Summary of evidence on COVID-19

1 July 2020

OBJECTIVE

This document has been produced to summarise and aid the dissemination of current evidence on COVID-19 that would be of immediate interest and use to clinicians and other healthcare workers at the frontline. The evidence summarised comes from various sources including expert opinion, current guidance documents, and studies published in peer-reviewed journals. Nevertheless, knowledge is changing rapidly and not all studies have been critically appraised. Evidence presented do not represent the formal WHO position. Individual clinicians will make care judgments based on the needs of their patients in the clinical setting.

Version history

Page	From	To	Date
14	Kawasaki disease in children and adolescent with COVID-19	Multisystem inflammatory syndrome in children and adolescent with COVID-19 to brief the current approach to the specified clusters and clinical data platform for further study.	11 June 20
26	Key findings from a study on the use of Remdesivir to 53 patients	Key findings from a preliminary study of the clinical trial of Remdesivir with 1059 patients in multi centres.	11 June 20
31	None	A section for traditional medicine is newly added to cover herbal medicines used in China and discussions in African region.	11 June 20
29	None	A section on the results of clinical trials on dexamethasone for severe COVID-19 cases is added.	1 July 2020

CONTENTS

1. General background

After initial reports of pneumonia cases of unknown aetiology in Wuhan, Hubei Province, China in December 2019 and following reports of similar cases in other countries, a Public Health Emergency of International Concern (PHEIC) was declared by WHO in January 2020. Subsequently, a worldwide pandemic of a new disease COVID-19 was declared by WHO in March 2020.

The causative agent for the newly reported disease has been identified as a novel enveloped RNA beta coronavirus now named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of 30 June 2020, a total of 10 185 374 confirmed cases had been documented globally. From the Pacific island countries and areas, there have been 378 of cases reported: Fiji (18), French Polynesia (62), Guam (247), Commonwealth of the Northern Marianas Islands (30), and New Caledonia (21).

New knowledge is emerging about the disease and the causative agent SARS-CoV2. This document is produced by the Science & Evidence Cell of the Health Ops Pillar of the Pacific Joint Incident Management Team. It focuses on, and summarises, available evidence related to clinical epidemiology of the disease which would be of interest to frontline clinicians and healthcare workers in the Pacific.

The document will be updated on a fortnightly basis and disseminated to Heads of Health and Directors of Clinical Services, Directors of Nursing, and Directors of Public Health across the Pacific. It will also be available at the JIMT document repository at this link: https://drive.google.com/drive/folders/1wrTUvOxrPQIIgtKJrHYSLJrrc8xeMSkx?usp=sharing

2. GRADE methodology and source of evidence

This document reviews available results of systematic reviews, meta-analyses, and recommendations from specialised medical societies that have considered the core elements of the GRADE evidence in the decision process, including certainty of evidence and balance between desirable and undesirable effects:

- Quality of evidence: study design, estimate of effect, level of confidence;
- balance between benefits, harms, and burdens;
- patients' values and preparedness; and
- resources and cost.

As per GRADE methodology, there are four tiers to show the level of evidence for recommendations:

- "strong" or "conditional": used if available studies and meta-analysis provide sufficient quality of evidence;
- "knowledge gap": labels for situations where studies suggest premature outcomes of diagnostics and treatments and potentially ineffective or harmful interventions;
- "in the context of a clinical trial": indicates situations where promising interventions were judged with insufficient evidence of benefit to support their use and with potential appreciable harms or costs; and
- when evidence is based on observational studies or retrospective studies, a knowledge gap is indicated as new evidence emerges.

3. The virus

3.1 Characteristics

Key evidence	Implications for clinical management in PICs
SARS-CoV-2 has some degree of similarities with Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) e.g. common mode of transmission, respiratory symptoms in most cases, but also shows very different characteristics such as highly contagious nature represented by higher R0, 3.28	Potentially, experience from managing cases of MERS and SARS, could be useful in COVID-19.
Coronaviruses are enveloped positive stranded RNA viruses that circulate among animals with some of them also known to infect humans. Bats are considered as natural hosts of these viruses, yet several other species of animals are also known to be a source. This is a new strain of viruses that has not been previously identified in humans.	Understanding of zoonotic characteristics of coronaviridae.

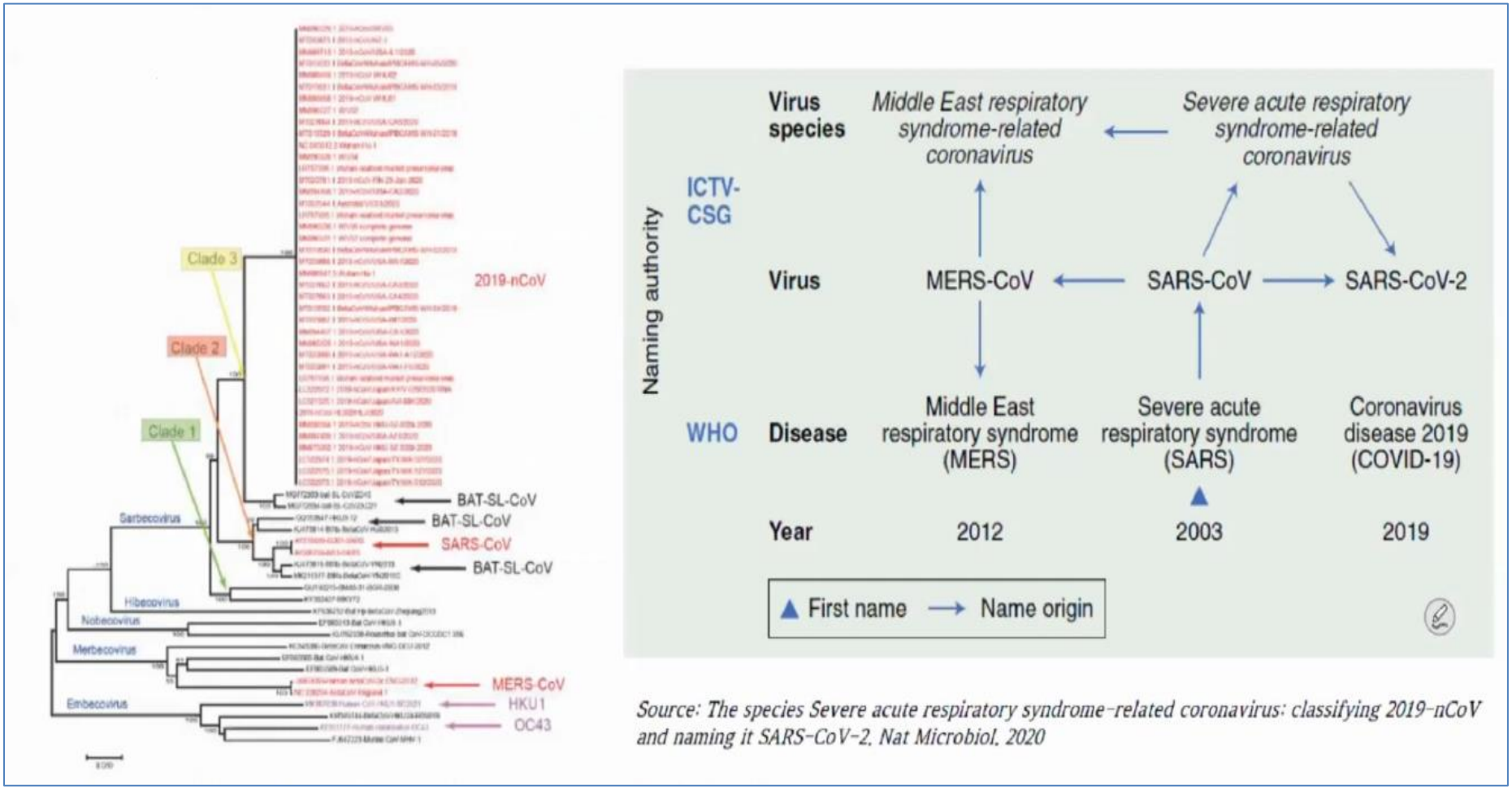


Figure 1 Phylogenetic analysis of SARS-CoV-2 and taxonomy of COVID-19 and SARS-CoV-2

3.2 Pathophysiology

Key evidence	Source of evidence [reference number]
The virus enters the cell, and then the envelope is peeled off, which let genomic RNA be present in the cytoplasm. Subgenomic RNAs produced through the transcription are translated into structural proteins which form a viral particle. Spike, envelope, and membrane proteins enter the endoplasmic reticulum, and the nucleocapsid protein is combined with the (+) strand genomic RNA to become a nucleoprotein complex. They merge into the complete virus particle in the endoplasmic reticulum-Golgi apparatus compartment and are excreted to extracellular region through the Golgi apparatus and the vesicle.	Observational study [4]
Cytokine storm There have been reports on elevated pro-inflammatory cytokines that suggest “cytokine storm” impacting younger adults. Significantly high blood levels of cytokines and chemokines were noted in patients with COVID-19 infection that included IL1-β, IL1RA, IL7, IL8, IL9, IL10, basic FGF2, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1α, MIP1β, PDGFB, TNFα, and VEGFA. Some of the severe cases that were admitted to the intensive care unit showed high levels of pro-inflammatory cytokines including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1α, and TNFα that are reasoned to promote disease severity.	Observational studies [6–14]
Myocardial injury The most common causes of COVID-19-related death are associated with the lungs and heart explained by two theories: the first theory pertains to the heart having similar ACE2 levels as the lungs, allowing viral entry into the myocardial cells; and the secondary theory involves a cytokine storm causing myocardial injury that includes acute coronary syndrome, heart failure, myocarditis, hypotension or shock, and sepsis. Among COVID-19 patients arrhythmias, malignant arrhythmias, including ventricular tachycardia and fibrillation have been observed. Cardiac markers such as troponin, N-terminal pro-B-type natriuretic peptide (NT pro-BNP), creatinine kinase – myocardial brand (CK-MB) might be increased which can independently predict severe COVID-19 cases.	Observational studies [7–11]

Acute kidney injury This can be explained by two hypotheses: 1) kidneys harbouring more ACE2 levels than the lung or heart, especially in the proximal convoluted tubules; and 2) the other theory pertains to injury via a cytokine storm. Patients may acquire continuous renal replacement therapy (CRRT) based on kidney injury severity. Speculation exists regarding CRRT potentially serving as a means of removing large cytokine levels from the system, regardless of kidney injury.	Observational studies [12–13]

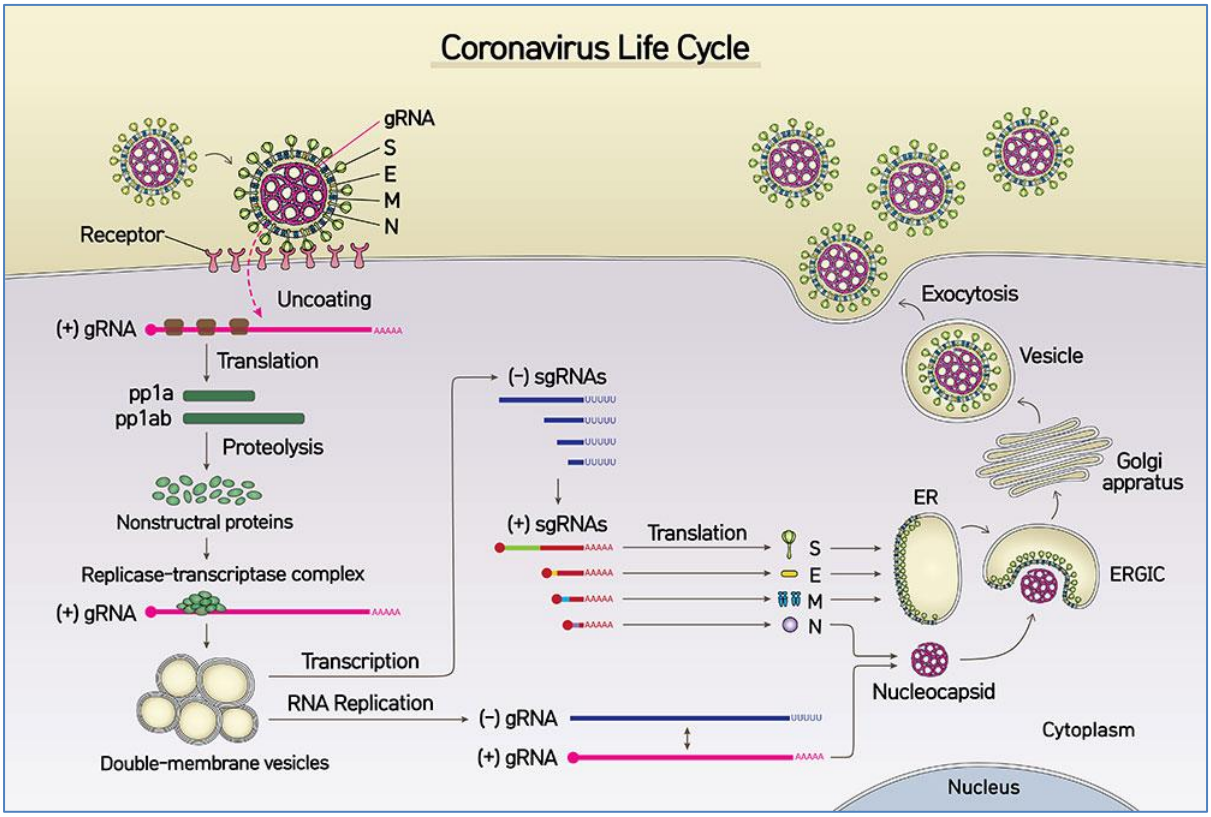


Figure 2 Natural life cycle of SARS-CoV-2

4. Clinical epidemiology

4.1 Transmissibility

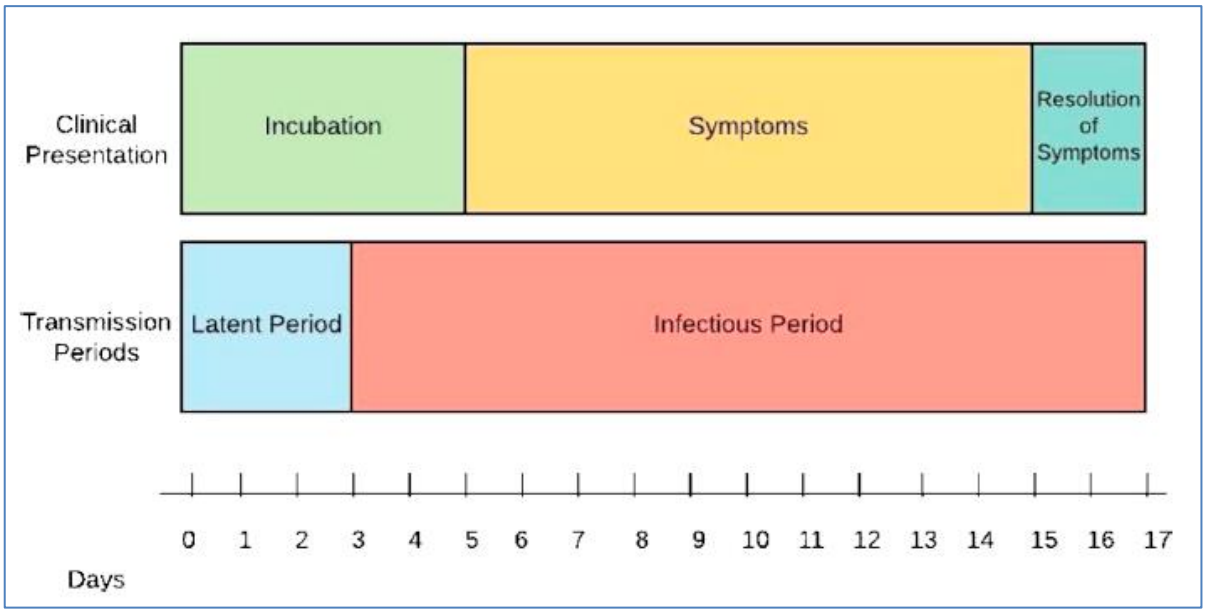
Key evidence	Source of evidence	GRADE	Implications for clinical management in PICs
Transmission is from close contact and droplet. There is scarce evidence to suggest airborne transfer. Very minimal to no RNA concentration is found in airborne samples. No RNA is detected in urine or serum samples of positive patients. Viral RNA can be detected on fomites including plastic.	Sanche S et al.	Strong	Standard and droplet precaution to ensure the prevention of nosocomial transmission.

4.2 Susceptibility

Key evidence	Source of evidence	GRADE	Implications for clinical management in PICs	Comments
SARS-CoV-2 is a novel coronavirus that all humans are susceptible to infection. Close contact with someone during their infectious period puts one at risk for acquiring the infection. However, the certainty of becoming infected is still unpredictable.	Burke et al.	Knowledge gap	Ensuring standard and droplet precaution	445 people were in close contact (at least 6 feet from the source for a minimum of 10 min) with 10 COVID-19-confirmed patients. After two weeks of testing, only two subjects became positive. Both subjects were household members that practiced isolation from the infected individuals.

4.3 Incubation period

Figure 3 Representation of COVID-19 clinical and transmission periods



Key evidence	Source of evidence	GRADE	Implications for clinical management in PICs
The mean incubation period is about 3–9 days, with a range between 0–24 days (Figure 3).	Observational studies	Knowledge gap	Contact tracing and general clinical management.

4.4 Infectious period

Key evidence	Source of evidence	GRADE	Implications for clinical management in PICs
The mean serial interval is about 3–8 days, presenting sooner than the end of incubation. This suggests that one becomes contagious before symptoms present (about 2.5 days earlier from the start of symptoms). About 44% of transmission is estimated to occur before symptoms arise.	Observational studies	Knowledge gap	Contact tracing and general clinical management.

4.5 Reproductive rate

Key evidence	Source of evidence	GRADE	Implications for clinical management in PICs
R0 is proportional to the contact rate and will vary according to the local situation. A recent review of 12 modelling studies reports the mean basic reproductive number (R0) for COVID-19 at 3.28, with a median of 2.79.	Modelling studies	Knowledge gap	It has been reported that SARS-CoV-2 has a higher reproductive rate, 3.28, than other types of coronavirus and influenza. To be able to continuously monitor the spread of the virus, Rt should be calculated based on actual epidemiological data.

4.6 Clinical presentation

4.6.1 Symptoms and clinical signs

Table 1 shows the rate of symptoms presented with positive cases of COVID-19. The most common symptoms include fever (82.2%) and cough (61.7%). These symptoms are similar to other viral respiratory diseases. However, the presentation of myalgia, sore throat, nausea, vomiting, and diarrhoea may suggest another infection instead.

Table 1 Rate of symptoms seen with COVID-19 cases

Symptoms	Rate (%)
Fever	82.2
Cough	61.7
Fatigue	44.0
Dyspnoea	41.0
Anorexia	40.0
Productive sputum	27.7
Myalgia	22.2
Sore throat	15.1
Nausea	9.4
Dizziness	9.4
Diarrhoea	8.4
Headache	6.7
Vomiting	3.6
Abdominal pain	2.2

4.6.2 Atypical presentation

Key evidence	Source of evidence	GRADE	Implications for clinical management in PICs
About 18% of cases remain asymptomatic. The potential of asymptomatic patients infecting others is proven by multiple studies concerning clusters. They can be asymptomatic and contagious regardless of lab or CT scan findings. Younger patients tend to remain asymptomatic (even if constantly around an infected individual), while the elderly usually show symptoms.	Observational studies	Knowledge gap	A significant proportion of COVID-19 may remain asymptomatic, especially in younger population.
A cross-sectional study demonstrated a high rate of asymptomatic infection among pregnant women in a pandemic situation.	Observational studies	Knowledge gap	Vulnerable populations such as pregnant women should be under close monitoring for early detection.
Possible role of COVID-19 in developing Kawasaki disease.	A case study published at Hospital Paediatrics	Knowledge gap	Atypical clinical presentations are being reported.
Increased risk of pulmonary thromboembolism that can be caused by COVID-19.	Case series reports	Knowledge gap	Pulmonary thromboembolism reported from radiologic studies.

Low-grade fever

A study with 51 lab confirmed cases in in Changzhou reported fever was the most common symptom at the onset of illness, with about half of the patients having a low-grade temperature (<38.0 °C) with a short duration of fever (<7 days). However, no significant differences were detected in the development of fever and other symptoms, including cough, sputum production, pharyngalgia, fatigue, myalgia, dyspnoea, and diarrhoea, between the three groups.

Multisystem inflammatory syndrome in children and adolescents with COVID-19

Recently, reports from Europe and North America have described clusters of children and adolescents requiring admission to intensive care units with a multisystem inflammatory condition with some features similar to those of Kawasaki disease and toxic shock syndrome. Case reports and small series have described a presentation of acute illness accompanied by a hyperinflammatory syndrome, leading to multiorgan failure and shock [13-15]. Initial hypotheses are that this syndrome may be

related to COVID-19 based on initial laboratory testing. Children have been treated with anti-inflammatory treatment, including parenteral immunoglobulin and steroids.

It is essential to characterize this syndrome and its risk factors, to understand causality, and describe treatment interventions. It is not yet clear the full spectrum of disease, and whether the geographical distribution in Europe and North America reflects a true pattern, or if the condition has simply not been recognized elsewhere.

WHO has issued an interim guideline providing clinical criteria to define preliminary case and introducing the global COVID-19 clinical data platform to share standardized and anonymized clinical data to study cases with multisystem inflammatory syndrome.

Pulmonary embolism and coronavirus

According to many reports, COVID-19 exposes patients to a particularly high risk for venous thromboembolism. Pulmonary embolism (PE) in COVID-19 patients has been reported [25-26]. Poissey et al. reports [28] that the frequency of PE in our COVID-19 series was twice higher than the frequency we found in this control period of influenza outbreak. Another radiologic report demonstrates patients with severe clinical features of COVID-19 infection, the proportion of patients with acute pulmonary embolus was 23% (95% CI: 15%, 33%) on pulmonary CT angiography.

4.6.3 Co-infection with other virus and bacteria

Table 2 presents the chance of co-infection with another microbe [22, 43-47]. Bacteria are more frequently encountered with COVID-19 compared to other viruses. The three most encountered co-infecting viruses were respiratory syncytial virus (RSV), Influenza A, and Influenza B. RSV presents with a rate of 1.44%. Influenza A and B presents with a rate of 6.47% and 5.76%, respectively. However, the calculated rate of influenza A and B co-infection was heavily influenced by the study conducted in Qingdao, China. Removing the study reduces the rate to 0.00% for both viruses.

The associated bacteria are those responsible for atypical pneumonia: Mycoplasma pneumoniae, Chlamydia pneumoniae, and Legionella pneumoniae. No studies exist presenting the rate of other bacteria, including Staphylococcus sp. and Streptococcus sp. IgM against Mycoplasma pneumoniae is most frequently encountered with a rate of 17.30%

Table 2 Summary table of co-infection of COVID-19 patients with other pathogens

Source	Lin et al. (Shenzhen, China) 2020 (N = 92) (n)	Xing et al. (Qingdao, China) 2020 (N = 30) (n)	Xing et al. (Wuhan, China) 2020 (N = 38) (n)	Chen et al. (Hubei, China) 2020 (n)	Woelfel et al. (Munich, Germany) 2020 (N = 16) (n)	Ai et al. (Xiangyang, China) 2020 (N = 102) (n)	Kim et al. (North Carolina, USA) 2020 (N = 116) (n)	Rate from total
Viruses								
RSV	3	0	1	-	0	0	6	2.5%
Flu A	0	18	0	-	0	0	1	4.8%
Flu B	0	16	0	-	0	0	0	4.1%
Corona NL63	0	-	-	-	0	-	-	0.0%
Corona 229E	0	-	-	-	0	-	-	0.0%
Corona HKU1	1	-	-	-	0	-	-	0.3%
Corona OC43	0	-	-	-	0	-	-	0.0%
Other coronaviridae	-	-	-	-	-	-	5	1.3%
Paraflu 1	0	0	0	-	0	-	1	0.3%
Paraflu 2	1	-	-	-	0	-	0	0.3%
Paraflu 3	0	-	-	-	0	-	1	0.3%
Paraflu 4	-	-	-	-	-	-	1	0.3%
Bocavirus	0	-	-	-	0	-	-	0.0%
Metapneumovirus	1	-	-	-	0	-	2	0.8%
Adenovirus	0	0	0	-	0	0	0	0.0%
Rhinovirus	0	-	-	-	0	-	8	2.0%
Bacteria								
Mycoplasma p.	-	7	1	29	-	2	0	8.9%
Chlamydia p.	-	0	0	22	-	3	0	5.8%
Legionella p.	-	6	0	-	-	-	-	1.5%
Coxiella burnetii	-	0	0	-	-	-	-	0.0%

4.7 Clinical course

Siddiqi and Mehra [15] have suggested three clinical stages that show three grades of increasing severity which correspond with distinctive clinical findings, response to therapy and clinical outcome (Table 3). In the figure, stage III represents hyper-inflammation phase that have intensified inflammatory reactions that show Acute Respiratory Distress Syndrome (ARDS), shock and cardiac failure as clinical outcomes. In most of guidelines, routine administration of corticosteroid is not recommended but when a critically ill patient present symptoms and signs of ARDS, use of steroid may help reduce inflammation reactions and increase survival rate.

Table 3 Clinical stages of COVID-19 case

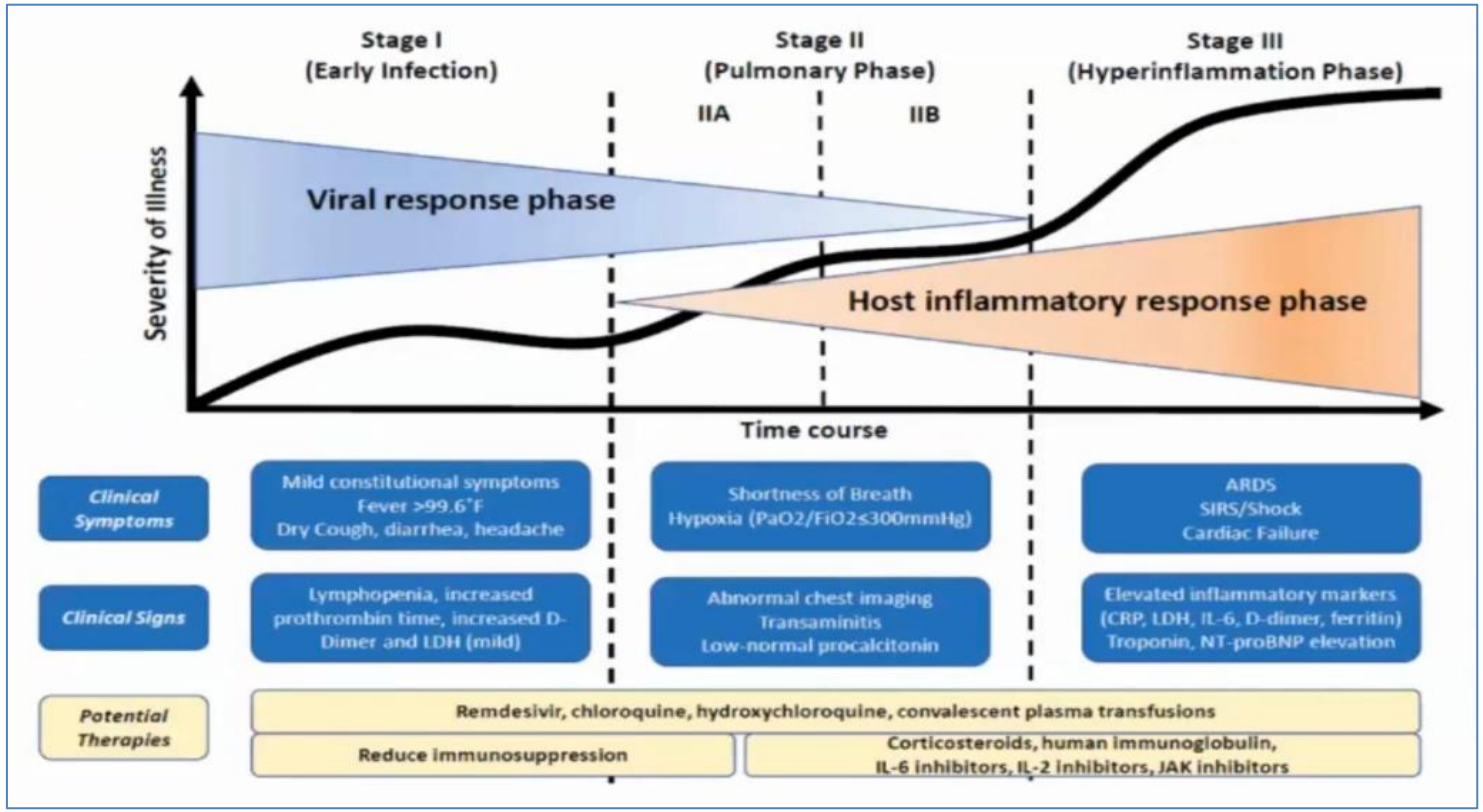


Table 4 Key evidence on clinical epidemiology of COVID-19

Key evidence	Source of evidence	GRADE	Implications for clinical management in PICs
• Symptoms tend to resolve after 10 days. • However, viral shedding continues despite symptoms disappearing. • COVID-19 RNA viral shedding persists for about 18 days (by nasopharyngeal swab) or 19 days (via faeces). • Mild and asymptomatic cases tend to shed 10 days (between 8–15 days) after symptom resolution, with 90% resolving after 10 days and nearly all cases resolving after 15 days. • Severe cases continue shedding up until 25 days after initial symptoms arise. • Severe cases also have 60 times more viral load than mild cases. • However, the infectious potential based on severity has not been discovered.	Observational studies	Knowledge gap	Due to these findings, the Chinese Municipal Health Commission has recommended against discharging patients until the patient has remained afebrile for three days and RT-PCR becomes negative.
• Prognosticating Factors • Risk factors associated with severe COVID-19 cases include elderly age, hypertension, cardiovascular disease, cerebrovascular disease, and chronic kidney disease. • Cardiovascular disease presents with a 10.5% CFR. • Other diseases that present with a high CFR include diabetes (7.3%), chronic lung diseases (6.3%), hypertension (6.0%), and cancer (5.6%). • Laboratory values contribute to survival prediction. These include elevated LDH, elevated high sensitivity-CRP, and lymphopenia. A significantly elevated LDH (> 365 units/L) presents a positive likelihood ratio of 58 for mortality based on the results.	Observational studies	Knowledge gap	

• High sensitivity-CRP also has a positive likelihood ratio of 17, but a negative likelihood ratio of 0. • Lymphopenia presents a small positive likelihood ratio of 2.65 and a small-moderate negative likelihood ratio of 0.37. • Other laboratory values that suggest a high mortality risk if elevated include aspartate aminotransferase (AST), alanine aminotransferase (ALT), D-dimer, neutrophil count, prothrombin time, procalcitonin, and high-sensitivity and regular cardiac troponin. • Low monocytes, platelets, and albumin also suggest high mortality risk. • Some chest CT scan findings, although rare with COVID-19 respiratory disease, suggest a high-risk case. These include architectural distortion, traction bronchiectasis, intrathoracic lymph node enlargement, and pleural effusions.			

Table 5 Characteristics of COVID-19, MERS, and SARS

Characteristics	COVID-19	MERS	SARS
Median incubation period	3-9 days	5 days	4-5 days
Mode of transmission	Respiratory droplets, close contact, fomites	Respiratory droplets, close contact	Respiratory droplets, close contact, fomites
Reproduction number (R0)	5.7 (95% CI: 3.8–8.9)	< 1	3
Symptoms	Fever, cough, fatigue, and dyspnoea	Fever, cough, fatigue, and shortness of breath	Fever, malaise, myalgia, headache, diarrhoea, and shivering
Number of countries affected	213 (2020. 5. 22)	27	29
Regions severely affected	China, Italy, US, Spain, France, Germany, Iran, ROK	Saudi Arabia	China, Hong Kong, Taiwan, Singapore, Canada
Number of cases globally	4,789,205 (2020. 5. 22)	2,519	8,422
Number of deaths globally	318,789 (2020. 5. 22)	866	916
Global case fatality rate	6.66% (2020. 5. 22)	34.3%	10.9%

Data source: COVID-19, Australia: Epidemiology Report 7. Commun Dis Intell. 2020; COVID-19 dashboard by JHU Center for Systems Science and Engineering; Sanche S, Lin YT, Xu C, Romero-Severson E, Hengartner N, Ke R. High contagiousness and rapid spread of severe acute respiratory syndrome coronavirus 2. Emerg Infect Dis. 2020 Jul [22 May 2020]. https://doi.org/10.3201/eid2607.200282; WHO, Consensus document on the epidemiology of severe acute respiratory syndrome (SARS), 2003.

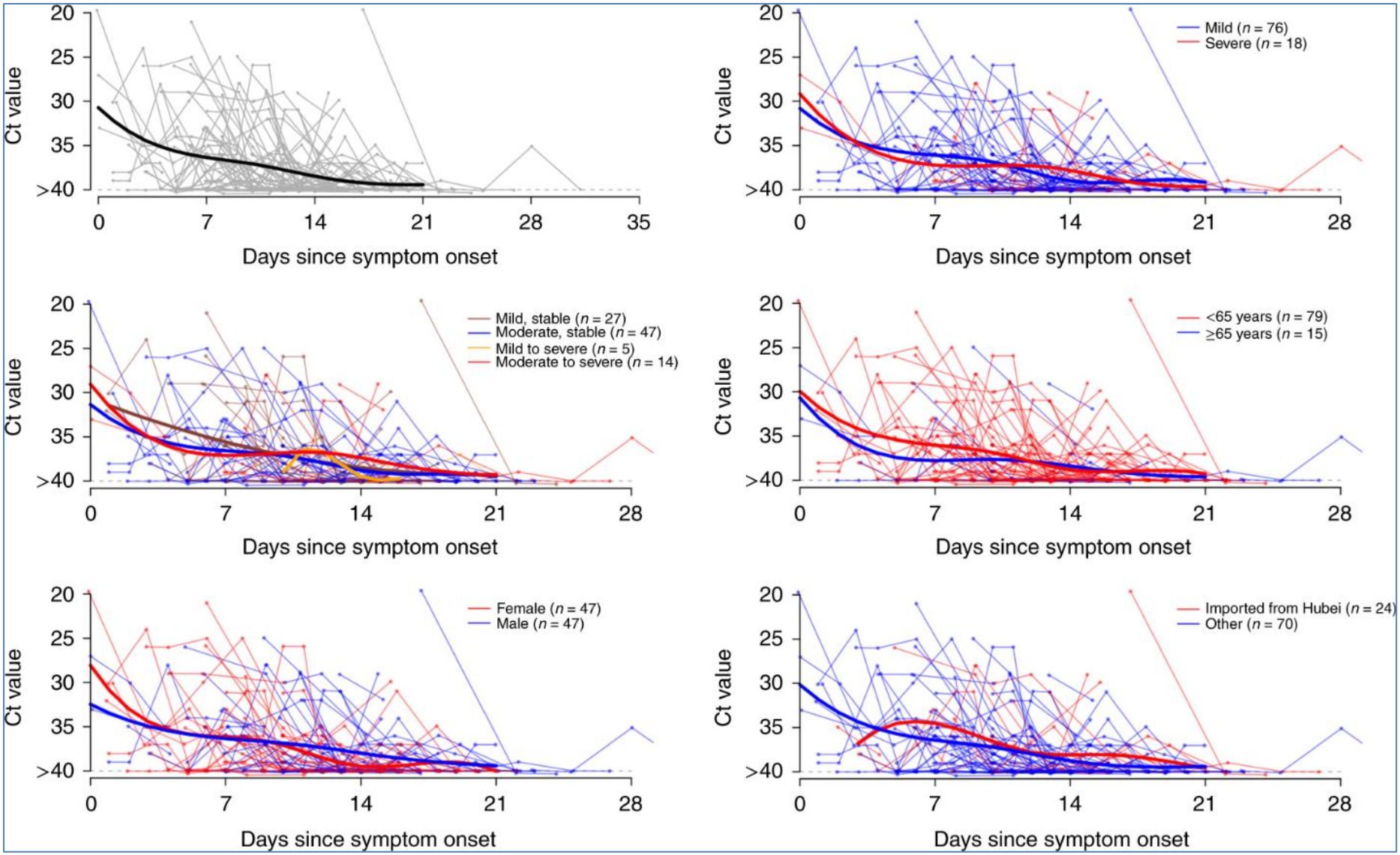


Figure 4 Temporal patterns of viral shedding

4.8 Diagnosis

Key evidence	Source of evidence	GRADE	Implications for clinical management in PICs
RT-PCR remains the gold standard for diagnosing COVID-19. While its specificity is nearly 100% from having no reported false positive cases or cross-reactivity with other viruses or estranged oligonucleotides, the sensitivity is low at 64%.	Validation studies	Strong	Continue to apply RT-PCR for diagnosing COVID-19 cases.
This correlates with a high positive likelihood ratio of 64, but a poor negative likelihood ratio of 0.3. Studies have started performing two sequential RT-PCRs to ensure true negative cases. RT-PCR tends to present negative-positive at a mean of 5.1 days, and positive-to-negative at 6.9 days.	Validation studies	Strong	Recommendations are to acquire a repeat RT-PCR 3 days after an initial negative result. Factors that may contribute to the low sensitivity of one RT-PCR may be from immature technology, variation of detection by manufacturers, low initial viral load, and improper sampling. Current evidence has led to the recommendation that two sequential RT-PCRs are done to ensure true negativity. However, testing kits are sparse during the pandemic. Some studies suggest employing chest CT scans if the initial RT-PCR is negative. CT scans have a sensitivity of 98%, despite a lower specificity.

4.8.1 Other laboratory findings

Laboratory values that suggest COVID-19 infections include lymphopenia, prolonged prothrombin time (PT), elevated lactate dehydrogenase (LDH), elevated alanine aminotransferase (ALT), elevated aspartate aminotransferase (AST), elevated D-dimer, elevated neutrophils, eosinopenia, elevated C-reactive protein (CRP), and elevated troponin (including high-sensitivity troponin). Table 4 displays the frequency of most suggested labs. The most common findings are eosinopenia (< 0.02×10^9/L) and lymphopenia (< 1.5×10^9/L) with 78.8% and 68.7%, respectively.

Table 6 Common COVID-19 lab findings

Lab findings	Rate (%)
Eosinopenia	78.8
Lymphopenia	68.7
Elevated AST	63.4
Elevated C-reactive protein	60.7
Elevated PT	58.0
Elevated LDH	47.2
Elevated D-dimer	46.4
Thrombocytopenia	36.2
Elevated ALT	21.3
Elevated HS-Troponin	12.5

4.8.2 Image findings

Key evidence	Source of evidence	Implications for clinical management in PICs
• Imaging modalities may serve as a surrogate to diagnose COVID-19. • Chest x-ray abnormalities present in 33%–60% of patients, despite most having CT scan findings. • Chest CT scans hold more potential to diagnose COVID-19 cases. • Chest CT scans of COVID-19 cases present with bilateral ground-glass opacification or consolidation (Figure 5). • Ground-glass opacification is dominant during early stages and consolidation presents at later stages. • More than two lobes are frequently affected with most patients presenting with infiltration in all five lobes.	Observational studies	Typical and atypical image characteristics of COVID-19 should be shared.

Severe cases present with more consolidation along with architectural distortion, traction bronchiectasis, lymph node enlargement, and pleural effusions. CT scan findings, compared to RT-PCR, show a sensitivity of 84%–98% and specificity of 80.5%–25%.

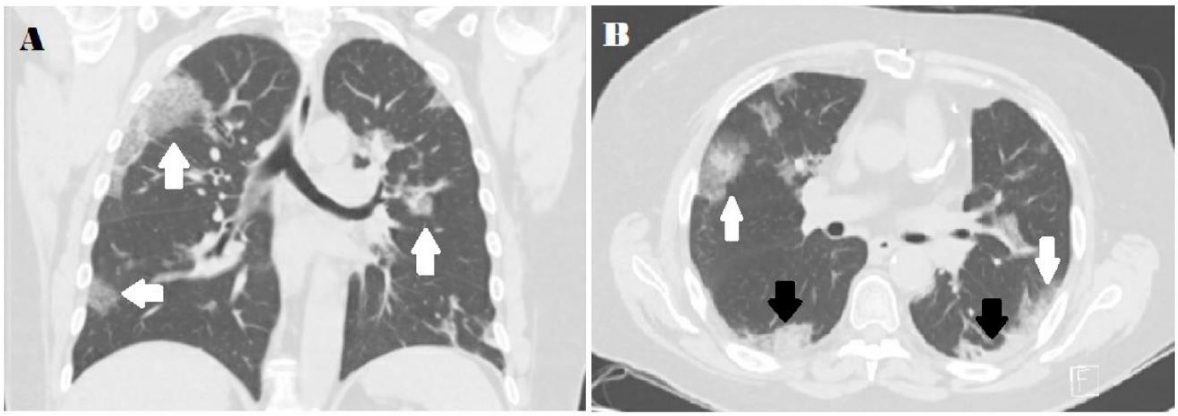


Figure 5 CT images of COVID-19 patient showing ground-glass opacities

4.9 Treatment–candidate medicines

Table 7 Summary table of candidate medicines for COVID-19

Key evidence	Source of evidence	GRADE	Implications for clinical management in PICs
Remdesivir	Preliminary reports from ongoing clinical trials	Knowledge gap	US FDA has recently approved the emergency use of Remdesivir. Coordinated efforts to ensure sufficient stockpile of Remdesivir once its effectiveness and safety is verified.
Hydroxychloroquine / chloroquine	Case studies from China and preliminary reports from ongoing clinical trials	Knowledge gap	Chloroquine is contra-indicated in the presence of glucose-6-phosphate dehydrogenase (G6PD) deficiency. In the Pacific, national estimates of G6PD deficiency are available for Solomon Islands (18.6%) and Vanuatu (6.1%). Coordinated efforts to ensure sufficient stockpile of Hydroxychloroquine/chloroquine once its effectiveness and safety is verified.
Convalescent plasma therapy	Case studies	Knowledge gap	US FDA has recently approved its investigational use for COVID-19 treatment. Guideline for convalescent plasma therapy needs to be developed with referencing other countries' clinical experience.
Lopinavir-ritonavir combined with interferon beta or other antivirals	Preliminary reports from ongoing clinical trials	Knowledge gap	Lopinavir-ritonavir is being used for investigational purpose and under clinical trials.
Dexamethasone or equivalent glucocorticoid	Preliminary reports from ongoing clinical trials	Conditional recommendation	Among hospitalized patients with severe COVID-19 (patients with SpO2 ≤94% on room air, and those who require supplemental oxygen, mechanical ventilation, or ECMO), there is a benefit in administering glucocorticoids rather than no glucocorticoids.

4.9.1. Remdesivir

Remdesivir (GS-5734) is a broad-spectrum antiviral nucleotide prodrug with potent in-vitro activity against a range of RNA viruses including Ebola virus, Marburg, MERS-CoV, SARS-CoV, respiratory syncytial virus, Nipah virus, and Hendra virus. The phase III clinical trial is being implemented to prove its efficacy and safety.

Pharmacologic mechanism

The mechanism of action of Remdesivir is premature termination of viral RNA transcription.

Target patients, dosage, and administration

Hospitalized and critically ill patients. The planned treatment in a study was a 10-day course of Remdesivir, consisting of a loading dose of 200 mg intravenously on day 1, plus 100 mg daily for the following 9 days. Supportive therapy was to be provided at the discretion of the clinicians.

Expected clinical outcomes

Therapeutic Remdesivir treatment initiated 12 hours post-inoculation reduced clinical signs, virus replication in the lungs, and decreased the presence and severity of lung lesions. A recent preliminary report of a double blinded, randomized, placebo-controlled trial of intravenous Remdesivir in 1059 adults hospitalized showed that the drug is effective in shortening the time to recovery in adults hospitalized (11 days (95% CI 9 to 12) vs. 15 days (95% CI 13 to 19)) (Figure 6).

Anticipated side effects

Adverse effects such as liver enzyme increased, diarrhoea, rash, renal impairment inter alia have been observed during the study.

Authorisation status by regulatory bodies and the status of clinical trials

Remdesivir is an investigational antiviral compound undergoing clinical trials in China, the United States, and the United Kingdom as a potential treatment for COVID-19. Globally, there are 7 investigational studies to see the efficacy of Remdesivir to COVID-19 patients. On 1 May 2020, US FDA approved the emergency use of Remdesivir.

Table 2. Outcomes Overall and According to Score on the Ordinal Scale in the Intention-to-Treat Population.*

	Overall*		Ordinal Score at Baseline							
			4		5		6		7	
	Remdesivir (N=538)	Placebo (N=521)	Remdesivir (N=67)	Placebo (N=60)	Remdesivir (N=222)	Placebo (N=199)	Remdesivir (N=98)	Placebo (N=99)	Remdesivir (N=125)	Placebo (N=147)
Recovery										
No. of recoveries	334	273	61	47	177	128	47	43	45	51
Median time to recovery (95% CI) — days	11 (9–12)	15 (13–19)	5 (4–6)	6 (4–8)	7 (6–8)	9 (7–11)	16 (NE– 10)	22 (NE– 12)	NE–NE	28 (NE– 22)
Rate ratio (95% CI)†	1.32 (1.12–1.55 [P<0.001])		1.38 (0.94–2.03)		1.47 (1.17–1.84)		1.20 (0.79–1.81)		0.95 (0.64–1.42)	
Mortality										
Hazard ratio (95% CI)	0.70 (0.47–1.04)		0.46 (0.04–5.08)		0.22 (0.08–0.58)		1.12 (0.53–2.38)		1.06 (0.59–1.92)	
No. of deaths by day 14	32	54	1	1	4	19	13	13	13	19
Kaplan–Meier estimate — % (95% CI)	7.1 (5.0–9.9)	11.9 (9.2–15.4)	1.5 (0.2–10.1)	2.5 (0.4–16.5)	2.4 (0.9–6.4)	10.9 (7.1–16.7)	15.2 (9.0–25.0)	14.7 (8.7–24.3)	11.3 (6.7–18.8)	14.1 (9.2–21.2)
Ordinal score at day 15 (±2 days) — no. (%)‡										
Patients with baseline and day 15 score data — no.	434	410	60	51	196	161	71	77	101	115
1	99 (22.8)	76 (18.5)	22 (36.7)	15 (29.4)	54 (27.6)	45 (28.0)	13 (18.3)	7 (9.1)	10 (9.9)	8 (7.0)
2	158 (36.4)	127 (31.0)	25 (41.7)	21 (41.2)	95 (48.5)	66 (41.0)	28 (39.4)	27 (35.1)	6 (5.9)	10 (8.7)
3	11 (2.5)	6 (1.5)	7 (11.7)	4 (7.8)	4 (2.0)	2 (1.2)	0	0	0	0
4	23 (5.3)	20 (4.9)	1 (1.7)	3 (5.9)	12 (6.1)	7 (4.3)	4 (5.6)	4 (5.2)	6 (5.9)	6 (5.2)
5	34 (7.8)	40 (9.8)	3 (5.0)	5 (9.8)	14 (7.1)	6 (3.7)	2 (2.8)	7 (9.1)	15 (14.9)	22 (19.1)
6	16 (3.7)	14 (3.4)	1 (1.7)	0 (0)	1 (0.5)	3 (1.9)	6 (8.5)	6 (7.8)	7 (6.9)	5 (4.3)
7	60 (13.8)	72 (17.6)	0 (0)	2 (3.9)	12 (6.1)	12 (7.5)	5 (7.0)	13 (16.9)	43 (42.6)	45 (39.1)
8	33 (7.6)	55 (13.4)	1 (1.7)	1 (2.0)	4 (2.0)	20 (12.4)	13 (18.3)	13 (16.9)	14 (13.9)	19 (16.5)
Odds ratio (95% CI)	1.50 (1.18–1.91 [P=0.001])		1.51 (0.76–3.00)		1.31 (0.89–1.92)		1.60 (0.89–2.86)		1.04 (0.64–1.68)	

* P values and confidence intervals have not been adjusted for multiple comparisons. NE denotes not possible to estimate.

† Recovery rate ratios and hazard ratios were calculated from the stratified Cox model; P values for these ratios were calculated with the stratified log-rank test. Recovery rate ratios greater than 1 indicate a benefit for remdesivir; hazard ratios less than 1 indicate a benefit for remdesivir.

‡ The ordinal score at day 15 is the patient's worst score on the ordinal scale during the previous day. In the remdesivir group, 103 patients did not have ordinal scale scores for the day 15 visit at the time of the data freeze (11 with mild-to-moderate illness and 92 with severe illness). In the placebo group, 109 patients did not have ordinal scale scores for the day 15 visit at the time of the data freeze (12 with mild-to-moderate illness and 97 with severe illness). Two patients died 15 days after randomization and are included in the ordinal scale scores but not in the estimate of mortality by day 14. Scores on the ordinal scale are as follows: 1, not hospitalized, no limitations of activities; 2, not hospitalized, limitation of activities, home oxygen requirement, or both; 3, hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection-control reasons); 4, hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (Covid-19–related or other medical conditions); 5, hospitalized, requiring any supplemental oxygen; 6, hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices; 7, hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); and 8, death. Odds ratios and P values were calculated with the use of a proportional odds model. Odds ratio values greater than 1 indicate a benefit for remdesivir.

Figure 6 Overall outcomes of Remdesivir and placebo treatment groups

4.9.2. Hydroxychloroquine/chloroquine

The recent publication of results showing the activity of chloroquine (CQ) against SARS-CoV-2 in vitro, some experts and researchers also have been recommended the efficacy of this antimalarial drug in patients with COVID-19. For this, the U.S. Food and Drug Administration (FDA) has been working to investigate the use of CQ in COVID-19. As a derivative of CQ, hydroxychloroquine (HCQ) has similar therapeutic effects and fewer adverse effects. However, the efficacy of HCQ in COVID-19 remains unknown. This document reviews the best knowledge on CQ and HCQ in treating COVID-19 patients.

Suggested pharmacologic mechanism

CQ and its derivatives have been broadly used as immunomodulators in the treatment of systemic lupus erythematosus (SLE) and other rheumatism. As the pharmacological mechanism of CQ is further elucidated, its additional clinical applications, especially the antiviral activity, are also increasingly valued. The efficiency of CQ has been proven in a variety of viruses, including human coronavirus. Researchers have even reported both prophylactic and therapeutic advantages of CQ for SARS-COV infection.

Target patients, dosage, and administration

Clinical trials targeting hospitalized patients had been undertaken in 2020 in China. Chen Z. et al.'s study and Chen J. et al.'s study had administered 400 mg/d for five days plus conventional treatment [30-31].

Expected clinical outcomes

The currently available best evidence failed to demonstrate or a beneficial effect of HCQ on clinical progression of COVID-19. Two clinical trials done in China have reported changes of radiological findings (RR: 0.61; 95% CI: 0.26, 1.43), or on viral clearance by PCR tests (RR: 2.00; 95% CI: 0.02, 20.00), clinical improvement (RR: 1.47; 95% CI 1.02, 2.11). However, the certainty in the evidence was rated as very low mainly due to small sample sizes, co-interventions, and risk of bias due to methodological limitations. Studies evaluating the addition of azithromycin to HCQ provided indirect comparisons of failure of virologic clearance to historical controls. The observed risk of mortality among patients receiving HCQ+AZ during hospital stay was 3.4% (6/175 patients), but an estimated mortality rate in an untreated cohort was not provided in the manuscript.

Anticipated side effects

Two studies described significant QT prolongation in electrocardiogram in 10 of 95 treated patients. In another prospective cohort study in 224 COVID-19 uninfected patients with SLE who received either CQ or HCQ for routine care, gastrointestinal side effects occurred in 7% of patients. CQ and HCQ are metabolized by cytochrome P450 isoenzymes 2C8, 2D6, and 3A4, therefore inhibitors and inducers of these enzymes may result in altered pharmacokinetics of these agents.

4.9.3. Convalescent plasma therapy

The COVID-19 patient guideline by the Infectious Disease Society of America (IDSA) has reviewed published articles and reports on the convalescent plasma therapy. There have been two case series of a total of 15 patients reporting on the outcomes of mortality, failure of clinical improvement (as inferred by need for continued mechanical ventilation), and treatment related adverse events among hospitalized patients with COVID-19 infection. The guideline concluded that:

Benefits

As compared with a 30% mortality rate in the historical control (3/10), no deaths were reported among patients receiving COVID-19 convalescent plasma. Out of eight patients across both studies on mechanical ventilation at time of treatment, 50% (n=4) were extubated at time of data collection.

Harms

Among 10 patients, no serious adverse reactions or safety events were recorded following COVID-19 convalescent transfusion.

Other considerations

The IDSA guideline panel agreed on the overall certainty of evidence as very low due to concerns with risk of bias and imprecision. Continuation of mechanical ventilation was used as a surrogate for failure of clinical improvement; however, the panel recognized the importance of the timeframe for extubation when associating it to plasma transfusion. Given the limited information provided about time of extubation, the panel recognized an additional knowledge gap with the assessment of this outcome.

4.9.4. Lopinavir-ritonavir combined with interferon beta or other antivirals

Lopinavir-ritonavir is a combination of protease inhibitors for the treatment of HIV infection. Lopinavir-ritonavir has been shown to have in-vitro antiviral activity against beta-coronaviruses such as SARS-CoV, and MERS-CoV. Since lopinavir-ritonavir is not specifically designed for treatment of coronavirus, lopinavir-ritonavir alone may not demonstrate a difference from placebo in reducing viral load when treatment was initiated at a median of 13 days after symptoms onset. In an open label treatment trial, lopinavir-ritonavir with ribavirin reduced the mortality and requirement of intensive care support of hospitalized SARS patients compared with historical control. Many interferons, especially interferon beta have been shown to have modest in-vitro antiviral activity against SARS-CoV and MERS-CoV. Lopinavir-ritonavir or interferon beta-1b has been shown to reduce viral load of MERS-CoV and improve lung pathology in a nonhuman primate model of common marmoset. Lopinavir/ritonavir and interferon-β1b alone or in combination are being evaluated in clinical trials.

4.9.5. Corticosteroid use in treating severe COVID-19 cases

In March 2020, RECOVERY trial, a randomized clinical trial, was established to test a range of potential treatments for COVID-19, including low-dose dexamethasone, with over 11,500 patients enrolled from 175 NHS hospitals in the UK.

In the study, a total of 2104 patients were randomized to receive dexamethasone 6 mg once per day (either by mouth or by intravenous injection) for ten days and were compared with 4321 patients randomized to usual care only. The analysis found that dexamethasone reduced deaths by one-third in ventilated patients (rate ratio 0.65 [95% confidence interval 0.48 – 0.88]) and by one fifth in other patients receiving oxygen only (0.80 [0.67 – 0.96]). There was no benefit observed among patients who did not require respiratory support (1.22 [0.86 – 1.75]) [52].

In the early days of the SARS-CoV-2 pandemic, based on experience in both SARS and MERS, recommendations cautioned against the use of systemic corticosteroids due to risk of worsening clinical status, delayed viral clearance, and adverse events [53-55]. Given the hyper-inflammatory state in COVID-19, immunomodulatory approaches, including steroids, continue to be evaluated to

address both ARDS and systemic inflammation. ARDS stemming from dysregulated systemic inflammation may translate into prolonged ventilatory requirements and in-hospital mortality. In non-viral ARDS settings there is increasing support for the role of steroids in the management of ARDS. A recent multicenter RCT in patients with moderate-severe ARDS demonstrated a reduced number of ventilatory days and reduction in mortality with use of a 10-day regimen of dexamethasone [56].

Despite clinical benefit of dexamethasone to severe COVID-19 cases, it has been known that patients receiving a short course of steroids may experience hyperglycemia, neurological side effects (e.g. agitation/confusion), adrenal suppression, and risk of bacterial and fungal infection [57-59]. Therefore, it is suggested that dexamethasone or equivalent corticosteroids apply to patients with severe COVID-19, patients with SpO2 ≤94% on room air, and those who require supplemental oxygen, mechanical ventilation, or ECMO only but there is no clear benefit for patients with COVID-19 without hypoxemia requiring supplemental oxygen. In the trial, a dose of 6 mg once daily for ten days has been used and for pregnancy or breastfeeding women, prednisolone (a milder corticosteroid) 40 mg administered by mouth has been used.

As a drug included in the WHO essential medicines list, dexamethasone is generally available in most countries and there are multiple manufacturers of the product.

4.9.6. Traditional and Complementary Medicine (TCM) and COVID-19

In exploring new therapeutic drugs and the effectiveness of existing drugs to treat COVID-19, the use of traditional and complementary medicine has been sought. This section summarizes current knowledge on the use of traditional medicines for COVID-19 treatment.

There have been several attempts, mostly in China, to use traditional medicine in the early stages of this outbreak to strengthen supportive care for COVID-19 patients. This is mainly because TCM proved to be effective among patients with severe acute respiratory syndrome (SARS) during the SARS epidemic. The Chinese Government promoted the use of TCM herbs, hence, 85% of COVID-19 patients in China received combined treatment with regular medication and traditional remedies. Various TCM formulas were used, including Yin Qiao San, Yu Ping Feng San and Lian Hua Qing Wen capsules.

In addition to activities exploring effective traditional and herbal medicine in the Western Pacific region, WHO Regional Office for Africa and Member States in Africa continue to support scientific research to identify therapeutic effects of traditional medicine. On 12 May 2020, WHO AFRO convened a regional meeting with African traditional medicine experts to discuss options for the conduct of clinical trials on candidate traditional medicines in the region. In particular, an Artemisia based drink sold as COVID-Organics which has been claimed as effective preventive and cure drugs, is under discussion as a candidate for clinical trials to prove its effectiveness.

Table 8 Key findings from review articles on traditional medicine and COVID-19

Authors	Journal and issued date (link)	Findings	Implications for the Pacific
Yang Y et al.	International Journal of Biological Sciences, 15 March 2020	• Reviewed herbal formula used for SARS-COV and its therapeutics effect. • Reviewed the identified modes of action of 14 herbal extracts. • Introduced CTM recommended by the Government-issued guideline such as Qing Fei Pai Du Tang for mild and general COVID-19 cases and Xue Bi Jing Injection, Re Du Ning Injection for critical cases.	• Regulatory authorization issues must be fully considered if TCMs are being explored • Evidence for therapeutic effectiveness and safety limited • Need for robust mechanisms to monitor safety and adverse events
Lin A et al.	Complementary Therapies in Clinical Practice, May 2020	• Reviewed the herbal formulae, and the composition of herbs recommended by recent guidelines for the treatment of pediatric COVID-19. • Of the total of 56 herbs recommended, the herb, *Armeniacae Semen,* was one of the highly use for the treatment for pediatric COVID-19.	
Lin A et al.	Integrative Medicine, 2 June 2020	• Identified 28 traditional medicine treatment guidelines (26 Chinese government issued guidelines and 2 Korean guidelines). • Found Glycyrrhizae Radix et Rhizoma, Armeniacae Semen Amarum, Ephedrae Herba, and Gypsum Fibrosum to be the herbs with the high frequency of usage in the Chinese guidelines.	

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