

1 **COVID-19 Pandemic – a focused review for clinicians**

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28 Key words: COVID-19, coronavirus, SARS-CoV-2, novel coronavirus

29 **Abstract**

30

31 **Background**

32 The COVID-19 pandemic caused by SARS-CoV-2 remains a significant issue for global health,
33 economics and society. A wealth of data has been generated since its emergence in December 2019
34 and it is vital for clinicians to keep up with this data from across the world at a time of uncertainty and
35 constantly evolving guidelines and clinical practice.

36

37 **Objectives**

38 Here we provide an update for clinicians on the recent developments about virology, diagnostics,
39 clinical presentation, viral shedding, and treatment options for COVID-19 based on current literature.

40

41 **Sources**

42 We considered published peer-reviewed papers and non-peer-reviewed pre-print manuscripts on
43 COVID19 and related aspects with an emphasis on clinical management aspects.

44

45 **Content**

46 We describe the virological characteristics of SARS-CoV-2 and clinical course of COVID-19 with an
47 emphasis on diagnostic challenges, duration of viral shedding, severity markers and current treatment
48 options.

49

50 **Implications**

51 The key challenge in managing COVID-19 remains the patient density. However, accurate diagnoses
52 as well as early identification and management of high-risk severe cases are important for many
53 clinicians. For improved management of cases, there is a need to understand test probability of
54 serology, qRT-PCR and radiological testing, and the efficacy of available treatment options that could
55 be used in severe cases with a high risk of mortality.

56 **Introduction**

57 The first cases of atypical pneumonia of unidentified aetiology were reported on December 30, 2019,
58 from Wuhan, China. By January 7, 2020, a novel betacoronavirus, severe acute respiratory syndrome
59 coronavirus (SARS-CoV-2) was identified, while the disease has been named COVID-19. COVID-19
60 has now been declared a pandemic, affected nearly every country, with over 2.3 million confirmed
61 cases and >160,000 deaths. The initial clinical case series from China largely comprised of
62 hospitalised patients with severe pneumonia. Further data suggested that approximately 80% patients
63 have mild disease, 20% require hospital admission, and approximately 5% require intensive care
64 admission [1]. Mortality rates are higher among people over 60 years and with coexisting conditions;
65 hypertension, diabetes and cardiovascular disease being the most common. Here we provide an
66 update for clinicians on the recent developments about virology, diagnostics, clinical presentation,
67 and treatment options for COVID-19 based on current literature.

68

69 **Virology**

70 Metagenomic sequencing and targeted real-time polymerase chain reaction (qRT-PCR) assays
71 identified a novel human CoV (SARS-CoV-2) in bronchoalveolar lavage fluid taken from the initial
72 patient cluster in Wuhan [2]. Infectious SARS-CoV-2 has been cultured on monkey Vero, human Huh7
73 and primary human airway epithelial cells [3], where it is cytopathic. Furthermore, serum antibodies
74 (IgM and IgG) from cases neutralized SARS-CoV-2 in cell culture and detected virus-infected cells by
75 indirect immunofluorescence [3].

76

77 Phylogenetic analysis reveals that SARS-CoV-2 is closely related to SARS-CoV (~80% similar) in the
78 *Sarbecovirus* sub-family (genus *Betacoronavirus*) [2]. While an intermediate host has yet to be
79 determined, it shares strong genetic similarity (>95%) to known bat coronaviruses from China,
80 suggesting a likely bat origin. Relatively similar coronaviruses have been found in pangolins whose
81 receptor-binding domain (RBD) of Spike (S) glycoprotein is more like to SARS-2-CoV-2 than known
82 bat viruses [4].

83

84 SARS-CoV-2 shares most of its gene content with SARS-CoV, including the S glycoprotein, the
85 RNA-dependent RNA polymerase (Nsp12) and two proteases papain-like protease (PLpro) and 3C-
86 like protease (3CLpro) [3]. There is also substantial antigenic cross-reactivity between SARS-CoV-2
87 and SARS-CoV [3, 5]. A recent study confirmed that the angiotensin-converting enzyme 2 (ACE2),
88 expressed in the human respiratory tract epithelium, is the entry receptor for SARS-CoV-2 similar to
89 SARS-CoV and has been shown to cause pneumonia in lab mice only expressing human ACE2 [6, 7].
90 This is likely mediated by the RBD of the S glycoprotein [8]. Although there is obvious homology
91 between SARS-CoV and SARS-CoV-2, and cross neutralization has been observed [9], significant
92 biological differences, specifically in the S glycoprotein have been noted [5, 10, 11].

93

94 **Clinical presentation**

95 A key difference between COVID-19 and seasonal influenza-associated pneumonia is the potential
96 severity of disease even in young adults without comorbidities [12]. In a study that compared three
97 well-conducted Chinese case series to a reference group of patients with influenza-associated
98 pneumonia from 73 German sentinel hospitals, the severity of pneumonia even in adults aged <60
99 years without chronic preconditions was significantly greater in COVID-19. For instance, 28% of
100 COVID-19 patients treated on the ICU had no reported comorbidity. The rate of ARDS and
101 mechanical ventilation was markedly higher among COVID-19 patients. The median duration of
102 ventilation was 9 days for non-invasive, and 17 days for invasive ventilation [12].

103

104 Across all studies, the most common symptoms at onset of illness were fever, cough, fatigue, and
105 myalgia. However, available data suggest that only half of patients are febrile at the time of admission
106 [13, 14]. Gastrointestinal symptoms, including anorexia, nausea, vomiting and diarrhoea are also
107 common, reported in nearly 40% patients in some cohorts [15, 16]. Furthermore, up to 10% patients
108 present with gastrointestinal symptoms without respiratory symptoms or fever [17]. COVID-19 has
109 been associated with a hypercoagulable state with increased risk of venous thromboembolism[18].
110 Neurological manifestations, including headache, dizziness, altered consciousness, ischaemic and

111 haemorrhagic strokes, as well as muscle injury, have also been reported [19]. A third of patients
112 reported taste or olfactory disorders in a small Italian cohort, including anosmia [20]. Other
113 extrapulmonary manifestations include skin and ocular manifestations. An Italian study reported
114 cutaneous manifestations in 20% patients [21]. Lastly, ocular manifestations consistent with
115 conjunctivitis was reported in 32% COVID patients in a Chinese case series [22].

116

117 The estimated mean incubation period is reported as 3-6 days (range 1.3-11.3) [12]. The duration
118 from symptom onset to dyspnoea was 5-6 days [13, 17] On average, disease progresses further
119 requiring hospitalisation at 7-8 days from symptom onset. Patients may initially appear relatively
120 stable, but they often rapidly deteriorate with severe hypoxia [13, 17]. The key feature seen in these
121 cases is acute respiratory distress syndrome (ARDS) [13, 17]. The interval from symptom onset to the
122 development of ARDS is approximately 8-12 days [13]. In addition, the incidence of cardiovascular
123 manifestations such as myocardial injury seems to be high, likely due to the systemic inflammatory
124 response and immune system disorders during disease progression[23].

125

126 Illness severity and development of ARDS are associated with older age and underlying medical
127 conditions [17]. Additionally, neutrophilia, raised lactate dehydrogenase and D-dimer, lymphocyte
128 counts, CD3 and CD4 T-cell counts, AST, prealbumin, creatinine, glucose, low-density lipoprotein,
129 serum ferritin, and prothrombin time were also associated with higher risk of severe disease and
130 ARDS [17]. In a cohort of 191 patients with a definitive clinical outcome (137 discharged and 54
131 died), mortality was independently associated with older age, higher qSOFA score, d-dimer >1 µg/mL
132 on admission, and the majority had severe disease and experienced complications, such as ARDS,
133 acute kidney injury, and sepsis [13]. Factors most associated with critical illness were admission
134 oxygen saturation <88%, first d-dimer>2500, first ferritin >2500, and first CRP >200 [24].
135 Furthermore, patients with cardiovascular disease were shown to be more likely to develop severe
136 symptoms[23] in keeping with picture seen in MERS-CoV and SARS.

137

138 In comparison, most children appear to have mild disease. Among 1391 asymptomatic and
139 symptomatic children (median age: 6.7 years) with known COVID19 contact in Wuhan Children's
140 Hospital [25], 171 (12.3%) were SARS-CoV2-positive; 27 (15.8%) had no symptoms or radiologic
141 features of pneumonia, 33 (19.3%) had upper respiratory symptoms, and 64.9% had pneumonia.
142 Three patients (with coexisting conditions) required intensive care and 1 death.

143

144 In terms of co-infections, a pre-print examining >8000 samples of COVID-19 contacts tested for
145 SARS-CoV2 in China reported viral co-infections in 5.8% of COVID-19 positive individuals
146 (including seasonal coronaviruses, influenza A virus and rhinoviruses [26]. Another study of 1206
147 patients identified viral co-infection in 24 of 116 (21%) SARS-CoV2-positive patients;
148 rhino/enterovirus, respiratory syncytial virus, and seasonal CoVs were most common [27]. Bacterial
149 and fungal co-infections with SARS-CoV-2 have been documented especially in the ICU setting,
150 including *Acinetobacter baumannii* and *Klebsiella pneumoniae* [28]. Among 191 patients, non-
151 survivors were more likely to have sepsis based on qSOFA score and secondary infection, although
152 detailed bacteriology results were not reported [13]. Secondary infection and positive association
153 between steroid administration and secondary infection should be explored further.

154

155 **Molecular and Serological Diagnosis**

156 The first genome sequence for SARS-CoV-2 was released on virological.org on 10 January (GenBank
157 accession number MN908947). This allowed the rapid development of several sensitive and specific
158 qRT-PCR assays [29]. Many laboratories worldwide are now able to test for SARS-CoV-2. Assays
159 have been described that detect <10 copies of SARS-CoV-2 per reaction and will not cross-react with
160 SARS-CoV or other human coronaviruses [29]. However, sensitivity and specificity of these tests
161 remain unknown and there is no clear consensus on which is preferred.

162

163 Viral RNA loads by qRT-PCR were substantially higher in sputum compared to throat swabs [3, 30,
164 31], suggesting that the type of sample may also influence the outcome of the test. Therefore,
165 currently submission of both lower and upper respiratory tracts samples is advised.

166

167 Precise molecular detection is hampered by the variability in viral loads in the upper respiratory tract,
168 especially at later stages of infection. In a study from China, among 241 COVID-19 patients with at
169 least one positive SARS-CoV-2 qRT-PCR test result, in the first test, 384 (63.0%) were negative [32].
170 In addition, several tests at different points were variable from the same patients during the course of
171 diagnosis and treatment.[32]. Therefore, a single positive test should be confirmed by a second qRT-
172 PCR assay targeting a different SARS-CoV-2 gene. Although, similar studies in Taiwan and Hong
173 Kong reported less false-negatives[33]. Secondly, a single negative SARS-CoV-2 test (especially if
174 from upper respiratory tract specimen) or a positive test result for another respiratory pathogen result
175 should not be used to exclude COVID-19 infection. These findings indicate that qRT-PCR has low
176 probability of ruling out an infection and in clinically high suspicious cases repeat sampling and also
177 CT images may need to be used to guide the diagnosis.

178

179 Antibody-based methods to detect seroconversion in serum or plasma based upon enzyme-linked
180 immunosorbent assays (ELISA), indirect-immunofluorescence or virus neutralisation have been
181 reported [34-36]. Around 40-50% patients develop an antibody response to SARS-CoV-2 infection
182 after 7 days, and the majority by 14 days [35, 37]. S1 has been shown to be more specific than S as an
183 antigen for SARS-CoV-2 in serological diagnosis [36]. The commercial S1 IgG and IgA assays have
184 lower specificity but IgA showing higher sensitivity [36]. Recently, an ELISA assay based on
185 detection of recombinant S protein by serum antibodies demonstrated robust and scalable
186 determination of seroconversion that will facilitate screening of potential exposed individuals for
187 evidence of past infection [38]. Since seroconversion occurs relatively late in infection, rapid antibody
188 tests have a limited role in the diagnosis of acute infection; qRT-PCR remains the 'gold standard'.

189

190 There is an ongoing work to understand protective antibody level and immunological marker. Among
191 175 recovered laboratory-confirmed COVID-19 patients, neutralizing antibodies (NAb) peaked at 10
192 to 15 days after disease onset. However, approximately 30% failed to develop good level of NAb
193 titres (ID50: < 500)[39]. In addition, patients who did not generate NAb at the time of discharge did

194 not develop NABs thereafter. These results highlight that some patients with SARS-CoV-2 would
195 recover without developing high titers of virus-specific NABs. These findings have some implications
196 for vaccine development and also for convalescent plasma treatment as the donor plasma should be
197 titrated before use in passive therapy. There is less information available on the T cell response during
198 SARS-CoV-2 infection and how it correlates with the NAb titres.

199

200 **Duration of viral shedding and isolation period**

201 SARS-CoV-2 RNA has been identified by qRT-PCR in respiratory tract samples 1-2 days prior to
202 symptom onset and can persist for 7-12 days in moderate cases, and up to 2 weeks in severe cases [35,
203 40]. SARS-CoV-2 has also been detected in whole blood [41], saliva [42], faeces [43], and urine [44]
204 by qRT-PCR (Table 1).. In several case series with serial sampling, viral loads were highest soon after
205 symptom onset [35, 45]. Patients with severe COVID-19 had significantly higher viral load and
206 longer period of viral shedding than mild cases [46]. Prolonged viral RNA shedding has been reported
207 from throat swabs up to 37 days among adult patients [13], and in faeces, for over one month after
208 illness onset in children[40, 47]. However, detection of viral RNA by qRT-PCR does not necessarily
209 equate with infectious virus. No live virus was cultured from 9 mild COVID-19 cases beyond day 8
210 after symptom onset in throat swabs or sputum despite ongoing high viral load [35]. Persistently high
211 levels of RNA were also identified in the stool of the mild cases, but no live virus was cultured [35].
212 These findings suggest that patients may continue to shed RNA in various samples for a long period,
213 but this does not equate to infectiousness potential (Table 1). This supports the current guidance of 7-
214 14 days self-isolation from symptom onset. Certain hospitals following a protocol to confirm viral
215 clearance prior to transfer out of dedicated COVID-19 wards, however, this may not be required
216 given the prolonged RNA shedding without the evidence of viable virus. However, whether faecal-
217 oral or faecal-respiratory transmission occurs, and the role of shedding in severe cases in transmission
218 requires further exploration.

219

220 **Transmission patterns**

221 A review of modelling studies based on Chinese case numbers report a median basic reproduction
222 number (R_0) of 2.79 [48], though R_0 as high as 5.7 have been reported [49]. These estimates are
223 substantially higher than the reproduction number for seasonal influenza (~ 1.3) [50], and indicate that
224 control measures would need to prevent $>60\%$ transmission to stop the epidemic. Of note, R_0 will
225 vary by setting, and can be substantially reduced by countermeasures, as have been observed in China
226 [51].

227 It is now clear that a significant proportion of individuals with COVID-19 have very mild or no
228 symptoms. Asymptomatic infection at the time of laboratory testing have been reported [52, 53],
229 though a large proportion go on to develop symptoms. For instance, among 55 asymptomatic carriers
230 with positive qRT-PCR for SARS-CoV-2 in pharyngeal swab samples, 14 went on to develop mild,
231 39 ordinary, and 2 severe COVID-19 [54]. There have been several reports of SARS-CoV-2
232 transmission from asymptomatic or presymptomatic persons [55, 56], which poses significant
233 challenges to contact tracing. Nevertheless, the relative contribution of asymptomatic or pre-
234 symptomatic transmission on the overall transmission dynamics of the pandemic remains uncertain.
235 Thus, household studies to study secondary human transmission of SARS-CoV-2 and serosurveys to
236 determine the incidence of asymptomatic and subclinical infections are needed.

237

238 A further consideration is superspreading events, whereby a small number of cases are responsible for
239 a disproportionate number of secondary cases. This was a feature of both SARS- and MERS-CoV,
240 responsible for multiple nosocomial outbreaks [57, 58]. Several superspreading events has been
241 reported for COVID-19 [17]. Rapid identification and mitigation of these events will be crucial to
242 controlling this pandemic.

243

244 **Treatment options in clinical trials**

245 At present, there are no approved antivirals for SARS-CoV-2. Several antivirals that have shown
246 promise against SARS- or MERS-CoV in vitro and in vivo are currently being evaluated in clinical
247 trials for COVID-19. Lopinavir/ritonavir (LPV/r), a protease inhibitor used as an antiretroviral,

248 showed inconclusive findings for the treatment of SARS, but demonstrated strong *in vitro* and *in vivo*
249 antiviral activity against MERS-CoV when combined with interferon-beta (IFN β) [59]. The first of a
250 number of clinical trials involving LPV/r was recently published [60]. Among 199 seriously ill
251 laboratory-confirmed COVID-19 patients, no significant difference in clinical improvement, mortality
252 or viral clearance was observed between LPV/r (n=99) and standard care (n=100) arms. However,
253 treatment was instituted late in infection; median time from symptom onset to treatment was 13 days,
254 and >40% of patients had undetectable viral load before or during treatment. The results were
255 complicated by the variable use of other treatments, including interferon, glucocorticoids and
256 antibiotics. Of note, day 28 mortality was lower (not significantly) in those with early treatment (19%
257 vs. 27%) and those who received LPV/r also had lower vasopressor and non-invasive ventilation use.
258 Another promising drug is remdesivir, a novel nucleotide analogue that interferes with nsp12
259 polymerase [61]. It has shown *in vitro* activity against a wide range of RNA viruses including SARS
260 and MERS-CoV [62, 63], and has also demonstrated superior antiviral activity compared to LPV/r-
261 IFN β against MERS-CoV in a mouse model [59]. Against SARS-CoV-2, it has shown promising
262 antiviral activity in Vero E6 cells and Huh7 cells [64]. Remdesivir has been given to a small number
263 of patients with severe COVID-19 through compassionate use, however, given the lack of
264 randomisation and control group interpretation of the findings is difficult [65]. There are ongoing
265 RCTs assessing its efficacy and safety in patients with COVID-19 worldwide, and a study in France
266 evaluating its impact on viral shedding in high and moderate risk contacts in confirmed COVID-19
267 cases (NCT04259892).

268
269 Other candidate antivirals are studied in RCTs, including favipiravir and hydroxychloroquine, which
270 has been shown to inhibit virus cell entry *in vitro* [66]. Hydroxychloroquine (HCQ), an analogue of
271 chloroquine, has demonstrated anti-SARS-CoV-2 activity *in vitro* [67]. Among a small open-label
272 non-randomised study, patients treated with HCQ and HCQ + Azithromycin showed viral load
273 reduction compared to controls. However, there has been significant concerns and ethical issues about
274 the content, the ethical approval of the trial and the peer review process prior to publication raised by
275 several physicians and also the International Society of Antimicrobial Chemotherapy. In a small RCT

276 of HCQ (n=30), there was no change in viral load or clinical outcome after 7 days [68]. Currently,
277 there are 45 trials evaluating chloroquine or HCQ for the treatment and prophylaxis of COVID-19,
278 including multi-centre RCTs in the UK (RECOVERY, ISRCTN50189673), Europe (DisCoVeRy,
279 NCT04315948) and also globally involving >70 countries (SOLIDARITY, ISRCTN83971151).

280

281 Host-targeted therapeutic options are also being explored, such as inhibition of human cytokine
282 interleukin-6 (IL-6), the abundance of which has been associated with worse prognosis [69]. A
283 preprint including 21 patients that received Tocilizumab (an IL-6 receptor inhibitor) reported
284 improvement in symptoms, hypoxaemia and CT changes in the majority of patients[70]. There are
285 ongoing RCTs evaluating tocilizumab and sarilumab, also an IL-6 receptor inhibitor. With insufficient
286 evidence of efficacy for any existing treatments, the IDSA recommends that experimental therapies
287 should only be offered to patients in the context of a clinical trial [71].

288

289 There is no licenced vaccine to protect against COVID-19. However, a number of experimental
290 candidates are in development with some already in early clinical trials. Most vaccine candidates
291 focus on immunisation with only the S glycoprotein, which is the major target for neutralization
292 antibodies. Candidate vaccines differ in the mode of S delivery and platforms dependent on
293 recombinant protein, mRNA or viral vectored approaches are being tested. Passive immunisation
294 through transfusion of convalescent sera or plasma containing neutralizing antibodies from recovered
295 donors have been reported in several case series, with clinical improvement reported in recipients [72,
296 73]. Clinical trials evaluating convalescent plasma as treatment for severe COVID-19 are ongoing.

297

298 **Conclusion**

299 A wealth of data has been generated already on COVID-19 since early January 2020. Nevertheless,
300 key questions remain regarding understanding the population at risk and age groups, proportion of
301 individuals that have had asymptomatic infections and their transmission potential, endemicity and
302 seasonality of COVID-19, and whether stringent physical distancing measures will be effective in

303 countries outside China. The main challenge in managing COVID19 remains the patient density,
304 however, accurate diagnoses as well as early identification and management of high-risk severe cases
305 remains a daily battle for many clinicians. For improved management of cases, there is a need to
306 understand test probability of serology, qRT-PCR and radiological testing, and the efficacy of
307 available treatment options that could be used in severe cases with high risk of mortality.

308

309 **Authors contributions**

310 MC, CM, AH drafted the first and subsequent versions of the manuscript, and all authors provided
311 critical feedback and contributed to the manuscript.

312

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314 None

315

316 **Conflicts of interest**

317 MC, CB and AT has nothing to disclose.

318

319

Source	Mode of transmission	RNA by PCR (Days since onset of symptoms)	Viable virus (Days since onset of symptoms)
Nasopharynx	Droplet	Up to 37 days	Up to 7 days (in mild cases)
Sputum	Droplet / airborne during aerosolize-producing procedures	Up to 37 days	Up to 7 days (in mild cases)
Stool	No evidence of faecal-oral transmission	> 30 days	Only 1 report; uncertain
Blood	No viable virus to date	Up to 14 days	No
Urine	No viable virus to date	No	No
Conjunctiva	No viable virus to date Macaques with corneal inoculation develop infection	Yes	No
Vertical	No strong evidence of vertical transmission to date	No	N/A

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