Clinical presentation and management of COVID-19

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Summary

- The rapid spread severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to the declaration of a global pandemic barely three months after emerging.
- A majority of patients presenting with coronavirus disease 2019 (COVID-19) will experience a mild illness that can largely be managed in the community. Patients with moderate illness or with risk factors for progressive disease require careful monitoring and early referral to hospital for any signs of clinical deterioration.
- Increasing age and the presence of co-morbidities are associated with more severe disease and poor outcomes
- Treatment for COVID-19 is currently supportive, with appropriate management of respiratory dysfunction the cornerstone of care.
- No good clinical evidence for any specific therapies (including antiviral and immune modulating agents) currently exists. Investigational therapies for COVID-19 should be used only in approved, randomized, controlled trials
- Australian clinicians will need to be able to recognise, diagnose, manage, and appropriately refer patients affected by COVID-19, with many thousands of cases likely to present over the coming year.

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Introduction

In December 2019 a novel coronavirus emerged in Wuhan, Hubei Province, China that is now the cause of a global pandemic. This virus, subsequently named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causes a clinical syndrome termed coronavirus disease 2019 (COVID-19).

First reports of an undiagnosed pneumonia in Wuhan on 8 December, were followed by an alert from China to the World Health Organisation (WHO) about a cluster of pneumonia cases on 30 December. Isolation of a novel coronavirus occurred on 3 January 2020. On 30 January, the World Health Organization (WHO) declared a public health emergency of international concern; and on 12 March, a pandemic was declared.

Clinical Presentation

The incubation period of COVID-19 infection has been estimated to have a median of 5.1 days (95% CI; 4.5-5.8 days) with 97.5% of those who will develop symptoms doing so within 11 days of exposure (95% CI: 8.2 – 15.6 days). This has informed the time interval of 14 days for quarantining of potentially exposed individuals (1).

The ratio of asymptomatic to symptomatic infection is currently unknown, and there may be differences in the rates in children compared to adults. The largest studies from adults in China estimated that less than 1% of PCR confirmed cases had no symptoms. One large paediatric study however reported up to 13% of PCR confirmed infected children being asymptomatic. In contrast higher rates of PCR positive asymptomatic (or pre-symptomatic) people were described amongst passengers on board the Diamond Princess Cruise Ship. This is an area of great ongoing interest.

Symptomatic COVID-19 infection usually presents as a respiratory syndrome, most commonly with fever and cough (2, 3).

Fever has been reported in up to 99% of people at some time during the course of their illness, but importantly has been reported to be present at the time of hospital presentation in only 44% of patients, and at some time during the hospital admission in 89% (4). Other common symptoms are cough, dyspnoea, fatigue, anorexia, anosmia, myalgia and confusion. Symptoms reported much less frequently (<5% of cases) include sore throat, rhinorrhoea, headache, chest pain, dizziness, abdominal pain, diarrhoea and nausea (2, 3).

Around 80% of COVID-19 infections present as a mild respiratory illness in a patient who is ambulatory and can generally be managed outside the hospital. Around 15% typically need hospital care (usually for moderate to severe pneumonia), and another 5% have critical illness requiring more intensive supports (5).

Of those who require hospitalisation, the median time from first symptoms to onset of dyspnoea is 5 days (IQR 1-10), the median time to hospital admission is 7 days (IQR 4-8) and the median time to acute respiratory distress syndrome (ARDS) is 8 days (IQR 6-12) (2). Approximately one quarter of patients who are hospitalised generally need transfer to the intensive care unit for the management of complications such as hypoxaemic respiratory failure or hypotension requiring vasopressor support (6).

At presentation to hospital the most common laboratory feature of COVID-19 infection is lymphopenia (reported in 70.3% of cases) (2). Radiologic imaging can reveal a clear chest or unilateral or bilateral consolidation or ground glass opacity.

Clinical features that have been identified more often in COVID-infected patients who have had a fatal outcome compared to those who survive are: reports of dyspnoea at presentation (median 70.6% versus 24.7%, p<0.001), lower initial oxygen saturations (median 85% vs 97%, p<0.001), higher serum white blood cell count at presentation with a lower lymphocyte count – reflected by a lower serum lymphocyte: total white blood cell ratio (median 4.45 versus 2.91, p<0.001) (7).

Diagnosis

Nasopharyngeal specimens or lower respiratory samples (sputum, bronchoscopy samples) sent for molecular detection of SARS-CoV-2 by PCR are currently the best means of specific diagnosis of COVID-19 in Australia. Faecal samples may also be PCR positive for COVID-19 but the role of the oral-faecal route for transmission remains unclear (8). Patients with more severe disease tend to have higher viral loads in respiratory samples. Mild cases have been shown to clear virus earlier with over 90% testing PCR negative by day 10 compared to severe cases who more often remain PCR positive beyond day 10 (9). Prolonged viral shedding up to 24 days after the onset of symptoms has been described in a Singaporean cohort (10). The virus has also been detected by PCR in asymptomatic patients with comparable viral loads to those still symptomatic (11).

Assessment

Patients with suspected or confirmed COVID-19 should be assessed for features of severe disease, and risk factors for progression to severe disease. This will assist with determination of whether a patient can be managed in the community or requires referral and admission to a facility able to provide acute inpatient care and critical care.

Current data suggest that older patients and those with comorbidities have increased risk of progression to severe disease and mortality. In a large surveillance report from China including over 44,000 confirmed cases of COVID 19, the case fatality rate (CFR) was <0.5% for those aged under 50 years, but rose to 8.0% for those in their 70s, and 14.8% in those aged over 80 (12). While these surveillance-based CFRs are possibly overestimates, being influenced under recognition of lower severity cases, the profound impact of increasing age and the presence of co-morbidities on risk of severe and fatal illness is well recognised (4).

Therefore, patients that are older, have co-morbidities or have moderate illness at presentation require more careful monitoring with earlier referral for hospital admission with any signs of clinical deterioration. Individual personal circumstances need to be considered when determining the ideal monitoring strategy and site of care for each patient (Table 1).

(TABLE 1 HERE)

General management

Patients with mild disease (approximately 80% of patients)(5) can be managed in the community if they are adequately counselled, are able to monitor their condition and are aware of what criteria should merit consideration of admission and how to escalate any concerns (13-15). Particular attention to monitoring and/or review between 5 to 8 days after the onset of symptoms when progression to severe disease is most frequent (13).

For some patients, education and self-monitoring may be adequate, for others active monitoring by phone or telehealth may be suitable; whereas some may require admission, or other forms of in-person monitoring (e.g. hospital in the home). Site of care should be individualised to patient circumstances. Patients whose home environment in not conducive to safe management, or which is unacceptable from an infection prevention perspective, should be admitted either to hospital or to alternative safe accommodation. Discussion with public health authorities is essential to ensure adequate follow up and that appropriate isolation and follow-up mechanisms are in place. Safe management of low risk patients in the community will be essential to preserve hospital capacity in the face of projected huge demands in the coming months.

Patients with moderate-severe disease should generally be admitted to hospital. This includes those who are dyspnoeic (when talking, sitting, standing or with minor exertion), tachypnoeic at rest (respiratory rate >22/minute), hypoxaemic (SaO2 <94% on room air), hypotensive (systolic BP <100mmHg), altered mental state, or who have extensive pulmonary infiltrates evident on chest imaging (13-15).

Severe illness, indicated by, amongst other features, respiratory rate >30 breaths/min, or SaO2 <92% on room air (13, 15) or sustained hypotension, warrants urgent hospitalisation and consideration of the need for intensive care.

It is critically important to ensure optimal infection prevention from the time a patient with suspected COVID-19 is first assessed until their infection is resolved, irrespective of the site of care.

Consideration of alternative and/or dual pathologies is important. Prompt recognition and treatment of sepsis and shock is crucial. Empiric antibiotic therapy for bacterial pneumonia should be considered in those whose illness is severe or where clinically deteriorating, especially if hypoxaemic and in those whose radiology is suggestive (SaO2<92%). (13, 14). Pending influenza PCR results, treatment with a neuraminidase inhibitor should be

considered (14, 15). De-escalation of empiric antimicrobial therapy should be undertaken as appropriate and guided by microbiology results and clinical judgement (15).

Respiratory management

Supplemental oxygen should be administered for patients with SaO2 <92% (13, 14). Once stabilised, the target SaO2 range is 92-96%. The target will be lower in those with chronic hypercapnoeic respiratory failure (e.g. 88-92%) (13-15).

Manoeuvres to improve gas exchange such as deep breathing, positioning patients appropriately in bed (on side with regular turning), elevating the bed head, sitting patients out of bed and mobilizing when able should be implemented where possible.

In the setting of progressive hypoxaemia despite low or moderate -flow oxygen (via nasal prongs or Hudson mask) then high flow oxygen can be considered. High flow oxygen devices (>10ml/min) are aerosol generating so strict attention to airborne precautions must be taken by staff (personal protective equipment using N95/P2 masks), and the patient should be in a single room with the door closed and using negative pressure where possible.

Nebulised medications should also be avoided where alternatives exist (such as metered dose inhalers plus spacers) as they are aerosol generating. Where these procedures are essential, they should be conducted with appropriate airborne transmission precautions in place.

In general, most guidelines recommend early consideration of intubation and mechanical ventilation for patients with acute respiratory distress syndrome (ARDS) (13-15). Non-invasive ventilation (CPAP and BiPAP) are aerosol generating procedures and should only be used with appropriate precautions in place. Their role is contentious and expert advice should be sought.

Specific therapies

A range of pharmacotherapies have been proposed as possible treatments for COVID-19. _No specific agent has yet been demonstrated to be clinically effective in the management of COVID-19_. The WHO's interim guidance on the clinical management of COVID-19 (15) asserts that investigational anti-COVID-19 therapeutics should be used only in approved, randomized, controlled trials. This position is endorsed by the Australian guidelines for the clinical care of people with COVID-19 (13), and the Australasian Society for Infectious Diseases (ASID) Interim guidelines for the clinical management of COVID-19 in adults (14).

Antimicrobials

Lopinavir-ritonavir

This combined antiretroviral agent was proposed as a potential treatment for SARS in 2003, based on apparent reductions in mortality in preliminary research in Hong Kong (16). Given the hypothesised role of lopinavir-ritonavir, five of the first 18 patients diagnosed with

COVID-19 in Singapore were administered this agent (17). Three improved, while two experienced progressive respiratory failure. Four of those receiving antivirals developed gastrointestinal side effects, and three developed liver function test derangement.

On 18 March a randomised, controlled, open-label trial of lopinavir-ritonavir in 199 hospitalised adults with COVID-19 in China was published (18). No benefit was observed in those treated with the antiviral compared with controls. Nearly 14% of those receiving lopinavir-ritonavir were unable to complete 14 days of treatments due to adverse events. The authors recommended further research in patients with severe illness, or potentially with combination therapies.

Remdesivir

The first patient diagnosed with COVID-19 in the United States received this investigational nucleotide prodrug in January 2020, with the drug supplied on a compassionate basis (19). Developed as a potential therapy for Ebola, there is in vitro evidence that remdesivir can inhibit replication of coronaviruses, including MERS-CoV and SARS-CoV-2 (20, 21). Based on in vitro and limited animal evidence of antiviral efficacy, several local guidelines recommended consideration of remdesivir for the treatment of COVID-19. Four clinical trials to assess the efficacy of remdesivir against COVID-19 have commenced in the United States, and two are registered in China (22).

Chloroquine / Hydroxychloroquine

Chloroquine and hydroxychloroquine are antimalarial agents which also have immunomodulatory properties which lead to established indications for use in the treatment of rheumatological conditions including systemic lupus erythematosus and rheumatoid arthritis. Adverse effects of chloroquine and hydroxychloroquine can include retinal toxicity, QTc prolongation and other cardiological and dermatological effects.

In early February 2020, chloroquine was reported to inhibit SARS-CoV-2 replication in vitro (20). By mid-February, treatment of COVID-19 with chloroquine was being hailed as a 'breakthrough' with a published letter stating that the results of treatment in over 100 patients in China had demonstrated that chloroquine was 'superior to control treatment'; no data were provided (23). A small French open-label non-randomized clinical trial examining hydroxychloroquine with or without azithromycin suggested a significant viral load reduction in those receiving therapy (24); however, concerns have been raised about the design and analysis of this study (25).

Similar to the situation with the antiviral agents discussed above, several institutional and local guidelines, and notable public figures, have supported the potential use of chloroquine or hydroxychloroquine for the treatment of COVID-19. In addition, there are reports of prophylactic use by Australian clinicians, for which there is no clinical evidence of efficacy. In light of reports of significant limitations of supply of hydroxychloroquine for patients with rheumatological conditions, the Pharmaceutical Society of Australia and ASID have called for immediate cessation of prescribing and dispensing of hydroxychloroquine for indications relating to COVID-19.

Further, sufficiently powered, well designed and conducted multicentre clinical trials are clearly needed to address questions of both therapeutic, and prophylactic efficacy. A recent systematic review identified 23 separate ongoing clinical trials of chloroquine and hydroxychloroquine, all in China (26).

<u>*Immunomodulatory treatments*</u>

Corticosteroids

Interim guidance from WHO states that routine use of corticosteroids should not be used in routine treatment of COVID-19 (15). This is based on systematic reviews in the context of SARS and MERS which showed lack of effectiveness, and possible harm (27).

In a study of 138 hospitalised patients with COVID-19 in Wuhan (28), 72.2% of ICU patients and 35.3% of non-ICU patients received glucocorticoid therapy. The authors commented that while the dose of methylprednisolone varied depending on disease severity, no effective outcomes were observed.

Outside of clinical trials, corticosteroids should only be used if there is an evidence-based indication for them e.g. acute exacerbation of asthma (14, 15).

Interleukin 6 (IL-6) antagonists

Tocilizumab is a humanised monoclonal antibody which binds to the IL-6 receptors resulting in reduced immune activation and inflammation. It is licensed in Australia for use in autoimmune conditions including rheumatoid arthritis and giant cell arteritis. In addition to complications of immunosuppression including serious infections, adverse effects can include hepatotoxicity and gastrointestinal complications.

The theory behind use of tocilizumab or other agents that target the IL-6 pathway in the context of COVID-19 is that part of the pathogenesis in some patients may be attributable to an acute inflammatory syndrome or 'cytokine storm', which is associated with elevated IL-6 levels. Guidelines have been issued in China regarding use of tocilizumab for severe or critical COVID-19 with elevated IL-6 levels, however clinical evidence of efficacy is not yet available, with two clinical trials currently underway (22).

<u>*Passive immunotherapy*</u>

Convalescent plasma

A preliminary, uncontrolled case series of 5 critically ill Chinese patients with COVID-19 who received convalescent plasma with demonstrated IgG to SARS-CoV-2 was published on 27 March 2020 (29). While improvement in clinical status was reported following this intervention, the small sample size and uncontrolled nature of the study precludes drawing any conclusions regarding the efficacy of this intervention. Once again, further research is needed.

Wholistic care

A global pandemic causes understandable fear and anxiety for many people in the community. For those at particular risk of worse outcomes of infection - older people, and those with significant pre-existing illness or multiple comorbidities, COVID-19 represents a particular threat. In addition, the health care workforce will be under substantial strain and facing a potentially overwhelming challenge in delivering care to their patients. Ensuring emotional care for those most vulnerable, and those experiencing high levels of stress, will be a fundamental determinant of the resilience of our society during this challenge.

For vulnerable and/or frail patients at particular risk of poor outcomes it is important to provide personalised care, and develop an understanding of each individual's perspectives and preferences for health management. Involving caregivers and family members in decision making and establishing goals of care is important (15). Discussing goals of care early, and where appropriate assisting patients to make advanced care directives or resuscitation plans early in illness (or prior to infection) may give substantial peace of mind and allow families to face the pandemic openly and with unity as they support vulnerable loved ones.

It is essential to ensure that all patients receive the best standard of care irrespective of the setting in which the care is delivered, or of the existence of any proposed limitations to life-extending interventions. Under no circumstances should the best possible symptom control and compassionate, individualised care be denied any patient affected by COVID-19.

Conclusion

The novel coronavirus SARS-CoV-2 which emerged in December 2019 is causing the greatest pandemic in a century, and has changed the daily lives of billions of people. It has exposed weaknesses in even strong and well-resourced health systems internationally, and the economic impact alone will be staggering.

However, never has the global community had the tools to address a pandemic threat that are currently available. A strong commitment to social and public health strategies and communicable disease control will ensure our health system retains the capacity to address COVID-19, including sufficient hospital and intensive care resources to care for those with severe illness. Based on current projections however, meeting this challenge will require massive systemic changes to all aspects of how we work as clinicians.

Biomedical innovations such as new and rapid point-of-care diagnostics, effective specific treatments, and preventive vaccines are very high priorities which are rightly attracting substantial attention and funding. In the interim, high quality, evidence-based clinical care – scaled up to face the pandemic challenge - will save the lives of thousands in Australia, and millions globally.

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Table 1: Assessing disease severity and consideration for setting of care for patients diagnosed with COVID-19.

Disease Severity	Clinical features	Setting of Care
Mild illness / lower risk of progression to severe disease	Mild upper respiratory symptoms (e.g. cough, sore throat, myalgia, fatigue) AND Age <60 AND No major co-morbidities	Ideally manage out of hospital (e.g. at home or in a step-down facility) * unless symptoms progress to develop lower tract symptoms (e.g. dyspnoea)
Moderate illness / intermediate risk of progression to severe disease	Stable patient presenting with respiratory and systemic symptoms or signs Characteristics: o severe asthenia, prostration, fever >38°C or productive cough o clinical or radiological signs of lung involvement but no signs of severe pneumonia o no clinical or laboratory indicators of clinical severity or respiratory impairment AND No major co-morbidities	If patient amenable to community level management, careful monitoring into second week of illness is recommended AND early referral for hospital admission if any evidence of clinical deterioration.
Severe illness	Patient meeting any of the following criteria: o dyspnoea at rest or minimal activity (talking, sitting) o SaO2 on room air of <92% o respiratory rate >22 breaths/min o haemodynamically unstable (sBP < 100mmHg) o extensive CXR infiltrate, or rapid worsening from baseline	Assessment for hospital admission
Clinical deterioration and at risk for critical illness	Worsening respiratory state as determined by any of the following criteria: o new requirement for oxygen support to maintain O2 saturation >92%	Early referral to Intensive Care Unit referral (ICU) if goals of care include ICU management.

| | o escalating oxygen requirements
o increasing respiratory rate or work of breathing
o oxygen requirement > 6L/min
o systolic BP decline not responding to judicious fluid therapy
o impairment of conciousness
o other organ failure | |

Adapted from *Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected* (World Health Organisation), *Interim guidelines for the clinical management of COVID-19 in adults* (Australasian Society for Infectious Diseases), and *Australian guidelines for the clinical care of people with COVID-19* (National COVID-19 Clinical Evidence Taskforce) (13-15)