Covid-19: Summary of Current Clinical Evidence for GPs and Frontline Clinicians

Updated 22 Sept 2020
Version 16b

This is a summary of the current clinical evidence around Covid-19, caused by the SARS-Cov2 virus.

This document also summarises relevant information regarding Covid-19 from DHHS Victoria, Department of Health (Australian Federal) and the National Covid 19 Clinical Evidence Taskforce.

It is hoped that this information will help to shape and inform our response in our individual contexts.

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Updates

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Case fatality rate (CFR) by age in Australia

Age	CFR (Australian Data[12] 25,599 cases)
>80 years old	22.7%
65-79 years old	5.1%
50-64 years old	0.5%
<50 years old	0.02%

CFR - China and Italy

Age	CFR (China Data[3] 72,314 cases)	CFR (Italy Data[21] 25,058 cases)
>90 years old		21.6%
> 80 years old	14.8%	18.8%
70-79 years old	8.0%	11.8%

60-69 years old	3.6%	3.2%
50-59 years old	1.3%	1.0%
40-49 years old	0.4%	0.3%
10-39 years old	0.2%	
0-9 years old	No fatalities	

CFR of hospitalised patients[12]:

Australia	10.9%
Europe (aggregate data 22 European countries)	24%
Canada	33%

Case fatality rate by gender (based on China Data[3])

- Male 2.8%
- Female 1.7%

Risk Factors (based on China Data[3])

1. Cardiovascular disease (case fatality rate 10.5%)
2. Diabetes (CFR 7.3%)
3. Chronic respiratory disease (CFR 6.3%)
4. Hypertension (CFR 6.0%)
5. Cancer (CFR 5.6%)

Children:

Clinical disease is generally less severe than in adult patients. However, young children, particularly infants (<1yo) may be vulnerable to infection.

Based on a study[14] of 2,143 paediatric cases (suspected and confirmed) in China, the proportion of severe and critical cases are as follows:

<1 years old	10.6%
1-5 years old	7.3%
6-10 years old	4.2%
11-15 years old	4.1%

>16 years old	3.0%

Nevertheless, overall there was a relatively small number of children reported from a paediatric population of several million. In addition, the proportion of severe and critical cases in children <18 years of age was 5.9%, compared to adult patients (18.5%).

Overall CFR in Australia as of 9 Sept 2020[12]: 2.3%

Summary of Case Fatality

Mortality is skewed towards an older population, and those with co-morbidities.

CFR rates vary depending on the preparedness of the country, social distancing policies and robustness of the health system. In Australia, the CFR of <50 years is lower than that of other countries, whereas the CFR of >80 years is comparable to that of other countries.

Overall, in countries and health systems that are prepared and implement social distancing policies early, CFR is closer to 1%.

In countries that are unprepared, CFR can be as high as 3-5%

In comparison, the seasonal flu is estimated to be 0.1%.

Paediatric Multisystem Inflammatory Syndrome (PIMS)

Believed to be a post-infectious manifestation of Covid 19 infection in children.

In a French case series of 108 children[30], 67% required intensive care. There was one fatality. Researchers estimated the risk of PIMS to be fewer than 2 cases per 10,000 children.

WHO Preliminary Case Definition (published 15 May 2020)

Children and adolescents 0–19 years of age with fever ≥ 3 days

AND two of the following:

1. Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet).
2. Hypotension or shock.
3. Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP),
4. Evidence of coagulopathy (by PT, PTT, elevated d-Dimers).
5. Acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain).

AND

Elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin.

AND

No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes.

AND

Evidence of COVID-19 **(**RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19.

Pregnancy:

Based on a US CDC report released on 26 June 2020[11], 31.5% of pregnant women with Covid 19 were hospitalised compared to 5.8% of non-pregnant women. Pregnant women were 50% more likely to be admitted to the ICU compared to non-pregnant women, and were 70% more likely to receive mechanical ventilation. This was based on data from 8,207 pregnant women and 83,205 non-pregnant women with Covid 19.

RANZOG's advisory on Covid 19 in pregnant women appears to be consistent with the data from the US CDC report.

"About 1 in 3 women who develop COVID-19 whilst pregnant will require admission to hospital. For some of these women, this will be to give birth at the end of pregnancy and not because of symptoms from COVID-19. In those women who do become unwell with COVID-19 and require hospital admission, about 1 in 10 will require admission to ICU for help with breathing or other organ support."

Stratification (based on DDHS Vic Guidelines)

Two key groups of patients:

1. Those systemically well with mild coryzal symptoms (estimated to be 80-85% of cases)
2. Those systemically unwell with evidence of lower respiratory tract infection, and symptoms such as shortness of breath, fever and productive cough (estimated to be 15-20% of cases)

Incubation Period

Median is 5-6 days (0-14 day range). Longer incubation periods occasionally occur, but are considered 'outliers'.[16]

Key Symptoms

Given delays in diagnostic confirmation of influenza vs covid-19 in the GP setting, accurate differentiation of influenza vs covid-19 based on symptoms will be crucial.

An epidemiological report[16] from the Australian Department of Health published on 3 Apr 2020 based on 2,257 confirmed cases (*non-hospitalised and hospitalised*) has revealed that key symptoms were:

More Common	**Less Common**
Cough (70%)	Runny nose (34%)
Fever (47%)	Muscle pain (32%)
Sore throat (45%)	Shortness of breath (22%)
Headache (49%)	Diarrhoea (18%)
	Nausea and Vomiting (15%)

Based on a study of *hospitalised* patients (N=138[8]) with Covid-19 in China the 10.1% of patients who initially presented with diarrhoea and nausea subsequently developed fever and dyspnoea 1-2 days later.

In comparison, in a study[9] of >1,000 patients with influenza, key differentiating symptoms from Covid-19 are:

1. Nasal congestion (84-92%)
2. Myalgia (49-86%)

Therefore, it may be extrapolated that, patients with:

- INFLUENZA are *more* likely to have rhinorrhoea, myalgias

While patients with:

- COVID 19 are *less* likely to have rhinorrhea and myalgias

Isolated anosmia is believed to be a significant symptom of Covid 19, based on anecdotal evidence from multiple countries around the world. In South Korea, 30% of positive patients are reported to have anosmia as their main presenting complaint. In Germany, it is believed that 2/3rds of positive cases have anosmia. See letter from ENT UK.

Clinical Progression

Patients may have mild symptoms in week one, before becoming systemically unwell in week two.

Those systemically unwell typically have clinical and radiological features of viral pneumonia[1].

Thereafter, patients may develop sepsis, acute respiratory distress syndrome (ARDS) or multi-organ failure[1,4].

The median time from onset of illness to hospitalisation for novel coronavirus pneumonia patients was seven days (range 4–8 days), with acute respiratory distress syndrome (ARDS) experienced on day eight (range 6–12 days)[8].

ARDS has a mortality rate of 40%.

Approximately 5% of symptomatic, confirmed cases require ICU admission.

Mortality rates of Covid 19 receiving invasive ventilation

A multicentre, prospective observational study[35] of ICU patients in Australia (N=204) showed that invasively ventilated patients had a mortality rate of 22%, which is significantly lower than figures from USA, Italy and China. The study does not address the complex decision-making process around ICU admission and advance care planning in Australia. Nevertheless, the median age of the ICU cohort in Australia was similar to that of the USA and Italian cohorts.

Mortality rates of ventilated, Covid 19 patients from New York City was 88.1%[29], which is consistent with figures from Wuhan, China[4] and Lombardy, Italy.

Advance Care Planning

Patients aged >80 years old admitted to ICU in Australia had a mortality rate of 64%[12].

This highlights the importance of advance care planning.

An excellent resource is available from Advance Care Planning Australia (click here).

Investigations

If patient fits criteria, send off *one* nasopharyngeal +/- throat swabs (use FLOQ swabs) for:

- Respiratory Multiplex PCR
- Coronavirus Covid-19

FBE demonstrates leucopenia in 25% of cases, and lymphopenia in 63% of cases.

Covid 19 Rapid IgG/IgM antibody tests. The Royal College of Pathologists in Australia have released a strong statement (1 Apr 2020) saying that these tests have *no* role in the acute diagnosis and early detection of Covid 19, as these tests rely on detecting antibodies to SARS-Cov2. Antibodies take 7-12 days to develop in a healthy individual, much longer in elderly and immunocompromised people.

These tests may have a role in detecting previously unrecognised infection and subsequent immunity.

Co-infection

A preprint published on medRxiv[24] found that 5.8% of cases infected with COVID-19 were co-infected with other pathogens including, influenza, respiratory syncytial virus, rhinovirus, metapneumovirus, parainfluenza, chlamydia, boca virus, mycoplasma pneumoniae, and other species of coronaviruses.

Imaging Findings

CXR: unilateral (25%) or bilateral (75%) interstitial/ground glass infiltrates[1]

In patients recovering from COVID-19 pneumonia (without severe respiratory distress during the disease course), lung abnormalities on chest CT showed greatest severity approximately *10 days* after initial onset of symptoms.[2]

In patients recovering from COVID-19 infection, four stages of evolution on chest CT were identified:

1. early stage (0-4 days);
2. progressive stage (5-8 days);
3. peak stage (10-13 days);
4. and absorption stage (≥14 days)

Complications of Covid 19

Non-respiratory complications have been reported, but are primarily confined to case series and case reports.

Thromboembolic disease

Case reports of thromboembolic disease, and stroke exist in the literature[33]. As such, based on a risk vs benefit assessment, peak bodies in Australia recommend DVT prophylaxis with enoxaparin 40mg or dalteparin 5000 IU once daily in adults with moderate COVID-19 or other indications, unless there is a contraindication, such as risk for major bleeding.

Cardiac

A case report, published on 27 Mar 2020[18] described an Italian woman who developed acute myopericarditis, without any respiratory symptoms or involvement throughout her clinical course.

A case series, published on 27 Mar 2020[19] documented that 27.8% of a cohort of 187 patients developed evidence of myocardial injury based on elevated troponin levels. 16 patients did *not* have underlying cardiovascular disease, but had elevated troponin levels. Mortality rate of this sub-group

was 37.5%. Overall mortality of the cohort of 187 patients was 23%, suggesting that a particularly unwell group of patients were recruited into this study.

Atypical Covid 19 patients may present with chest pain.
Gastrointestinal

A case series of 204 hospitalised patients[20] in China found that those with gastrointestinal symptoms (18.6%) had delays in their diagnosis and treatment. Almost 3% of this case series had gastrointestinal symptoms but no respiratory symptoms.

Atypical Covid 19 patients may present with diarrhoea, nausea, vomiting and rarely abdominal pain.

Management

The National Covid 19 Clinical Evidence Taskforce, endorsed by ASID (Australasian Society for Infectious Diseases) and ANZICS (Australian and New Zealand Intensive Care Society) has been established.

These guidelines primarily recommend supportive care.

Patients at risk of developing ARDS need to be in a facility where they can be mechanically ventilated, to improve their survival chances.

The use of Dexamethasone in patients requiring oxygen supplementation (including mechanical ventilation) is endorsed.

"The suggested regimen of corticosteroid use is 6 mg of dexamethasone (oral or intravenous) daily for up to 10 days. In patients for whom dexamethasone is not available, acceptable alternative regimens include:

- *hydrocortisone: intravenous (50 mg), every 6 hours for up to 10 days*
- *prednisolone: oral (50 mg), daily for up to 10 days."*

Source: National Covid 19 Clinical Evidence Taskforce

The use of Remdesivir may be considered outside of a trial setting. Other therapies are only recommended in the context of a trial.

As of 22 September 2020, two multi-centre RCTs of antiviral therapies for COVID-19 are continuing to recruit hospitalised patients in Australia and New Zealand: REMAP-CAP (endorsed by ANZICS), and ASCOT (endorsed by ASID).

Possible Therapeutics under trial

1. Dexamethasone. An RCT based in the UK released a pre-print[34] of their findings. 2,104 patients received dexamethasone, compared with 4,321 patients who received standard care. Dexamethasone reduced deaths by one-third in patients receiving invasive mechanical ventilation (29.0% vs. 40.7%, RR 0.65 [95% CI 0.51 to 0.82]; p<0.001), by one-fifth in patients receiving oxygen without invasive mechanical ventilation (21.5% vs. 25.0%, RR 0.80 [95% CI 0.70 to 0.92]; p=0.002), but did not reduce mortality in patients not receiving respiratory support at randomization.
2. Remdesivir. ACTT-1 trial: an international, multi-centre RCT of 1,063 patients showed that Remdesivir reduced recovery time in hospitalised patients with evidence of lower respiratory tract infection from 15 days to 11 days[31].
3. Lopinavir and Ritonavir - HIV medication. Had activity against SARS and MERS. As of 18 Mar 2020, an RCT trial with Lopinavir and Ritonavir has not demonstrated promise (see trial). However, it is believed that anti-virals were likely commenced too late in the course of the disease. Hence, trials are ongoing to commence anti-virals within 12 days of symptom onset.

Hydroxychloroquine (HCQ). On 17 June 2020, WHO announced that the hydroxychloroquine (HCQ) arm of the Solidarity Trial to find an effective COVID-19 treatment was being stopped. Data from Solidarity (including the French Discovery trial data) and the recently announced results from the UK's Recovery trial both showed that hydroxychloroquine does not result in the reduction of mortality of hospitalised COVID-19 patients, when compared with standard of care.

Medications - Anti-inflammatories and ARBs

The use of anti-inflammatories, ie. ibuprofen is discouraged, based on anecdotal reports of serious disease in four young patients after using NSAIDs. See BMJ commentary.

There has been controversy regarding Angiotensin Receptor Blockers (ARBs) in the Covid 19 pandemic. The reason is because:

1. The entry site for the SARS-Cov2 virus is ACE 2 (Angiotensin Converting Enzyme 2), of which Angiotensin 2 is a substrate
2. ARBs are known to increase ACE 2 expression by 3-5 fold, because plasma levels of Angiotensin 2 increases with ARB dosing.

Hence a theoretical risk that ARBs may increase one's vulnerability to Covid 19 infection.

However, there is currently no evidence linking ARBs with more severe outcomes in Covid 19.

Hence the strong recommendation from peak bodies, ie. Heart Foundation (Australia), and European Society of Cardiology for patients already on these medications to *continue* taking them.

Nevertheless, Professor Esler (senior director of the Baker Heart and Diabetes Institute), in the Journal of Hypertension[17] suggests:

1. If on ARBs to remain on current dose and do not escalate the dose
2. Do not cease, as it may precipitate CCF or unstable blood pressure
3. If not on ARBs, consider other agents for hypertension control
4. Don't commence ARBs if not hypertensive

The role of ACE inhibitors is less clear, but ACE inhibitors reduce plasma levels of Angiotensin 2, and hence theoretically reduces ACE 2 expression.

Aerosol generating procedures (AGPs)

Aerosol generating procedures (AGPs) should be avoided where possible, as this may cause the virus to become airborne.

Nebuliser use should be discouraged and alternative administration devices (for example, spacers) should be used[5].

Other examples of AGPs include: endo-tracheal intubation, non-invasive ventilation (BiPAP, CPAP, HFOV), manual ventilation before intubation (bag and mask), cardiopulmonary resuscitation, sputum induction, suctioning.

Patient placement and toilets

A dedicated toilet / commode should be used where possible, ensuring the lid is closed when flushed to reduce any risk of aerosolisation.

Persons under investigation and suspected cases of COVID-19 infection may be cohorted together where single rooms are not available.

Maintain a record of all persons entering the patient's room including all staff and visitors.

Environmental cleaning and disinfection

For all routine and discharge cleaning, after cleaning with a neutral detergent use a chlorine-based disinfectant (for example, sodium hypochlorite) at a minimum strength of 1000ppm[26], or other products with claims against coronaviruses. Examples are:

> *White King Bleach, sodium hypochlorite 4% chlorine may be diluted to 0.5% chlorine (5,000 ppm) to form a 'hospital-grade' intermediate-level disinfectant which will be bactericidal, virucidal, mycobactericidal, and sporicidal. Formula: 1 part bleach 4%, 7 parts water[25]*
>
> *Hydrogen Peroxide 0.5%*
>
> *Ethanol 62-71% (Click here[15] for source)*
>
> *Coles and Woolworths stock products based on benzalkonium chloride. A minimum concentration of 0.05% is required. Click here[13] and here for two international sources.*

A one-step detergent/chlorine-based product may also be used.

The patient isolation room should be cleaned at least once daily and following any aerosol generating procedure (AGP) or other potential contamination.

Droplet and contact precautions (surgical mask, protective eyewear, gloves, gown) should be implemented during any cleaning and disinfection of a room.

Discharge cleaning

If there is a possibility that the virus may have become airborne because:

1. an aerosol generating procedure was performed (ie. nebuliser used)
2. severe symptoms suggestive of pneumonia

It is recommended that the room be left for 30 minutes before cleaning and disinfection is commenced.

The exact duration in which SARS-Cov2 can persist in the environment is unclear at this time, but the coronaviruses that caused SARS and MERS were able to persist in the environment for over 48 hours, at an average room temperature of 20 degrees celsius.

Recovery

Based on 391 cases in Shenzhen, China[16], median time to recovery:

- 20-29 year olds: 27 days
- 50-59 year olds: 32 days
- >70 year olds: 36 days

Long-term Immunity

A study into the persistence of the serological response post-infection showed that the serological response to SARS-Cov2 was short-lived. This study looked at 37 people infected with symptoms and 37 asymptomatic. 8 weeks after recovery, antibody levels fell to undetectable levels in 40% of asymptomatic people and 13% of symptomatic people[28]. This is in stark contrast to SARS-CoV and MERS-CoV where circulating antibodies lasted for at least 1 year.

Similar studies on duration of serological responses based in the UK and Spain have produced similar results and conclusions.

Transmissibility post-recovery

Although there are case reports of patients testing positive post-recovery[10], it is believed these are usually ‘false positives’ due to the detection of dead virions or viral fragments.

Nevertheless, the protocol before sometime is declared ‘non-infectious’ is outlined below.

Protocol for release from isolation of Covid 19 positive cases (DHHS Vic Guidelines)

1. **Confirmed cases who are asymptomatic**

The case can be released from isolation if at least **10** days have passed since the first respiratory specimen positive for SARS-CoV-2 by PCR was taken **and** no symptoms have developed during this period.

2. **Confirmed or probable cases with mild illness (not requiring hospitalisation or admitted to hospital for reasons not directly related to acute COVID-19)**

The case can be released from isolation if they meet all of the following criteria:

- at least **10** days have passed since the onset of symptoms; and
- there has been resolution of fever and respiratory symptoms of the acute illness for the previous **72** hours

3. **Confirmed or probable cases with more severe illness (hospitalisation was indicated for acute COVID-19, regardless of whether or not the case was hospitalised)**

a. Confirmed and probable cases with resolution of fever and respiratory symptoms of acute illness

The case can be released from isolation if they meet all of the following criteria:

- at least **14** days have passed since onset of symptoms; and
- there has been resolution of fever and respiratory symptoms of the acute illness for the previous **72** hours

b. Confirmed and probable cases without complete resolution of symptoms of acute illness

The case can be released from isolation if they meet all of the following criteria

- at least **14** days have passed since the onset of symptoms; and
- there has been substantial improvement in symptoms of the acute illness (including resolution of fever for the previous **72** hours); and
- the case has had two consecutive respiratory specimens negative for SARS-CoV-2 by PCR taken **at least 24 hours apart at least 11 days from symptom onset**.

4. **Significantly immunocompromised persons.**

In **addition** to meeting the appropriate criteria described in points 1, 2, or 3a above, persons who are significantly immunocompromised and are identified as confirmed or probable cases must meet a higher standard requiring additional assessment. They can be released from isolation when they meet the following additional criterion:

- PCR negative on at least two consecutive respiratory specimens collected at least 24 hours apart at least 7 days after symptom onset.

Definition and Management of Close Contacts (DHHS Vic Guidelines)

For the purposes of testing, the department advises a precautionary understanding of close contact Close contact means greater than *15 minutes* face-to-face, cumulative over a week, or the sharing of a *closed space for more than two hours*, with a confirmed case during their infectious period without recommended personal protective equipment (PPE). Recommended PPE includes droplet and contact precautions.

Contact needs to have occurred during the period of *48 hours prior to onset of symptoms* in the confirmed case until the confirmed case is no longer considered infectious to be deemed close contact.

For all close contacts the department will:

- Advise self-quarantine including restriction on travel until *14 days* from the last contact with a confirmed case.
- Consider testing early in quarantine period to determine if close contact is a potential acquisition source for the case.
- Recommend to have testing at *day 11* of their quarantine period, regardless of whether or not they display symptoms. If tested, they must complete 14 days of quarantine and return a negative result prior to being released from quarantine

Asymptomatic cases and transmission

Based on data from the Diamond Princes cruise ship, up to 50.5% of positive cases were asymptomatic at the time of testing. Sample size of 634 positive cases[23].

There are case reports of asymptomatic transmission of the virus, up to 48 hours before the onset of symptoms. The first known case report[22] was published in NEJM on the German cluster on 30th January 2020.

A study[27] based in Singapore concluded that 6.4% of 157 cases of community transmission were from asymptomatic transmission. This underscores the importance of social distancing to reduce the spread of Covid 19.

DHHS Vic Guidelines have a precautionary approach and consider a positive case to be infectious 48 hrs prior to the onset of symptoms, for the purpose of contact tracing.

Topics not covered

As the purpose of this summary is to provide clarity on topics where there is clear evidence and established guidelines, certain topics have been excluded from in this document. These topics include:

1. Covid 19 Vaccines

2. Transmission of Covid 19 contact/droplet vs aerosol/airborne
3. Ivermectin

As more evidence emerges, these topics may be included in future iterations of this summary.

Disclaimer

Written by a rural GP, for other GP colleagues and frontline clinicians. This document is not meant to replace authorised guidance from the department of health, or any formal health authority.

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