.67	266.31	265.39	0.36
8	114.6	5.56	2.76	14.99	137.91	135.15	2.00
9	208.4	1.32	1.84	24.99	236.55	234.71	0.78
10	277.16	2.93		30.82	310.91	310.91	0.00
11	320.88	43.72	3.68	77.47	445.75	442.07	0.83
12	573.1	3.32	2.76	54.96	634.16	631.4	0.44
13	885.7	4.99	3.68	84.97	979.34	975.66	0.38
14	104.2	0.49	0.92	10	115.61	114.69	0.90
15	34.38	1.25	0.92	20	56.55	55.63	1.63
16	618.84	22.98	191.66	61.64	895.12	703.46	21.41
17	3594.9	19.98	47.13	40.81	3702.82	3655.69	1.27
18	263.58	10.5	2.76	119.95	396.79	394.03	0.70
19	127.12	1.66	1.84	25	155.62	153.78	1.18
20	156.3	1	1.84	20	179.14	177.3	1.03
21	45.84	1.63	0.92	25	73.39	72.47	1.25
22	156.3	0.76	0.92	10	167.98	167.06	0.55
23	52.1	0.35	0.92	5.83	59.2	58.28	1.56
24	3230.2	20.59	48.06	36.65	3335.49	3287.44	1.44
25	260.5	1.09	2.76	30	294.35	291.59	0.94
26	68.76	2.42	1.84	35	108.02	106.18	1.70
27	22.92	1.12	0.92	15	39.96	39.04	2.30
28	45.84	1.7	1.84	25	74.38	72.54	2.47
29	80.22	3	1.84	40	125.06	123.22	1.47
Total		463.99	570.17	1322.07	19575.51	19005.34	

nb. IV access costs are not included for patients 5-10 as these patients had a Hickman line in situ which was used for drug administration purposes.

Table 7.4b: Comparison of NIVP study costs with alternative therapy as hospital inpatient

Patient ID	StudyDrugCost	AltHospTotDrugCost	StudyConsumableCost	AltHospTotConsumableCost	StudyA1StaffTime(Cost)	AltHospA1StaffTime(Cost)	StudyA1StaffTime(mn)	AltHospA1StaffTime(mn)	AltHospTotTime(Cost)	StudyA1Cost	AltHospA1Cost	Difference(Study-AltHosp)
1	137.52	128	4.86	14.72	5.83	5.83	160	35	28.64	146	169.36	-21.36
2	833.6	62.62	6.36	7.36	7.5	7.5	80	45	13.32	847.45	83.3	764.16
3	68.76	178	4.05	20.24	5.83	5.83	220	36	36.63	78.84	232.87	-154.23
4	2019.96	623.45	274.67	20.24	489.82	489.82	2760	2760	36.63	2754.45	523.45	2231
5	364.7	207.84	3.83	36.84	2.5	2.5	60	15	10	371.03	254.88	116.89
6	2282.4	2182.32	14.88	388.82	30.82	30.82	630	185	105.21	2338.08	2674.95	-338.27
7	280.5	62.62	3.22	7.36	1.87	1.87	80	10	13.32	285.98	83.3	182.08
8	114.6	302.1	5.96	78	14.99	14.99	300	90	50	135.15	430.1	-294.95
9	208.4	62.62	1.32	7.36	24.98	24.98	80	160	13.32	234.71	83.3	151.41
10	277.16	962.12	2.93	103.74	30.82	30.82	390	185	65	310.91	1120.86	-808.86
11	320.88	356.85	43.72	23.48	77.47	77.47	85	465	14.11	442.07	384.42	47.65
12	573.1	182.12	3.32	7.36	54.98	54.98	80	330	13.32	631.4	212.8	418.6
13	885.7	62.62	4.89	7.36	84.97	84.97	80	510	13.32	875.66	83.3	892.36
14	104.2	62.62	0.49	7.36	10	10	80	60	13.32	114.89	83.3	31.58
15	34.38	62.62	1.25	7.36	20	20	80	120	13.32	55.63	83.3	-27.87
16	618.84	888.72	22.98	77.28	81.64	81.64	840	140	140	703.46	1106	-402.64
17	3594.9	462.84	18.98	77.28	40.81	40.81	245	245	1106	2655.69	462.84	3192.85
18	263.58	126.38	10.5	66.24	118.95	118.95	720	720	118.88	394.03	312.48	81.55
19	127.12	62.62	1.86	7.36	25	25	80	150	13.32	153.78	83.3	70.48
20	166.3	62.62	1	7.36	20	20	80	120	13.32	177.3	83.3	94
21	45.84	62.62	1.83	7.36	25	25	80	150	13.32	72.47	83.3	-10.63
22	156.3	62.62	0.76	7.36	10	10	80	6	13.32	167.06	83.3	83.76
23	52.1	12.34	0.35	3.88	5.83	5.83	40	35	6.66	58.28	22.88	35.6
24	3230.2	2355.57	20.59	388.82	36.65	36.65	630	220	105.21	3287.44	2847.6	439.84
25	260.5	62.62	1.09	7.36	30	30	80	180	13.32	291.59	83.3	208.29
26	68.76	165.24	2.42	33.12	35	35	360	210	60	106.18	258.36	-152.18
27	22.82	62.62	1.12	7.36	15	15	80	80	13.32	38.04	83.3	-44.26
28	45.84	63.48	1.7	6.52	25	25	160	150	10	72.54	79	-8.46
29	80.22	183.8	3	36.8	40	40	400	240	66.6	123.22	287	-163.78
total	17219.28	10030.38	483.99	1362.96	1322.07	1322.07	5935	7881	989.1	19005.34	12388.45	6616.89

Table 7.5a: Comparison of NIPV study costs with alternative therapy as Hospital inpatient for all patients except orthopaedic infection patients

Patient ID	StudyDrugCost	AltHospTotDrugCost	StudyConsumableCost	AltHospTotConsumCost	StudyAlIstaffTime(cost)	AltHospTotIstaffTime(cost)	StudyAlIstaffTime(min)	AltHospTotIstaffTime(min)	AltHospTotITime(cost)	StudyAlITime(cost)	AltTherAlITime(cost)	Difference(Study-AltTher)
1	137.52	128	14.72	5.83	160	35	26.64	169.36	148	83.3	-21.36	
2	833.6	62.62	7.36	7.5	80	45	13.32	847.45	847.45	83.3	764.15	
3	68.76	176	20.24	5.83	220	35	36.63	232.87	79.64	232.87	-154.23	
5	207.84	32.62	36.84	2.5	60	15	10	371.03	371.03	254.68	116.35	
7	260.5	302.1	7.36	1.67	80	10	13.32	285.39	285.39	83.3	162.09	
8	114.6	302.1	7.36	14.99	300	90	50	135.15	135.15	430.1	-294.95	
9	208.4	62.62	7.36	24.99	80	150	13.32	234.71	234.71	83.3	151.41	
10	277.16	952.12	103.74	30.82	390	185	65	1120.86	310.91	1120.86	-809.95	
11	320.88	356.85	43.72	77.47	85	465	14.11	394.42	442.07	394.42	-47.65	
12	573.1	192.12	7.36	54.98	80	330	13.32	212.8	631.4	212.8	-418.6	
13	885.7	62.62	4.89	84.97	80	610	13.32	975.66	975.66	83.3	892.36	
14	104.2	62.62	7.36	10	80	60	13.32	114.89	114.89	83.3	31.39	
15	34.35	62.62	7.36	20	80	120	13.32	56.63	56.63	83.3	-27.67	
18	263.58	126.36	66.24	119.95	720	720	119.88	312.48	394.03	312.48	81.55	
19	127.12	62.62	7.36	25	80	150	13.32	153.78	153.78	83.3	70.48	
20	156.3	62.62	7.36	1	80	120	13.32	177.3	177.3	83.3	94	
21	46.84	62.62	7.36	25	80	150	13.32	72.47	72.47	83.3	-10.83	
22	156.3	62.62	7.36	10	80	6	13.32	167.06	167.06	83.3	83.76	
23	52.1	12.34	3.68	5.83	80	6	6.86	56.28	56.28	22.88	35.8	
25	260.5	62.62	7.36	30	80	180	13.32	291.59	291.59	83.3	208.29	
26	88.76	165.24	33.12	35	360	210	80	106.18	106.18	253.36	-152.18	
27	22.92	62.62	7.36	15	80	90	13.32	39.04	39.04	83.3	-44.26	
28	45.84	63.48	5.52	1.7	60	150	10	72.54	72.54	79	-6.46	
29	80.22	183.6	36.6	40	400	240	66.6	123.22	123.22	287	-163.78	
Total	5462.98	3617.49	515.04	692.33	3835	4101	638.68	4774.21	6266.22	4774.21	1482.01	
average	227.62	150.73	21.59	28.65	159.79	170.88	26.61	193.83	261.09	193.83	62.17	

Table 7.5b: Comparison of NIV study costs with Alternative therapy as hospital inpatient for orthopaedic patients

Patient ID	StudyDrugCost	AltHospTotDrugCost	StudyConsumableCost	AltHospTotConsCost	StudyAlstafftime(cost)	AltHospTotTime(min)	StudyAlstafftime(min)	AltHospTotTime(min)	StudyAllCost	AltHospAllCost	Difference(Study-AltHosp)
6	2292.4	2182.32	14.86	386.82	30.82	630	185	105.21	2632.08	2674.35	-395.27
4	2019.86	523.45	274.87	77.28	459.82	840	2760	140	2754.45	523.45	2231
16	618.84	888.72	22.86	77.28	61.84	840	370	140	703.46	1108	-402.84
17	3594.9	482.84	19.89	386.82	40.81	630	245	105.21	3653.69	482.84	3182.85
24	3230.2	2355.57	20.59	850.92	36.85	2100	220	350.42	3287.44	2847.6	439.84
Total	11756.3	6412.9	353.09	283.64	628.74	700.00	3780	116.81	12739.12	7614.24	5124.88
average	2351.26	1282.58	70.62	283.64	125.95	700.00	756.00	116.81	2547.82	1522.85	1024.98

Table 7.6: Comparison of costs of patients treated with teicoplanin who could have received ceftriaxone during NPIV study

Patient ID	TeicoplaninAllDirectCosts	CeftriaxoneAllDirectCosts	Diff(Teicoplanin-Ceftriaxone)
2	847.45	197.21	650.24
5	371.03	86.55	284.48
6	2338.08	549.92	1788.16
7	265.39	62.19	203.2
9	234.71	72.15	162.56
12	631.4	184.36	447.04
13	975.66	284.78	690.88
14	114.69	21.95	92.74
19	153.78	72.5	81.28
20	177.3	55.38	121.92
22	167.06	45.14	121.92
23	58.28	17.64	40.64
25	291.59	88.39	203.2
<b>total</b>	<b>6626.42</b>	<b>1738.16</b>	<b>4888.26</b>
<b>average</b>	<b>509.72</b>	<b>133.70</b>	<b>376.02</b>

Table 7.7: NIPIV study costs calculated on the basis that patients were treated where possible with ceftriaxone and compared with hypothetical hospital inpatient costs.

Patient				
ID	Allstudycosts(ceftriax)	AltTherAllCosts	Diff(Study-AltTher)	
1	148	169.36	-21.36	
2	197.21	83.3	113.91	
3	78.64	232.87	-154.23	
4	2754.45	523.45	2231	
5	86.55	254.68	-168.13	
6	549.92	2674.35	-2124.43	
7	62.19	83.3	-21.11	
8	135.15	430.1	-294.95	
9	72.15	83.3	-11.15	
10	310.91	1120.86	-809.95	
11	442.07	394.42	47.65	
12	184.36	83.3	101.06	
13	284.78	212.8	71.98	
14	21.95	83.3	-61.35	
15	55.63	83.3	-27.67	
16	703.46	1106	-402.54	
17*	3655.69	462.84	3192.85	
18	394.03	312.48	81.55	
19	72.5	83.3	-10.8	
20	55.38	83.3	-27.92	
21	72.47	83.3	-10.83	
22	45.14	83.3	-38.16	
23	17.64	22.68	-5.04	
24*	3287.44	2847.6	439.84	
25	88.39	83.3	5.09	
26	106.18	258.36	-152.18	
27	39.04	83.3	-44.26	
28	72.54	79	-6.46	
29	123.22	287	-163.78	
total	14117.08	12388.45	1728.63	
average	486.80	427.19	59.61	

\* suitable only for treatment with teicoplanin

Table 7.8a: NIPIV study costs calculated on the basis that patients were treated where possible with ceftriaxone and compared with hypothetical hospital inpatient costs but excluding all orthopaedic infection patients

Patient ID	Allstudycosts(ceftriaxone)	AlternativeTherapyAllCosts	Diff(Study-AltTher)
1	148	169.36	-21.36
2	197.21	83.3	113.91
3	78.64	232.87	-154.23
5	86.55	254.68	-168.13
7	62.19	83.3	-21.11
8	135.15	430.1	-294.95
9	72.15	83.3	-11.15
10	310.91	1120.86	-809.95
11	442.07	394.42	47.65
12	184.36	83.3	101.06
13	284.78	212.8	71.98
14	21.95	83.3	-61.35
15	55.63	83.3	-27.67
18	394.03	312.48	81.55
19	72.5	83.3	-10.8
20	55.38	83.3	-27.92
21	72.47	83.3	-10.83
22	45.14	83.3	-38.16
23	17.64	22.68	-5.04
25	88.39	83.3	5.09
26	106.18	258.36	-152.18
27	39.04	83.3	-44.26
28	72.54	79	-6.46
29	123.22	287	-163.78
total	3166.12	4774.21	-1608.09
average	131.92	198.93	-67.00

Table 7.8b: NIPIV study costs for orthopaedic infection patients calculated on the basis that patients were treated with ceftriaxone where possible and compared with hypothetical hospital inpatient costs

Patient ID	Allstudycosts(ceftriaxone)	AlternativeTherapyAllCosts	Diff(Study-AltTher)
4	2754.45	523.45	2231
6	549.92	2674.35	-2124.43
16	703.46	1106	-402.54
17*	3655.69	462.84	3192.85
24*	3287.44	2847.6	439.84
<b>total</b>	<b>10950.96</b>	<b>7614.24</b>	<b>3336.72</b>
average	2190.192	1522.848	667.344

\* patients suitable only for treatment with teicoplanin

Table 7.9 Summary and comparison of the average direct treatment costs associated with NIPIV treatment and hospital inpatient treatment under different conditions.

Condition 1	Average direct treatment cost of NIPIV treatment  n=29  £655	Average direct treatment cost of hypothetical hospital inpatient treatment  n=29  £427	Cost difference  £228 (favours hospital treatment)
Condition 2	Average direct treatment cost of NIPIV treatment minus orthopaedic patients  n=24  £261	Average direct treatment cost of hypothetical hospital inpatient treatment minus orthopaedic patients  n=24  £199	£62 (favours hospital treatment)
Condition 3	Average direct treatment cost of NIPIV treatment for orthopaedic patients  n=5  £2,548	Average direct treatment cost of hypothetical hospital inpatient treatment for orthopaedic patients  n=5  £1,523	£1,025 (favours hospital treatment)
Condition 4	Average direct treatment cost of NIPIV treatment using ceftriaxone where possible  n=29  £486	Average direct treatment cost of hypothetical hospital inpatient treatment  n=29  £427	£60 (favours hospital treatment)

cont Table 7.9

Summary and comparison of the average direct treatment costs associated with NIPIV treatment and hospital inpatient treatment under different conditions.

Condition 5	<p>Average direct treatment cost of NIPIV using ceftriaxone where possible minus orthopaedic patients</p> <p>n=24</p> <p>£132</p>	<p>Average direct treatment cost of hypothetical hospital inpatient treatment minus orthopaedic patients</p> <p>n=24</p> <p>£199</p>	<p>Cost difference</p> <p>£67 (favours NIPIV treatment)</p>
Condition 6	<p>Average direct treatment cost of NIPIV using ceftriaxone where possible for orthopaedic patients</p> <p>n=5</p> <p>£2,190</p>	<p>Average direct treatment cost of hypothetical hospital inpatient treatment</p> <p>n=5</p> <p>£1,523</p>	<p>£667 (favours hospital treatment)</p>

**Table 7.10 Bed day capacity of IDU 1994**

	<b>No of beds</b>	<b>Bed days*</b>
<b>Ward 1</b>	<b>10</b>	<b>3,650</b>
<b>Ward 9E</b>	<b>22</b>	<b>8,030</b>
<b>Ward 9W</b>	<b>22</b>	<b>8,030</b>
<b>Total</b>	<b>54</b>	<b>19,710</b>

\* Bed days = No of beds x 365

Table 7.11: Transportation mileage and costs

Patient ID	Total mileage - own transport	Reimbursement cost (£)	Total taxi cost (£)
1	34	5.44	
2	120	19.2	
3	14	2.24	366.33
4			
5	14	2.24	
6			126
7	60	9.6	
8	12	1.92	
9	24	3.84	
10	84	13.44	
11	56	8.96	
12			52.4
13			60.7
14	4	0.64	
15			54
16	60	9.6	
17			510
18			102.5
19			12
20			13.8
21			19.8
22			25.2
23	4	0.64	
24			63
25	150	24	
26			105
27	8	1.28	
28	16	2.56	
29			88
total	660	105.6	1598.73

**Table 7.12 Patient perceived benefits of NIPIV treatment**  
**n=29, 60 responses**

<b>Perceived benefit</b>	<b>% expression</b>
<b>Freedom of being at home e.g. cook, shopping, sleep in own bed, etc.</b>	<b>79</b>
<b>Less stressful</b>	<b>38</b>
<b>Can return to work/deal with personal matters</b>	<b>31</b>
<b>Less family disruption</b>	<b>31</b>
<b>Increase social contact</b>	<b>21</b>

**Table 7.13 Concerns about NIPIV treatment expressed by patients and relatives**

<b><u>Nature of patient expressed concern</u></b>	<b><u>Nature of relative expressed concern</u></b>
<ul style="list-style-type: none"> <li>◦ Feels safer in hospital but self rationalised that this is because this form of treatment is a new idea</li> </ul>	<ul style="list-style-type: none"> <li>◦ Mother (x2) concerned about the level of care given on the NIPIV programme might not be the same in hospital</li> </ul>
<ul style="list-style-type: none"> <li>◦ Could envisage difficulties arranging for children to be cared for</li> </ul>	<ul style="list-style-type: none"> <li>◦ Wife thought that better treatment would be given in hospital</li> </ul>
<ul style="list-style-type: none"> <li>◦ Didn't like the idea of having an iv access in situ at home</li> </ul>	<ul style="list-style-type: none"> <li>◦ Wife needed reassurance that it was OK for her husband to go home with an infection</li> </ul>

**Table 7.14 Results of 'End of NIPIV Study' questionnaire n=26**

<u>Question</u>	<u>Replied Yes (%)</u>
Did you encounter any problem?	8 (33)
Would you repeat this form of therapy?	24 (92)
Did this form of therapy improve your quality of life?	24 (92)
Did this form of therapy allow you more control of your treatment?	18 (69)
Did this form of therapy cause you any 'out of pocket' expenses?	5 (19%)

**Table 7.15 Summary of results from question 4 from 'End of NIPIV Study' questionnaire, 'Could you give examples of the sort of things you were able to do which you would not have been able to do had you stayed in hospital? n=26, 60 responses**

<u>Example</u>	<u>% expression</u>
Freedom of being at home e.g. cook, shopping, sleep in own bed, etc.	85
Less stressful	19
Can return to work/deal with personal matters	62
Less family disruption	38
Increase social contact	27

**Table 7.16 Summary of key points from patient focus discussion group (n-9) of NIPIV therapy provided by experts from Bradford Management Centre.**

- **Reaction to the NIPIV service was favourable, the principal benefits being the ability to recuperate at home and to go back to work if so desired.**
- **The orientation about the service was effective.**
- **The service was perceived positively by all respondents.**
- **GPs had limited awareness and knowledge of the service.**
- **No-one said that the family/carers had expressed a concern about the treatment.**
- **Several ways were suggested to make the service even better. these included:**
  - a specific location for the service**
  - appointments**
  - a single named contact person**
  - creating greater awareness amongst GPs.**



Table 7.18 Organisational options for a NPIV service and GP response

Option	NPIV therapy in the community	In favour	Not in favour	Need more information
A	Cost of drugs - hospital Responsibility of patient - hospital	34	2	2
B	Cost of drugs - GP Responsibility of patient - hospital	5	25	7
C	Cost of drugs - GP Responsibility of patient - shared care	4	19	12

## Chapter 8

### 8. Summary and Conclusions

The work in this thesis sets out to examine whether economic evaluation of selected antimicrobial usage in the secondary care sector can influence decision making and lead to more efficient resource allocation.

Chapter 2 looked at the methods used by different governments to control national drug expenditure as a whole. Although a highly visible component of healthcare spends, the drug budget only represents some 10-12% of the total. The methods directed at controlling drug expenditure are reflective of the system of healthcare financing in different countries. UK government controls have been of a cost-containment nature primarily directed at the primary care sector even though drug usage in the secondary care sector can have a substantial impact on the primary sector. The government has vired responsibility for the control of their own drug costs to the secondary care sector. An issue raised is that although the Government recognises that economic evaluation has a role to play in ensuring cost-effective healthcare resource allocation, there is a lack of an infra-structure to support such evaluation.

Chapter 3 looked at the methods used to control drug expenditure in the secondary care setting. The drug budget has, traditionally, been viewed in isolation from other cost centres within the sector. Formularies have been an important cornerstone in containing costs but the manner in which they have been constructed may well impact on other healthcare utilisation. It is important therefore that caution is exercised in the limitation of formularies in order that the quality of healthcare is maintained and patient outcome is not compromised.

To guarantee that cost-effective drugs are chosen for use there is a need to integrate knowledge of patient outcome into the drug selection procedure i.e. a need exists for pharmacoeconomic evaluation. The largest, single, therapeutic group of drugs responsible for up to 30% of a hospital's drug budget is the antimicrobials. It should be important therefore, to those responsible for resource allocation, that these drugs are used in the most cost-effective manner.

Chapter 4 clarifies the issues why the selection and use of antibiotics are in need of further evaluation and how this can be taken forward.

Chapter 5 examines the various qualities and characteristics an outcome measure can possess and how they may be used in the comparative economic assessment of antimicrobial treatment.

Conventional evaluation of antimicrobial therapy has relied on a wide variety of narrow spectrum, unidimensional, patient and process outcome measures and most financial appraisal has tended to focus on drug acquisition costs rather than taking a holistic view of all treatment costs. Consequently, the value of various therapies in relation to each other remains largely unknown. What is needed is some form of easily applied measurement which responds to treatment effect. As discussed in chapter 5 the ideal measure would be a single index drawn together from those dimensions which affect all the costs and benefits of a therapy. Much research remains to be carried out before this ideal is reached.

The two studies undertaken for this thesis have attempted to demonstrate how the combination of the costs of treatment with clinical and process measures of outcome can be used to avoid resource wastage.

Chapter 6 reports and discusses the first study, which was an audit of aminoglycoside utilisation and the general antibiotic management of gram-negative bacteraemia. The first part of this study involved the systematic collection of clinical practice data, which were then analysed for appropriateness of care. This was carried out by comparing the observed practice with published evidence based care. Analysis showed the aminoglycosides to be poorly managed and associated with several opportunity costs. Three readily measurable indicators of adverse outcome of hospital antibiotic therapy associated with marked increases in hospital treatment costs were characterised. These were: -

- Change to an alternative iv drug regimen,
- Retreatment with antibiotics in hospital,
- Readmission with infection.

In addition, another area of wastage was the excessive use of the iv route for antibiotic administration.

The second phase of this study was a detailed feedback of these findings to selected clinicians. In addition to heightening clinicians awareness to the management problems and associated cost of the aminoglycosides, this informational feedback was

also an attempt to persuade prescribers to reduce the overall use of iv antibiotics by taking advantage of oral administration thereby limiting resource wastage. Data were collected pre- and post informational feedback to determine what impact, if any, the intervention had on prescribing behaviour. Statistical analysis appeared to show a significant reduction in the usage of the iv route, however, the method for this phase of the study was seriously flawed due to the presence of several confounding variables and the lack of a control group (fully discussed in Chapter 6). Consequently, it was not possible to undisputedly infer that the informational feedback was responsible for the decreased frequency of use of the iv route. However, for one particular disease state, epididymo-orchitis, a dedicated change in treatment did immediately follow the intervention. It can be argued that this particular change in prescribing behaviour was as a direct result of the informational feedback because the treatment protocol proposed at feedback was both more effective and less expensive than that used historically.

Despite the presence of methodological flaws in the second phase of this study the overall findings have led to several local initiatives which minimised the opportunity costs identified. These initiatives include;

- The development of a policy for once daily administration of aminoglycosides.
- Publication and dissemination of treatment guidelines for suspected sepsis and consultant review of patients with bacteraemia in the Directorates of Medicine and Surgery.
- Strategic changes in the location of patients with epididymo-orchitis from acute surgical beds in the Urology unit to acute medical care beds in the Infectious Diseases unit (following the results of the study routine treatment of these patients is now by the oral route).
- Implementation of guidelines and standards for the use of parenteral and oral antibiotics in the Directorate of Medicine.

The presence of confounding variables (both known and unknown) is a major problem with studies which are of an observational nature and which do not have a control group. A published study which serves to highlight this particular problem is one by Horn *et al* (1996). This observational study of cost containment strategies examined

drug usage for five disease states in six HMO's scattered across the US. The results led workers to conclude '*In the case of limited formularies, we found the unintended consequence of increased utilisation of healthcare resources*'. The inference being that the formularies scrutinised were performing in a paradoxical manner, i.e. as drug formulary restriction increased so did other healthcare resource utilisation. However, this study was methodologically flawed by its uncontrolled, observational nature. The heterogeneity of HMO's and the type of patient directed to them are well recognised and as such it is difficult to control for these differences, as a result unidentified confounding variables may exist within the populations observed. Other criticisms (Ross-Degnan *et al*, 1996) levelled at this work include the use of only one observation time period and the fact that clinical practice varies so widely throughout the US. It is possible therefore that there may be one or more other explanations for the increase in healthcare resource utilisation observed in this study other than the presence of a restrictive formulary. In a rejoinder to the criticisms levelled at their work, Horn (1996) agreed that the data generated did only justify cautious inference that the presence of a restrictive formulary in an HMO may lead to an increase in other healthcare resources.

If the aminoglycoside/bacteraemia study reported in Chapter 6 were to be repeated it would benefit from several modifications to the design, primarily in Phase II.

Although the prospective clinical data collected in the first phase of the study could be limited to that which was required to answer questions set *a priori*. A mistake that was made in the phase I data collection set was the tendency to over collect data '*because it may come in useful or prove interesting*'. An example of this was the collection of daily TPR measurements for each patient in the study when it was only necessary to have measurements for the first and last day the patient was on the study.

Phase II was methodologically flawed because of the presence of several confounding variables. These variables could be controlled for in the following manner:-

- 1) The timing of prescribing data collection pre- and post intervention should be carefully planned to avoid any change in medical staff during this time period i.e. a static study population is necessary.
- 2) Ensure that all aspects of informational feedback reach all members of medical staff who have input to the prescribing process.

- 3) Control for patient case-mix pre- and post informational feedback.
- 4) Include a matched control group for the study population (i.e. the prescribers targeted for informational feedback), this would involve measuring the prescribing habits of clinicians not given informational feedback, on similar wards with a similar case-mix of patients. Ideally the matched control group would be in another hospital, if the control group were within the same unit or hospital as the study population it is possible that the study population could speak to the controls post informational feedback thereby introducing a bias.

Sponsorship for this study came from the commercial sector. In an effort to avoid the problem of bias from this source, mechanisms appropriate to the study proposed by Hillman *et al* (1991) were put in place prior to commencement. These workers (Hillman *et al*, 1991) discussed the reasons, how and why, bias occurs. In this paper they make 8 recommendations to limit bias introduced by commercial sponsorship. The recommendations relate specifically to economic evaluation type studies, in summary these are;

First, written agreement between the sponsor and investigator(s) should be in the form of a research grant and should stipulate that the researchers publish findings regardless of their nature.

Second, the selection of alternatives to be compared in an economic analysis should be based on their clinical relevance and at a minimum meet FDA requirements for comparators in controlled trials.

Third, if a study is designed by the sponsor, the investigator should be allowed to include additional costs, economic perspectives and comparator drugs as they deem necessary. If the funding group constrains the investigator this should be made explicit in the reporting of results.

Fourth, if a project is funded by instalment, results should be withheld from the sponsor until publication of results are guaranteed and funded.

Fifth, investigators should ensure that results of an economic analysis are not influenced in the favour of the sponsoring company. Results should be supported by sensitivity analyses.

Sixth, investigators should publish valid results regardless of their promotional value to the sponsoring company.

Seventh, researchers who receive a grant should not act as consultants on projects related to the study medication during the active period of the grant.

Finally, researchers should take all reasonable steps to ensure that the level of funding permits methodologically sound, clinically relevant results with enough statistical power to detect important differences among the alternatives compared.

The implementation of these mechanisms would appear to have been successful as no apparent bias was detected. To a large extent this lack of bias related to the nature of the study i.e. specific drugs were not being compared against each other.

The second study undertaken for this thesis is reported and discussed in chapter 7. This study examined the feasibility of treating patients with intravenous antibiotics on an ambulatory basis and also compared the costs and benefits of such a programme with traditional, hospital inpatient treatment. The perspective of both patient and provider were factored into the study. A not dissimilar study has recently been reported by Kayley *et al* (1996), although, two important differences exist between the two studies. Kayley *et al* (1996) specifically targeted patients with AIDS who required antibiotic treatment greater than two weeks, and secondly, no assessment of treatment costs were made. The feasibility study reported in this thesis, a) did not target any specific patient group, essentially patients (meeting enrolment criteria) with or without pre-existing disease were enrolled onto the study with any infection expected to require more than 5 days treatment, and b) the economic viability of non-inpatient intravenous treatment (NIPIV) was explored.

Both this study and the Kayley *et al* (1996) study concluded that NIPIV care is feasible and preferred to in-hospital treatment by patients. Kayley *et al* (1996) reported no serious complications, however, the issue of safety was raised in the feasibility study reported in this thesis by two patients experiencing a serious adverse event. As a result the notion of what constitutes 'acceptable risk' deserves exploration in the further development of NIPIV care. Another contrast between the two studies is brought about by economic evaluation. Kayley *et al* (1996) concluded, without any hard evidence, that this form of therapy would probably benefit NHS budgets. The

study in this thesis, which incorporated a comparison of direct, variable costs, demonstrated that this assumption could well be ill-founded. Initial inspection of the direct, variable NIPIV treatment costs appeared higher than the comparative treatment costs in hospital, therefore making NIPIV care appear economically unattractive. Despite this, cost-effective aspects of NIPIV treatment were identified by carrying out a sensitivity analysis. NIPIV care was found to be cost-effective provided high acquisition cost drugs were not used and treatment of long duration infection was excluded. During the NIPIV feasibility study it was calculated that bed day consumption was reduced by 4% which equated to 'hotel cost savings' of £166,516. However, the point has been made (Chapter 7) that unless fixed costs were decreased, which is unlikely with a negligible bed day consumption of 4%, the 'hotel cost savings' would be illusory.

As stated in the discussion of chapter 7, further development of a quality NIPIV service would require establishment of an infrastructure for support and provision. However, barriers to the implementation of NIPIV therapy in the acute care sector, currently exist at resource management level. In the US there is a financial incentive to the Hospital to get people home quicker. This incentive does not exist in the NHS as explained by Lawson (1993). Currently, patient stay in hospital is calculated on average cost/day (i.e. total cost of treatment (most of which occurs in the first few days of hospitalisation) divided by number of days in hospital) rather than on cost/successful outcome. This is an inadequate way of evaluating the cost of treatment as it doesn't relate to efficiency. If length of stay is reduced, although there is a lower cost/successful outcome the average cost/day is increased. In the pursuance of efficiency a move away from using the term average cost/day to cost/successful outcome is needed, it is only then that incentives will exist to explore other non-inpatient modalities such as NIPIV care.

One of the major drawbacks of this feasibility study was the small number of patients recruited. If the study were repeated it would benefit by expanding the demand for the service. A greater database would provide further information concerning safety, patient preference, patient outcome etc. This could be moved forward by changing the patient selection criteria to include those patients who require less than 5 days antibiotic treatment, recruiting patients who require antibiotics from other units within

the hospital and/or incorporating other conditions amenable to NIPIV therapy, such as congestive cardiac failure, peripheral vascular disease and some long term AIDS care. Another drawback to this feasibility study was the bias introduced by the commercial sponsorship despite preventative mechanisms suggested by Hillman *et al* (1991) being put in place. Although the antibiotics chosen for use in the study would have remained the same, regardless of the source of funding (selection was based on their antimicrobial spectra and their once daily dosing requirement), a sponsorship agreement predetermined that both antibiotics be employed equally. A sensitivity analysis was conducted to examine the impact of this bias, which has been reported fully in Chapter 7. An improvement to this study therefore would be non-commercial sponsorship such that antibiotic utilisation could be left entirely to the discretion of the prescriber.

An ideal feasibility study for NIPIV care would therefore be one which:

- a) had a large patient population,
- b) was randomised between NIPIV care and in-hospital care,
- c) was controlled,
- d) compared a wide variety of antibiotics, and
- e) was non-commercially funded.

In summary, the work undertaken for this thesis has provided a small degree of evidence that basic economic evaluation can be used to inform decision making and indicate where efficient resource allocation lies, however, as discussed, there are many improvements which could be made to the design of both studies should they be repeated. Both studies were sponsored by the commercial sector and although no apparent bias due to this source occurred in the first study, some bias was introduced into the feasibility study of NIPIV care. This serves to highlight a major problem that can occur with commercial sponsorship. The ideal situation would be if this type of Health Services Research could be funded from non-commercial sources.

Published evidence of hospitals using economic evaluation is thin on the ground. One hospital (Delaney, 1996), however, has recently reported their use of pharmacoeconomic evaluation to justify the use of an expensive acquisition cost drug (enoxaprin). Without the pharmacoeconomic evaluation the drug would almost

certainly have been excluded from use within the hospital as it was estimated that raw drug cost alone per annum would have increased the drug budget by almost 5% (IR£21,500). Nevertheless, because enoxaprin reduces the incidence of post-operative deep vein thrombosis from 20% to 6%, annual treatment costs of IR£96,350 for this adverse event can be averted, as a result this cost avoidance more than offsets the increase in drug budget.

Currently, many drugs, antibiotics included, are used without knowledge of how they impact on the utilisation of other healthcare resources, as a consequence this indicates that there is a place for the use of economic evaluation in the decision making process of resource allocation. The proportion of any national healthcare spend accounted for by antibiotics is relatively small, in 1996 this was in the region of 6-7% for England and Scotland. It would be unrealistic therefore to imagine that the economic evaluation of antimicrobial use would become a specific target within a national strategy to evaluate healthcare. It will remain therefore, in the interests of those parties that antimicrobial use has the greatest impact on, to ensure they are used in the most efficient manner.

Purchasers of healthcare 'need' (in the economic sense of 'capacity to benefit') economic information on clinical practice such that resources can be allocated in the most efficient manner. Unfortunately a two fold problem exists; firstly the information needs to be in existence and secondly, the information needs to be readily accessible. A solution to this problem lies with government sponsored clinical audit and the National Register of Research recently commissioned by the NHS Executive. Clinical audit provides a forum for gathering economic information, the results of which should be stored on the aforementioned Register. It is estimated that the NHS Executive will have spent £834million by the end of the century (Anon., 1996b) on clinical audit project's yet finds it difficult to assess the benefit of spending this money. If a condition for funding of future clinical audit project's be that some form of economic assessment is incorporated into the project, service provision cost and benefit data, could be assembled. Information of this nature could then be used to assist in the efficient allocation of resources.

Although the National Register of Research is intended to compile a complete picture of all applied health research it only incorporates research projects funded by the

NHS, major charities and the MRC. It does not encompass that research undertaken funded by other means, for example, the commercial sector. Unless this is addressed in some manner a complete picture cannot be achieved and useful information may not be made nationally available.

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**Chronic Health Evaluation**

Indicate whether any of the following chronic conditions were evident prior to this hospital admission:

**Liver Disease**

Biopsy proven cirrhosis and documented portal hypertension	Yes/No
Episodes of past upper GI bleeding attributed to portal hypertension	Yes/No
Prior episodes of hepatic failure/encephalopathy/coma	Yes/No

**Cardiovascular disease**

Angina or symptoms at rest or minimal exertion eg getting dresses	Yes/No
---	--------

**Respiratory disease**

Chronic restrictive, obstructive or vascular disease resulting in severe exercise restriction i.e. unable to climb stairs or perform household duties	Yes/No
---	--------

Documented chronic hypoxia, hypercapnia, secondary polycythaemia, severe pulmonary hypertension (>40mmHg) or respiratory dependency	Yes/No
---	--------

**Immuno-compromised state**

Indicate if, prior to hospital admission, the patient had:

- |   |        |
|---|--------|
| a) Any therapy that suppresses resistance to infection e.g. immuno-suppression, chemotherapy, radiation, long term low dose steroids during 30 days prior to admission to hospital or recent high dose steroids (>15mg/kg for 5 days or more) | Yes/No |
| b) Evidence of a disease that is sufficiently advanced to suppress resistance to infection e.g. leukaemia, lymphoma, AIDS, documented diffuse metastatic cancer   | Yes/No |

**Site of Infection**

Sample	Date taken	Result and sensitivities

Operation within 48hr? Yes/No

Specify operation:

Invasive procedure within 48hr? Yes/No

Urinary catheterisation Yes/No

Intravenous cannula Yes/No

Long iv line Yes/No

Cardiac pacemaker Yes/No

Swan Ganz/other art catheter Yes/No

Peritoneal dialysis Yes/No

Other (specify) Yes/No

No detectable primary site of infection Yes/No





**Clinical progress and treatment changes**

Date: Day of week: Day of treatment:							
<b>Clinical Progress</b> Temp (highest): Frequency of observation:  Pulse (highest): Frequency of observation:  MAP (lowest): Frequency of observation:  Systolic bp:							
<b>Changes in treatment</b> Drug: By whom?: Reason:  Drug: By whom?: Reason:  Drug: By whom?: Reason:  Drug: By whom?: Reason:  Drug: By whom?: Reason:							

## Appendix B

### GP Letter and Proforma

Dear Dr

**Re: Aminoglycoside/Septicaemia study 1990-1992**

We are carrying out a study involving those patients within Dundee Hospitals who have:

- a) Been prescribed an aminoglycoside, or
- b) Have been septicaemic.

Your patient (patient name and DoB) has been entered into this study. we would be grateful if you could supply us with information regarding all antibiotic prescriptions (if any) that (patient name) has had in the three month period post dischrge (discharge date specified).

A pro-forma is enclosed with a self addressed envelope for return.

Many thanks,

Yours sincerely

Sharon E Parker  
Research Pharmacist

pp Dr PG Davey  
Infectious Diseases Consultant

**Aminoglycoside/Septicaemia study  
Three month follow-up Proforma**

Patient name:..... Date of Birth:.....

Patient ID No:.....

Date of discharge from.....Hospital:.....

Date	Antibiotic	Dose and frequency	Length of treatment	Indication

Other information if appropriate:

Please specify if no antibiotics prescribed within this period

Patient has died      Yes/No      If yes, Date of death.....

.....  
Signature of General Practitioner

## Appendix C

### Calculation of sepsis scores

Physiological assessment	Score
Maximum daily temperature (°C)	
37.5-38.4	1
38.5-39	2
>39	3
<36	3
Haematology	
haemoglobin (g/L)	
70-100	1
<70	2
white blood cells (x 10 <sup>9</sup> /L)	
10-30	1
>30	2
<3	3
platelets (x 10 <sup>9</sup> /L)	
100-150	1
<100	2
Biochemistry	
plasma albumin (g/L)	
<25	2
plasma bilirubin (umol/L)	
>25	2
glucose (mmol/L)	
<10	2
creatinine (umol/L)	
<20	2
>140	3
Underlying condition	
diabetes	2
hepatic disease	3
renal disease	3
Site of infection	
urinary tract	
lower	1
upper	2
postoperative	add 4
respiratory tract	
oropharyngeal	1
bronchitis/bronchiectasis	2
pneumonia	4
hospital-acquired	add 3
septicaemia	
pyrexia of unknown origin	1
postprocedural	2
postoperative	3

**Appendix D**

## ***RATIONAL ANTIBIOTIC PRESCRIBING: THE RELATIVE ROLE OF INTRAVENOUS AND ORAL THERAPY***

*An audit of antibiotic prescribing in Tayside Hospitals between September 1990 and January 1991 revealed that, in a number of cases, intravenous therapy was administered to patients in whom the oral route was not compromised and in situations where a suitable oral agent was indicated. This Note examines the reasons for overuse of intravenous antibiotics, the advantages and disadvantages of this route and argues that, in many instances, oral therapy is often appropriate from the outset, or at least soon after i.v. therapy is initiated.*

### ***The Antibiotic Audit - Summary of Conclusions:***

- (i) The intravenous route is frequently used in cases where oral antibiotic therapy is appropriate.
- (ii) Early transfer from i.v. to oral antibiotic therapy is often possible in cases where the oral route is initially compromised.
- (iii) Failure to adequately assess the likely cause of infection leads to over-reliance on broad spectrum drugs, despite their disadvantages.

### ***Recommendations when initiating antibiotic therapy:***

- (i) Consider the likely infecting pathogen(s).
- (ii) Select an antibiotic regimen accordingly.
- (iii) Choose the route of administration, remembering that oral therapy is frequently appropriate.
- (iv) Monitor the patient's response and consider changing from i.v. therapy (if used initially) to oral therapy when possible.

### ***Intravenous antibiotic therapy***

Intravenous administration delivers a drug directly to the systemic circulation and therefore guarantees 100% bioavailability. It is reasonable to select this route routinely in an intensive care setting and for initial treatment of life-threatening infections.

***However intravenous drug therapy has certain disadvantages.***

Intravenous access is associated with a risk of local infection and the possibility therefore of septicaemia.

Many intravenous antibiotics produce irritation and thrombophlebitis at the injection site or tissue necrosis during extravasation. The final concentration and rate of administration may be critical and require careful manipulation.

Finally, intravenous antibiotic therapy is invariably more expensive than equivalent oral therapy (e.g. 10 times more in the case of ciprofloxacin, see text), and overuse of the i.v. route can add significantly to the drug budget.

In addition to the drug itself, the cost of personnel time involved in its preparation and administration, the use of consumables (giving sets, syringes, etc.) and possibly plasma monitoring too (e.g. gentamicin) must be taken into account. For example the audit revealed that the *"total cost" of antibiotic regimen which included an aminoglycoside (these drugs are rarely given alone) was increased by 50% by these "hidden" costs, despite the fact that gentamicin is a relatively inexpensive drug.*

A further consideration, in the case of the aminoglycosides, is the difficulty in calculating the real cost of treatment in the event of toxicity. From the audit, a few patients who developed acute renal failure incurred the, not inconsiderable, additional expense of haemodialysis as a result.

***In summary, the advantages of i.v. antibiotics are recognised in "intensive care" and acute severe infections where the oral route may be compromised. However, it must be stressed that, in many cases, oral therapy is possible from the outset or, if not, soon after i.v. therapy is started.***

### ***Oral antibiotic therapy***

Several studies have shown that oral antibiotics can be substituted for i.v. therapy, or indeed used in place of i.v. therapy, without loss of therapeutic efficacy. Many oral antibiotics are rapidly and extensively absorbed without removal during first pass (i.e. there is little or no presystemic elimination). The advantages in terms of convenience to both patients and personnel, without the inherent risks associated with i.v. access and the (usual) considerable increase in cost of i.v. therapy are obvious. This is particularly true in the case of *ciprofloxacin*, *metronidazole* and *Augmentin* (co-amoxiclav), see over.

**Ciprofloxacin**

Bioavailability is approximately 70%. However, food delays the rate, but not extent, of absorption which is also reduced by concurrent use of antacids.

Plasma concentrations are similar following a single oral dose of 500mg and a 30 minute i.v. infusion of 200mg.

Daily cost of i.v. and oral therapy is £48.00 and £3.00 respectively.

**Metronidazole**

The oral bioavailability is high. Peak plasma concentrations are similar for a one hour i.v. infusion and an equivalent oral dose.

Daily cost of i.v. and oral therapy is £14.34 and 70p respectively.

**Augmentin (co-amoxiclav)**

Unlike ampicillin, the bioavailability of amoxicillin is high (approximately 85%). The drug is minimally affected by first pass metabolism.

The usual dose is 500mg/100mg clavulanate, 8-hourly but up to 1g/200mg clavulanate, 6-hourly may be administered.

The addition of clavulanate does not alter bioavailability and clavulanate itself is well absorbed, achieving peak plasma concentrations within 40-60 minutes.

Daily cost of i.v. (1.2g 8-hourly) and oral therapy is £8.10 and £2.10 respectively.

*Therefore when antibiotic therapy is indicated, consider the following:*

1. What is the likely infecting pathogen(s)? Guidance is available in the Antibiotic Policy or, if not, seek further advice.
2. Is oral therapy possible and can the drug selected be administered by this route?
3. If the oral route is initially compromised, remember to transfer as soon as possible from the i.v. route to the oral route where suitable oral therapy exists.

Various criteria can be used to assess whether or not oral therapy is suitable:

- (i) *an oral drug is available,*
- (ii) *the oral route is no longer compromised,*
- (iii) *clinical improvement in the patient's condition is apparent,*
- (iv) *the patient's temperature is reducing,*
- (v) *there is no clear evidence of septic shock.*

4. Use the Data Sheet as a guide to dosage and route of administration.

This reflects the Product Licence but note that differences in drug dosage between the i.v. and oral routes may be apparent since dosage forms of a given drug may be separately licensed.

This is particularly true in the case of the beta-lactam antibiotics which have relatively poor bioavailability. For example, *cefuroxime sodium* injection and oral *cefuroxime axetil* tablets do not have identical licensed indications and are not necessarily interchangeable.

*Therefore when transferring from i.v. to oral antibiotic therapy (i) confirm that the oral form is licensed for the purpose intended and (ii) prescribe drugs using upper dose ranges as a guide.*

Some examples of antibiotics which may be considered by the i.v. and oral routes and their licensed dose ranges are included, below.

<i>Drug</i>	<i>i.v. dose</i>	<i>upper range oral dose</i>
<i>Augmentin (co-amoxiclav)</i>	1.2g (1g amoxicillin) 8-hourly	2 tablets (500mg amoxicillin) 8-hourly
<i>Ciprofloxacin</i>	200-400mg 12-hourly	500-750mg 12-hourly
<i>Metronidazole</i>	500mg 8-hourly	400mg (or 1g rectally) 8-hourly

*Does an alternative oral agent apply in the event that an antibiotic given initially by the i.v. route is unavailable in oral form or the Product Licence does not recognise the oral route for the given indication?*

It may indeed be possible to substitute oral therapy under these circumstances. Once again however, the need to review the infecting pathogen(s) and select a drug rationally using the Data Sheet as a guide to indication and dosage is stressed.

Examples in which an oral antibiotic may be considered as a replacement for initial i.v. therapy include:

*Ciprofloxacin* 750mg p.o. 12-hourly for *gentamicin* or *ceftazidime* in pseudomonas infections.

*Augmentin (Co-amoxiclav)* 2 tablets p.o. 8-hourly for *cefuroxime sodium* where *cefuroxime axetil* does not have a licensed indication e.g. intra-abdominal sepsis, bone and joint infection.

### ***Choice of antibiotic***

The Tayside audit also found inconsistency in the selection of an antibiotic or antibiotic combination for a given clinical situation. For this reason there was a tendency to use multiple drug regimen unnecessarily and broad spectrum antibiotics inappropriately.

Many infections which are frequently encountered can be readily linked with one or other common pathogens when antibiotic therapy, even empirically, may be suitably refined. It is often mistakenly assumed however that "broad spectrum" equates with "enhanced antibiotic potency" when in fact such agents are more likely to be associated with the emergence of multiple resistance and superinfection.

*Further advice may be available in the Antibiotic Policy or from other local guidelines. If not, contact Medical Microbiology or the Drug Information Service.*

**Appendix E**  
**Seminar Questionnaire**  
**Surgical**  
**Rational Antibiotic Prescribing**

Name.....

Ward.....

Please circle position held

JHO

SHO

Reg

Snr Ref

Consultant

1. Did you have the opportunity to read the Drug Information Note 'Rational Antibiotic Prescribing: The relative role of iv and oral therapy? Yes/No

2. Which of the following aspects of the presentation did you find of most interest, please choose one or more if you wish:-

- a) Aminoglycoside audit findings
- b) General antibiotic usage NW 9&10 audit data
- c) Other, please specify

3. Having listened to this presentation do you think your prescribing practice will be affected

Yes/No

If Yes, which aspect (s)?

4. Do you think this type of audit should be repeated on a regular basis

Yes/No

If Yes, how frequently?

If No, why not?

**Seminar Questionnaire**  
**Medical**  
**Rational Antibiotic Prescribing**

Name.....

Ward.....

Please circle position held

JHO

SHO

Reg

Snr Ref

Consultant

1. Did you have the opportunity to read the Drug Information Note 'Rational Antibiotic Prescribing: The relative role of iv and oral therapy? Yes/No

2. Which of the following aspects of the presentation did you find of most interest, please choose one or more if you wish:-

- a) All Tayside audit findings
- b) NW 5&6 audit data
- c) Costs of iv therapy
- d) Other, please specify

3. Having listened to this presentation do you think your prescribing practice will be affected

Yes/No

If Yes, which aspect (s)?

4. Do you think this type of audit should be repeated on a regular basis

Yes/No

If Yes, how frequently?

If No, why not?

**Seminar Questionnaire**  
**Urology**  
**Rational Antibiotic Prescribing**

Name.....

Ward.....

Please circle position held

JHO

SHO

Reg

Snr Ref

Consultant

1. Did you have the opportunity to read the Drug Information Note 'Rational Antibiotic Prescribing: The relative role of iv and oral therapy? Yes/No

2. Which of the following aspects of the presentation did you find of most interest, please choose one or more if you wish:-

a) General aminoglycoside audit findings

b) Epididymo-orchitis information

c) Cost data

d) Other, please specify

3. Having listened to this presentation do you think your prescribing practice will be affected

Yes/No

If Yes, which aspect (s)?

4. Do you think this type of audit should be repeated on a regular basis

Yes/No

If Yes, how frequently?

If No, why not?

**Appendix F**

**Phase II  
Septicaemia/Aminoglycoside Study  
Clinical Record Form**

Patient ID No:.....

Page 1

Patient Name:

Ward:

Unit No:

Dob:

Sex: M/F

Date of admission:

Date of discharge:

Consultant:

Weight:

Presenting complaint:

Diagnosis:

**Absorption**

Abnormal GI state:

Other:

**Administration**

Compromised oral route:

Compromised other routes:

Comprehension/compliance:

**Missed doses**

Date	Drug	Time	Reason

**Site of Infection**

Sample	Date taken	Result and sensitivities

Operation within 48hr? Yes/No

Specify operation:

Invasive procedure within 48hr? Yes/No

Urinary catheterisation Yes/No

Intravenous cannula Yes/No

Long iv line Yes/No

Cardiac pacemaker Yes/No

Swan Ganz/other art catheter Yes/No

Peritoneal dialysis Yes/No

Other (specify) Yes/No

No detectable primary site of infection Yes/No





## Appendix G

## *INFORMATION SHEET FOR PATIENTS ABOUT THE STUDY OF HOME ANTIBIOTIC THERAPY.*

### **What is this study?**

We are investigating the use of two antibiotics which have been successfully used to treat many types of infections worldwide. They are not new or experimental drugs. For nearly 10 years people with different infections in many parts of the world, especially the USA, have been treated successfully with these antibiotics at home. We want to repeat this experience in the UK.

### **Why should I take part?**

The infection that has led you to be admitted into hospital requires you to receive a course of intravenous (injectable) antibiotics given through a small plastic line (venflon) that lies in one of the veins in your arm. You would normally receive this type of treatment in hospital for a period of a few days or longer depending on your condition. Giving these antibiotics at home would allow you to get home more quickly.

### **Are the antibiotics safe?**

These antibiotics are safe (millions of patients have received them worldwide) and if you agree to take part, you will already have received at least one dose before you go home. The other advantage of these antibiotics is that they are easy to make up and are only given once daily.

### **For how long will I receive these antibiotics?**

Your course of antibiotics will last for 2 weeks.

### **What does saying yes involve?**

As these antibiotics are given by an injection you will have a venflon put into your arm while you are receiving the treatment. Your nurse and doctor will explain to you how they work and there will always be someone to contact if you experience any difficulties with either the venflon or the antibiotics.

If you agree to have home treatment you will return to the ward each day to receive your injection and to see one of the medical staff.

### **Will my medical care be different if I take part?**

Your overall care will not be affected by your participation in this study. We may reassure you that you will not be asked to participate in this study if we did not think that your medical condition was suitable. You may withdraw at any time without affecting your medical care. We will require your signed consent if you are willing to participate.

You will be closely supervised by the doctors at King's Cross Hospital throughout your treatment. You will be covered by the usual insurance against medical negligence from the Dundee Teaching Hospitals Trust.

NON-INPATIENT IV CARE STUDY  
INITIAL SCREENING - HOME IV THERAPY

Patient label

Study No.....

Antibiotic.....

1. Do you live alone or with a relative? Alone/Relative

If relative specify .....

2. Do you possess a phone? Yes/No

Phone no.....

If no, do you have access to a phone? Yes/No

Please specify .....

3. Have you ever had iv therapy before? Yes/No

4. Manual dexterity Full/Compromised

If compromised specify.....

5. What benefits do you think being treated as an outpatient gives you?  
.....  
.....

6. Do you have any concerns regarding iv therapy at home? Yes/No

If yes, specify.....

7. Have you discussed your form of treatment with other family members?..... Yes/No

If Yes what relationship?.....

Was their response positive? Yes/No

If No Why not?.....

8. Which area/space do you plan to use for carrying out the injections?.....

9. Who will administer the antibiotic? Self/Relative

If relative specify.....

10. Will you be able to return for a review visit every 3-4 days Yes/No

11. Would you like transport arranging for you Yes/No

GP contacted      date phone call..... date letter sent.....

NON-INPATIENT IV CARE STUDY  
INITIAL SCREENING - OUTPATIENT

Patient label

Study No.....

Antibiotic.....

1. Do you live alone or with a relative? Alone/Relative

If relative specify .....

2. Do you possess a phone? Yes/No

Phone no.....

If no, do you have access to a phone? Yes/No

Please specify .....

3. Have you ever had iv therapy before? Yes/No

4. Physical mobility Full/Compromised

If compromised specify.....

.....

5. What benefits do you think being treated as an outpatient gives you?

.....

.....

6. Do you have any concerns being treated as an outpatient? Yes/No

If yes, specify.....

.....

7. Have you discussed your form of treatment with other family members?..... Yes/No

If yes was there response positive? Yes/No

If Yes what relationship?.....

If No Why not?

CONSENT FORM

I \_\_\_\_\_ (full name and address);

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

freely and voluntarily consent to take part in a clinical research study on.

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

which so far as is known should not carry any unusual risk.

I have read the accompanying information sheet. The nature and purpose of the study has been explained to me by Dr. \_\_\_\_\_.

I have had the opportunity to ask any questions and I understand fully what is proposed.

I recognise that I may receive no benefit personally from the study. I accept that there may be other risks associated with the procedures which are not directly attributable to negligence on the part of those undertaking the procedures.

I understand that I am free to withdraw my consent at any time without prejudice to me or my medical care. I have been assured that any information obtained from me will not be disclosed to any other party in a manner which will reveal my identity.

Signature \_\_\_\_\_ Date \_\_\_\_\_

I confirm that I/Dr. \_\_\_\_\_ have/has explained the nature and purpose of the clinical research study and the procedure in respect of which consent has been given by the above named.

Signature \_\_\_\_\_ Date \_\_\_\_\_

NON-INPATIENT IV CARE STUDY  
PATIENT INFORMATION - HOME IV THERAPY

Patient Name.....

You have been prescribed an antibiotic called Teicoplanin (TARGOCID<sup>®</sup>) at a dose of mg once a day.

Although you will have been trained to prepare and self-administer this antibiotic whilst in hospital, here are a set of instructions to help refresh your memory if you are unsure of what to do next. In addition other useful information is included such as general guidelines and contact telephone numbers etc.

Contents	Page number
Supplies	2
General points	2
Quick reference guide to preparing and administering your antibiotic	3
Full preparation and administration instructions for your antibiotic	4-5
Possible complications	6
Contact telephone numbers	6

## SUPPLIES

You will be provided with:-

- doses of antibiotic and water
- ampoule breaker
- syringes
- needles
- alcohol swabs
- Hepsal
- Gauze dressings and adhesive tape
- disposable paper towels
- cardboard trays
- 'Sharps' bin

When you have finished treatment please return any remaining items to the hospital - the Sharps bin must be returned for destruction. This can be done at your follow-up visit.

## GENERAL POINTS

1. Try to establish a routine and use the same area each time. Somewhere you can keep as clean as possible, for example, kitchen surface, trolley or tray. Wash area thoroughly with a detergent solution before and after use. Dry area completely. Use disposable towels for washing and drying the area of choice.
2. Only allow people in the room with you who are helping.
3. Avoid distractions, for example, unplug the telephone for a short time if necessary and don't have small children or pets in the room.
4. When you have assembled your equipment and antibiotic it is always good practice to check the name, strength and expiry date of the antibiotic before preparation and administration. You will be shown where to locate this information on the antibiotic vial.

## QUICK REFERENCE GUIDE TO PREPARING AND ADMINISTERING YOUR ANTIBIOTIC

- Step 1                      Wash and dry hands  
   ↓
- Step 2                      Assemble equipment and antibiotic  
   ↓
- Step 3                      Wash and dry hands  
   ↓
- Step 4                      Prepare syringes and needles  
   ↓
- Step 5 & 6                Prepare antibiotic  
   ↓
- Step 7                      Prepare hepsal  
   ↓
- Step 8                      Wash and dry hands  
   ↓
- Step 9                      Check iv line  
   ↓
- Step 10                    Flush line with hepsal  
   ↓
- Step 11                    Administer antibiotic  
   then  
   Flush line with hepsal  
   ↓
- Step 12                    Apply dressing  
   ↓
- Step 13                    Tidy up waste

## FULL INSTRUCTIONS

### PREPARATION AND ADMINISTRATION OF YOUR ANTIBIOTIC

#### Step 1

Wash your hands thoroughly and dry with a disposable paper towel - this is one of the most important means of preventing infection.

#### Step 2

Assemble all equipment and drugs before starting the procedure. On a cardboard tray you will need

Antibiotic powder ampoule plus the water ampoule for reconstitution

Hepsal ampoule

Ampoule breaker

Syringes

Needles

Alcohol swabs

Fresh gauze dressing and adhesive tape

Also another cardboard tray will be required for the prepared antibiotic injection and hepsal injection.

nb Do not use any items that are damaged.

#### Step 3

Wash and dry hands as before.

#### Step 4

Open a syringe and needle pack onto a clean surface and attach the needle to the syringe leaving the cover over the needle. Prepare a second syringe and needle. one is for the antibiotic and one for the hepsal.

#### Step 5

Using an alcohol swab clean the neck of the antibiotic ampoule and water for reconstitution ampoule. Allow to dry.

#### Step 6

Break the ampoule tops of the antibiotic and water, remove the cover from one needle and syringe and draw up the entire contents of the water ampoule. Add this slowly to the powdered antibiotic and roll the ampoule gently until the powder is completely dissolved, taking care to avoid formation of foam. If the solution does become foamy then allow to stand for about 15 minutes for the foam to subside. Draw up the entire contents of the dissolved antibiotic ampoule with the needle and syringe, expel any trapped air bubbles by holding the syringe upright and tapping the syringe with a fingernail before pressing the plunger. Ensure that there are no visible particles in the antibiotic solution, this is a highly

unlikely event but if so discard and prepare another. Place the needle and syringe on the new cardboard tray.

**Step 7**

Using an alcohol swab clean the neck of a hepsal ampoule and allow to dry. Remove the cover from the second needle and syringe and draw up the entire contents of the ampoule, expel any trapped air. Place the needle and syringe on the new cardboard tray.

**Step 8**

Wash and dry hands as before.

**Step 9**

Remove dressing from over the iv line and check that it is still in position in the vein. Briefly examine surrounding area for signs of redness, swelling, pain or discomfort. Should any of these signs be apparent contact the hospital before proceeding, however if everything appears to be in order proceed as follows.

**Step 10**

Carefully unclip the green cover of the iv line. Remove the needle from the hepsal syringe, taking care not to touch the hub of the syringe attach it to the iv line. Slowly inject about 2mls into the line, remove the syringe and place back on the cardboard tray taking care not to touch the hub of the syringe.

**Step 11**

Remove the needle from the antibiotic syringe taking care not to touch the hub of the syringe, attach the syringe to the iv line. Slowly inject the entire contents into the iv line over a 3 to 4 minute time period. Remove the syringe and replace with the remaining hepsal syringe. Slowly inject the remaining contents of the hepsal syringe into the iv line. Remove and replace the green cover.

**Step 12**

Place a clean, dry gauze dressing over the iv line.

**Step 13**

With the exception of the paper covering the needles and syringes, paper towels and the cardboard trays, all other waste, broken ampoules, needles, syringes, swabs, used dressing etc. must be placed in the 'Sharps' disposal bin and not with household rubbish.

## POSSIBLE COMPLICATIONS

Although infrequent, there are a few mild complications that can occur, these include:-

Blocked iv line - i.e. it becomes impossible to push the contents of the syringe into the iv line, although this shouldn't happen if the line is always flushed through both before and after the antibiotic has been administered it does occasionally occur. **DO NOT FORCE THE PLUNGER OF THE SYRINGE.** Contact the hospital.

Dislodged iv line - although extremely unusual, if an event occurs which causes the line to become dislodged for example by catching the line on something during your daily activities contact the hospital as it will probably need to be replaced.

Redness, discomfort or pain of exit site of iv line - this may be a local infection or an indication that the line may need changing. Contact the hospital.

If there are any other events which give cause for concern please do not hesitate to contact the hospital.

## CONTACT TELEPHONE NUMBERS

Ninewells Hospital	0382 60111	(This switchboard answers for Kings Cross Hospital)
Ward 1	extn 6951	
Ward 9 East	extn 6959	
Ward 9 West	extn 6999	

or ask the hospital telephonist to bleep the doctor on call for Infectious Diseases for Kings Cross Hospital Wards 9

Research Pharmacist-Sharon Parker extn 6946 or ask switchboard to radiopage (Mon-Fri 9-5 only)

## OUTPATIENT INFORMATION

### POSSIBLE COMPLICATIONS

Although infrequent, there are a few mild complications that can occur, these include:-

Dislodged iv line - although extremely unusual, if an event occurs which causes the line to become dislodged for example by catching the line on something during your daily activities contact the hospital as it will probably need to be replaced.

Redness, discomfort or pain of exit site of iv line - this may be a local infection or an indication that the line may need changing. Contact the hospital.

If there are any other events which give cause for concern please do not hesitate to contact the hospital.

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NON-INPATIENT IV CARE STUDY  
END OF STUDY PATIENT QUESTIONNAIRE

For completion by the patient and/or carer.

Patient label

Study No.....

1. Did you experience any problems with this therapy? Yes/No

If Yes please specify?.....

.....

2. Would you repeat this form of therapy again? Yes/No

If No Why not?.....

.....

3. Did this form of therapy improve any of the following areas:

a) 'Quality of life' Yes/No

b) Allow more control of your therapy Yes/No

c) Other please specify.....

4. Could you please give examples of the sort of things you were able to do which you would not have been able to do had you stayed in hospital.....

.....

.....

5. Do you think this form of therapy caused you any out-of-pocket expenses?

Yes/No

If Yes please specify.....

.....

Dear Dr

Re: Non-Inpatient IV Antibiotic Care

Non-Inpatient IV Care has been provided as a routine service in the USA for the last decade.

Since January 1994 we have been conducting a feasibility study of Non-Inpatient IV Care for suitable patients within Tayside. We approach this in one of two ways. A patient either attends the hospital once daily as an outpatient to have their antibiotic administered and their iv access and progress evaluated or, the patient/relative/carer is taught how to prepare and administer the once daily prescribed antibiotic at home but the patient attends the hospital twice weekly to have their iv access and general progress evaluated. Patients requiring less than seven days treatment usually attend daily as an out-patient and those requiring greater than seven days usually prefer to be taught for self-administration, but the options are flexible. The type of patients selected for this type of care are medically stable, are prepared to go home and are resident as an in-patient only because of their iv therapy. To date we have met with great enthusiasm from the patients offered this service and we feel it is a success.

We would like to introduce this form of care as an ongoing service. However before doing so we need to know what the referral pattern of individual Tayside GP practices are for patients requiring iv therapy and what the GPs feel about such a service.

A member of our team will contact your practice in the next few days to arrange a suitable time to canvas your response by telephone. Could we ask you to discuss and complete the short enclosed questionnaire with your partners so that we take as little of your time as possible.

We would be extremely grateful for your co-operation with this matter

yours sincerely

Sharon E Parker  
Senior Research Pharmacist

Dr D Nathwani  
Consultant  
Infectious Disease

Dr P G Davey  
Consultant  
Infectious Disease

## GP Survey of Non-Inpatient IV Antibiotic Care

GP practice:

Date:

No. Partners in practice:

1) Could you estimate approximately how many patients in your practice were sent to hospital for management of infection since January 1994?

Don't know

1 - 10

11 - 20

21 - 30

2) What conditions did they have? (Unprompted)

(Prompted)

Skin & soft tissue

Osteomyelitis

Pneumonia

Severe UTI

3) What do you /your partners feel would be the main advantages and disadvantages of this type of service to yourself?

Advantages

Disadvantages

4) What do you /your partners feel would be the main advantages and disadvantages of this type of service to your patients?

Advantages

Disadvantages

5) How would you (your partners) respond to the availability of such a service?

In favour

Not in favour

Need more information