This is not a clinical guideline or an SOP. It is a summary of the evidence internationally on the presentation of COVID-19 and some suggestions as to how cases may need to be assessed which clinicians may find useful. It is subject to change as more evidence becomes available, but we thought it useful to bring it together to support clinicians

Symptoms

	Guan et al[1] (n=1081)	Young et al[2] (n=18)	Yang et al[3]. Critical Care admissions (n=52)	Chen et al[4] (n=99)	Huang et al[5] (n=41)	Xu et al[6] (n=62)
Constitutional						
Fever	473 (43%)	13 (72%)	46 (88%)	82 (83%)	40 (98%)	48 (77%)
Myalgia	164 (15%)		6 (12%)	11 (11%)		
Headache	150 (14%)		3 (6%)	8 (8%)	2 (8%)	21 (34%
Upper Respiratory						
Rhinorrhoea	53 (5%)	1 (6%)	3 (6%)	4 (4%)		
Sore Throat	153 (14%)	11 (61%)		5 (5%)		
Lower Respiratory						
Dyspnoea	205 (19%)	2 (11%)	33 (64%)	31 (31%)	22 (55%)	2 (3%)
Chest Tightness						
Cough	745 (68%)	15 (83%)	40 (77%)	81 (82%)	31 (76%)	50 (81%)
Sputum	370 (34%)				11 (28%)	35 (56%)
Haemoptysis	10 (1%)				2 (5%)	2 (3%)
Gastrointestinal						
Nausea/ Vomiting	55 (5%)		2 (6%)	1 (1%)		
Diarrhoea	42 (4%)	3 (17%)		2 (2%)	1 (3%)	3 (5%)

We are continuing to learn about the presentation of the disease. The consistent features seem to be continuous cough and fever, but other features can be present.

COVID-19 may cause constitutional symptoms, upper respiratory symptoms, lower respiratory symptoms, and, less commonly, gastrointestinal symptoms. Most patients will present with constitutional symptoms and lower respiratory symptoms (e.g. fever and cough).

The frequency of fever is variable between studies (ranging from 43% to 98% as shown in the table above). This may relate to exact methodology used in various studies, different levels of illness severity between various cohorts, or different strains of the virus present in various locations.

Regardless of the exact numbers - absence of a fever does not exclude COVID-19.

Gastrointestinal presentations: up to 10% of patients can present initially with gastrointestinal symptoms (e.g. diarrhea, nausea), which precede the development of fever and dyspnoea[7]

"Silent hypoxemia" - some patients may develop hypoxemia and respiratory failure without dyspnoea (especially elderly).[8]

Physical examination is generally nonspecific. About 2% of patients may have pharyngitis or tonsil enlargement[1].

Clinical assessment

History taking and Examination where presentation is atypical, paying particular reference to pre-existing conditions or features that might suggest alternative causes for deterioration or fever. This will need to be face to face where there is diagnostic uncertainty despite telephone or ideally video consultation

Patients can be divided into three groups, essentially

Category One Patients with probable COVID-19 who are acutely deteriorating and for whom urgent hospital assessment and or resuscitation is required

Category Two Patients with probable COVID-19 other causes for deterioration having been discounted who after physical assessment are deemed not to need hospital admission

Category Three Patients with probable COVID-19 disease, but whose symptoms are such that they are not significantly compromised and can manage at home with adequate safety netting

There will be a small group who are identified clinically as having other causes for being unwell or deterioration and in whom COVID-19 is highly unlikely. These patients will need to be managed according to standard guidelines where possible.

Understandably there is no tool that is validated for use in assessing patients with COVID-19, so clinical judgement is important. Recording physiology sufficient to be able to calculate a NEWS2 [9, 10]value would seem appropriate. Firstly, it is an objective measure of deterioration which is all cause and is well understood by both ambulance and hospital services, consequently it helps with communication and stratification of concern when there is maximum pressure on all services.

Secondly in recording the physiology associated with NEWS2 in patients who you consider well enough not to need hospital admission you are making an objective record of their relative wellness at the time of your assessment and aiding subsequent clinicians to detect change and deterioration.

Physiological parameter	Score 3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO_2 Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

How the scores match with COVID-19 patients is not clear, and clinical judgement is still important plays a part. The table below is a proposal as to how NEWS could be used to aid standardisation of difficult decisions at times of pressure and allow equity of access to all whilst still respecting clinical judgement. Consideration should be given for patients who have Emergency Health Care Plans or for whom escalation of care to hospital would be burdensome and ultimately unsuccessful, e.g. extreme elderly, frail or end stage dementia.

NEWS as an adjunct to clinical judgement in COVID-19			
0-2	**3-4**	**5-6**	**7**
Physiology suggests very low probability of significant illness	Physiology suggest low probability of significant illness	Physiology suggests moderate possibility of significant illness	Physiology suggests strong possibility of significant illness
Clinician judgement may be needed	Needs clinician assessment and judgement to confirm	Needs clinician assessment and judgement to decide if escalation of care is appropriate and not burdensome	If escalation is appropriate and clinical judgement confirms Resuscitation and urgent assessment may be required

From what we know about sepsis, increased respiratory rate, low blood pressure and newly altered cognition/confusion are all strong indicators of being significantly unwell with infection. Pulse and temperature are less so. Oximetry is important as one of the mechanisms of acute deterioration in COVID-19 is respiratory failure which may be better picked up with good quality oximetry. Ideally this should be done with a medical grade oximeter[11]

There is no equivalent scoring tool for children, who will need to be assessed clinically.

COVID-19 Safety Netting Advice

Let me tell you what signs to look out for, that might indicate things were getting worse. If you start to:

- become significantly breathless,
- or develop pains in your chest,
- or become pale and clammy 'like someone who is about to vomit",
- or seem muddled or confused

'then you should seek urgent medical advice

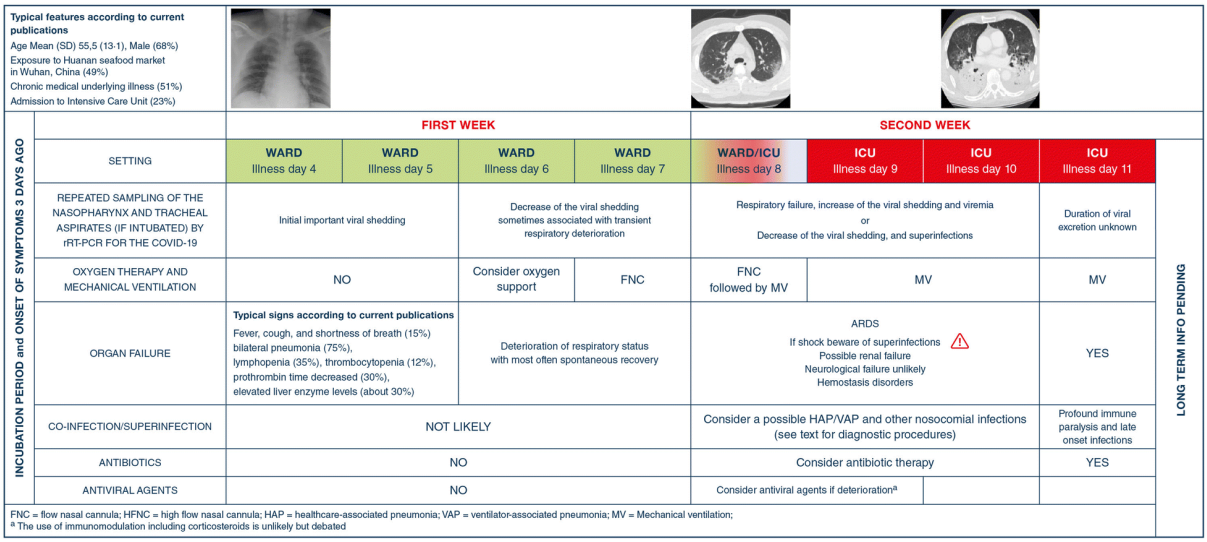
Pathophysiology

- (1) ARDS
  - The primary pathology is ARDS, characterized by diffuse alveolar damage (e.g. including hyaline membranes). Pneumocytes with viral cytopathic effect are seen, implying *direct* virus damage (rather than a purely hyper-inflammatory injury;
- (2) Cytokine storm
  - Emerging evidence suggests that some patients may respond to COVID-19 with an exuberant "cytokine storm" reaction (with features of bacterial sepsis or hemophagocytic lymphohistiocytosis).
  - Clinical markers of this may include elevations of C-reactive protein and ferritin, which appear to track with disease severity and mortality[12]

Stages of illness

- There seem to be different stages of illness that patients may move through[13].
  - (#1) Replicative stage – Viral replication occurs over a period of several days. An innate immune response occurs, but this response fails to contain the virus. Relatively mild symptoms may occur due to direct viral cytopathic effect and innate immune responses.
  - (#2) Adaptive immunity stage – An adaptive immune response eventually kicks into gear. This leads to falling titres of virus. However, it may also increase levels of inflammatory cytokines and lead to tissue damage – causing clinical deterioration.
- This progression may explain the clinical phenomenon wherein patients are relatively OK for several days, but then suddenly deteriorate when they enter the adaptive immunity stage[2]
- This has potentially important clinical implications:
  - Initial clinical symptoms aren't necessarily predictive of future deterioration. At present we do not have a tool to predict outcomes although we are starting to understand the groups who are prone to poor outcomes. These groups are currently being advised to shelter and socially isolate
  - Anti-viral therapies might need to be deployed *early* to work optimally (during the replicative stage).

Typical hospital progress



Typical features according to current publications Age Mean (SD) 55,5 (13·1), Male (68%) Exposure to Huanan seafood market in Wuhan, China (49%) Chronic medical underlying illness (51%) Admission to Intensive Care Unit (23%)									
INCUBATION PERIOD and ONSET OF SYMPTOMS 3 DAYS AGO		FIRST WEEK				SECOND WEEK			LONG TERM INFO PENDING
	SETTING	WARD Illness day 4	WARD Illness day 5	WARD Illness day 6	WARD Illness day 7	WARD/ICU Illness day 8	ICU Illness day 9	ICU Illness day 10	ICU Illness day 11
	REPEATED SAMPLING OF THE NASOPHARYNX AND TRACHEAL ASPIRATES (IF INTUBATED) BY rRT-PCR FOR THE COVID-19	Initial important viral shedding		Decrease of the viral shedding sometimes associated with transient respiratory deterioration		Respiratory failure, increase of the viral shedding and viremia or Decrease of the viral shedding, and superinfections			Duration of viral excretion unknown
	OXYGEN THERAPY AND MECHANICAL VENTILATION	NO		Consider oxygen support	FNC	FNC followed by MV	MV		MV
	ORGAN FAILURE	**Typical signs according to current publications** Fever, cough, and shortness of breath (15%) bilateral pneumonia (75%), lymphopenia (35%), thrombocytopenia (12%), prothrombin time decreased (30%), elevated liver enzyme levels (about 30%)		Deterioration of respiratory status with most often spontaneous recovery		ARDS If shock beware of superinfections ⚠ Possible renal failure Neurological failure unlikely Hemostasis disorders			YES
	CO-INFECTION/SUPERINFECTION	NOT LIKELY				Consider a possible HAP/VAP and other nosocomial infections (see text for diagnostic procedures)			Profound immune paralysis and late onset infections
	ANTIBIOTICS	NO				Consider antibiotic therapy			YES
	ANTIVIRAL AGENTS	NO				Consider antiviral agents if deterioration[a]			

FNC = flow nasal cannula; HFNC = high flow nasal cannula; HAP = healthcare-associated pneumonia; VAP = ventilator-associated pneumonia; MV = Mechanical ventilation;
[a] The use of immunomodulation including corticosteroids is unlikely but debated

Figure 1 Severe SARS-CoV-2 infections: practical considerations and management strategy for intensivists[14]

Treatment

Supportive treatments are the mainstay of treatment currently, with the majority of patients improving without need of hospital intervention. Tamiflu and other anti-influenza drugs appear ineffective. Treatments specific for Coronavirus are actively being sought.

Steroids have previously been unhelpful for MERS and SARS[15] and should not be used unless there is diagnostic uncertainty e.g. Asthma or COPD. They must be used where patients are at risk of Addisonian Crisis.

Investigations

This currently includes ruling out other respiratory infections such as influenzas, or acute deterioration such as appendicitis, sepsis or other lung conditions. Currently Reverse transcriptase Polymerase Chain reaction RT-PCR and CT scans can be used to detect Corona viruses

Sensitivity

Sensitivity compared to CT scans

In a case series diagnosed on the basis of clinical criteria and CT scans, the sensitivity of RT-PCR was only ~70% [16]

Sensitivity varies depending on assumptions made about patients with conflicting data (e.g. between 66-80%;[17]

Among patients with suspected COVID-19 and a negative initial PCR, repeat PCR was positive in 15/64 patients (23%). This suggests a PCR sensitivity of <80%. Conversion from negative to positive PCR seemed to take a period of days, with CT scan often showing evidence of disease well before PCR positivity[17]

A single negative RT-PCR doesn't exclude COVID-19 (especially if obtained from a nasopharyngeal source or if taken relatively early in the disease course).

If the RT-PCR is negative but suspicion for COVID-19 remains, then ongoing isolation and re-sampling several days later should be considered.

Summary

Coronavirus probably causes direct damage to the lungs in addition to provoking a massive inflammatory response. The circulatory collapse and generalised organ failure is akin to that seen in septic shock and can be just as sudden.

Inflammatory markers seem to track the severity of the disease.

The mean onset time is 5.2 days. The presentation is variable with the primary features being temperature and dry cough. Initial symptoms do not appear to be predictive of outcome. The majority of patients make a largely uneventful recovery, but a small proportion show an acute deterioration about day five of their illness.

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