LIBYAN RESPIRATORY BOOK ON COVID-19

كتاب الصدرية الليبي عن مرض كورونا

لجنة استشاري الأمراض الصدرية – اللجنة الاستشارية العليا لمواجهة جائحة كورونا
الجمعية الليبية للصدرية

يونيو 2020

توطئـــة

في ظل ما يشهده العالم من انتشار جائحة كورونا المستجد، فقد رأت الجمعية الليبية للصدرية من خلال ثلة من استشاريي وأخصائيي الأمراض الصدرية أعضاء لجنة استشاريي الأمراض التنفسية أن تصدر هذا الدليل والذي يتناول في جوانبه طرق التشخيص وإمكانية العلاج وعزل المرضى وشروط الدخول والخروج من مراكز العزل والتعريف بالحالة المرضية وما يجري من أبحاث لعلاج هذه الجائحة، وكذلك اللقاحات المتوقعة لها.

وإذ نقدم هذا الكتاب للسادة الأطباء في بلادنا للاستفادة والإفادة سواء في القطاعين العام والخاص ومراكز العزل لهذه الجائحة، فإننا نسأل الله العظيم أن يحمي بلادنا من كل سوء ومكروه.

والله من وراء القصد

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Contents

Introduction

Coronaviruses are important human and animal pathogen. In Dec 2019, a novel coronavirus was identified as the cause of cluster of pneumonia cases in Wuhan, a city in Hubei province of china. It rapidly spread, resulting in an epidemic throughout china, followed by an increasing number of cases in other countries throughout the world. On January 30, 2020, the World Health Organisation declared covid-19 outbreak a global health emergency. On March 11, 2020, the who declared covid-19 a global pandemic, its first such designation since declaring H1N1 influenza a pandemic in 2009. The virus that causes covid-19 is designated severe acute respiratory syndrome coronavirus-2 (SARS-COV2). Cases are rising daily in Africa the Americas, and Europe.

The WHO, the American CDC and countries are racing to slow the spread of the virus by testing and treating patients, carrying out contact tracing, limiting travel, quarantining citizens, and concealing large gatherings such as sporting events, schools and business closures. These policies may be required for long periods to avoid rebound viral transmission.

CONSULTANCY SCIENTIFIC COMMITTEE AGAINST
PANDEMIC CORONA VIRUS - GNA, Libya.
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Diagnostics in COVID-19

All patients admitted to medical or respiratory department with suspected or confirmed COVID-19 should have the following work up, to support diagnosis, assess severity, assess prognosis and guide further investigations and treatments.

Biochemistry

- RFT and LFT as baseline.
- Ferritin, CRP and LDH are non-specifically elevated.
- Procalcitonin (PCT): This is raised in bacterial infections, however, please consider superadded bacterial infections, especially hospital-acquired.
- Troponin: If elevated, may indicate viral myocarditis, or an ischaemic event (ACS).
- Arterial Blood Gas: to assess severity of disease, guide ICU admission and timing of intubation.

Haematology

- CBC with differential count as lymphopenia (<1.1) is relatively common, but non-specific.
- D-Dimers, elevation is associated with poorer prognosis.
- Clotting profile (PT & APTT) as baseline

PCR testing

Nucleic acid amplification testing (NAAT) using PCR is the diagnostic gold standard for COVID-19.

PCR swab from the nasopharynx (ideally paired with an oropharyngeal swab) should be taken on patient arrival to department, whilst patient is isolated in a single room.

If result is negative, a repeat sample is sent 24 hours later. If clinical suspicion remains despite repeated negative PCR, this is treated as a “probable case”, and all isolation precautions should still be maintained.

Further samples for PCR such as repeat nasopharyngeal swabs, bronchial secretions, bronchoalveolar washes or other sites is left to senior clinician’s discretion.

Quantitative Serology Testing

Serology testing (SARS-COV2 IgM/IgG) can be used as an additional diagnostic tool in suspected patients. Such tests use ELISA or CLIA techniques on venous blood samples to detect antibodies. IgM antibodies starts rising 3 days after onset of symptoms, and IgG starts to rise 7-10 days after onset of symptoms. Sensitivity and specificity can be up to 96% and 95% respectively, in relation to PCR-based testing.

SARS-COV2 IgM and IgG can be requested on admission to hospital.

If PCR and serology remain negative despite clinical suspicion, serology can be repeated once a week.

If serology is positive, weekly testing can be performed to follow-up disease activity. However, no evidence is available to support prognostication of disease in relation to antibody titre value or trend.

A patient with positive serology is not reportable as a confirmed case, and therefore, contact tracing would not take place. Nevertheless, all aerosol precautions and treatment options for COVID-19 should be observed for such patients.

Rapid Diagnostic Testing (RDT) – Qualitative Testing

RDT can provide a qualitative measure of IgM and IgG within a few minutes. The rapid test uses lateral flow assay technique. However, sensitivity and specificity for COVID-19 is unknown. There are many brands and manufacturers, with variable degrees of kit performance.

RDT, if available, can be requested as an additional diagnostic tool. But should not be relied upon to confirm or refute the diagnosis of COVID-19.

High Resolution Computed Tomography (HRCT)

HRCT should never be used as a criteria for admission to a COVID-19 hospital or non-COVID-19 hospital. Decision to direct patient should be made on clinical basis, not the presence or absence of HRCT findings on HRCT.

HRCT chest can aid the diagnosis of COVID-19, just as an additional diagnostic tool, therefore, patients with at least moderate disease should have HRCT.

Strict adherence to droplet precautions must be maintained before, during and after scanning such patients.

There could be a dedicated COVID-19 CT scanner.

HRCT findings in favour of COVID-19 include see Figure (1):

- Ground glass opacifications: bilateral, sub-pleural, lower lobe predominant, discrete or confluent.
- Consolidations: bilateral, discrete or confluent.
- Other findings: Reticulations, crazy-paving, septal thickening, air bronchograms, thickened visceral pleura.
- No lymphadenopathy, no major pleural effusion, no masses, no cysts and no airway invasion.

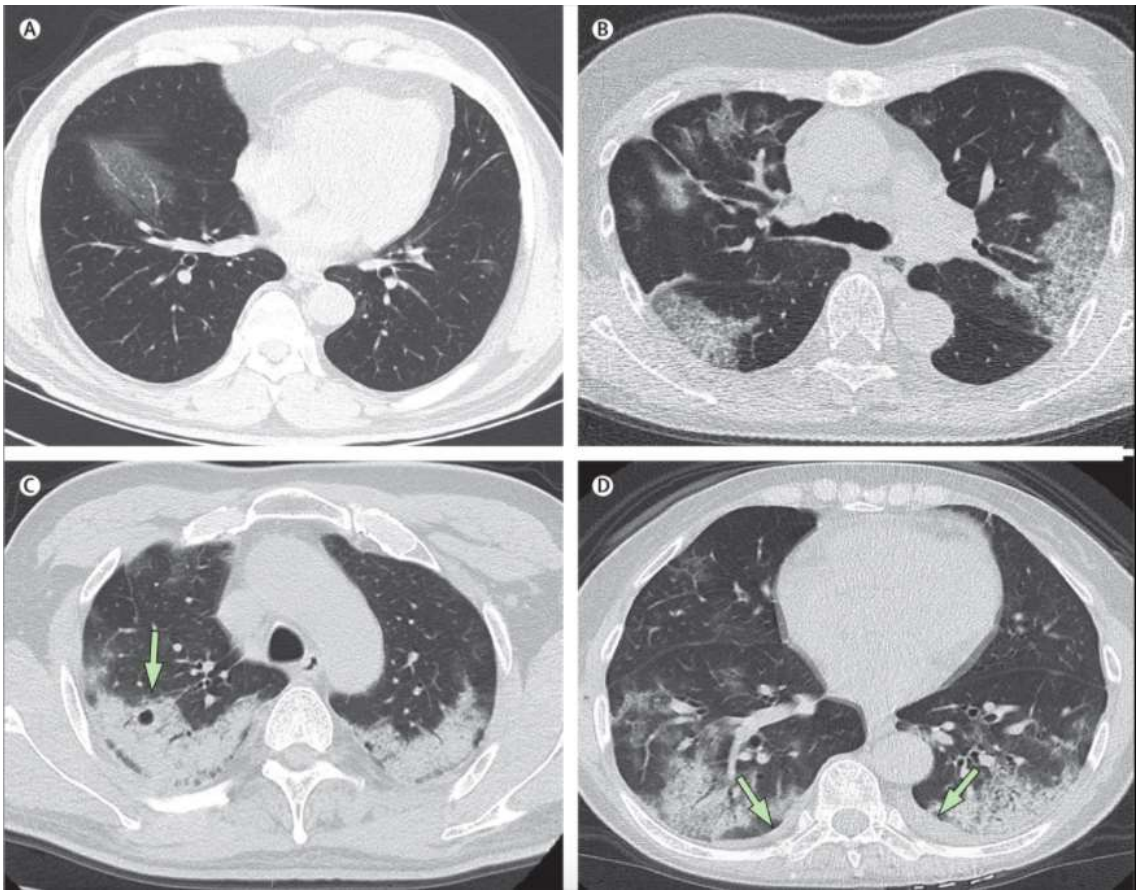

Figure (1) CT changes in COVID-19 (A) Focal ground-glass opacity associated with smooth interlobular and intralobular septal thickening in the right lower lobes. (B) Bilateral, peripheral ground-glass opacity associated with smooth interlobular and intralobular septal thickening (crazy-paving pattern). (C) Bilateral and peripheral predominant consolidation pattern with a round cystic change internally (arrow). (D) Bilateral, peripheral mixed pattern associated with air bronchograms in both lower and upper lobes, with a small amount of pleural effusion (arrows).

Number of segments involved is directly correlated with disease severity.

Patients, especially sick ones, will carry more than one diagnosis in the CT, therefore, care must be taken not to overlook findings in keeping with heart failure, emphysema, bacterial pneumonia, cancer, bronchiectasis or interstitial lung disease.

Chest x-ray

All admitted patients should receive a CXR, irrespective of recent radiological work up. Unless a CXR has been taken a few hours prior to patient's arrival on the department.

Lung Function Tests

Confirmed, suspected or probable COVID-19 patients should not have lung function testing given the risk of infection transmission.

Recovered patients and non-COVID-19 patients may have lung function testing, provided universal standard precautions are followed.

Point of Care Ultrasonography (POCUS) for COVID-19

Lung ultrasonography gives the results that are similar to chest CT and superior to standard chest radiography for evaluation of pneumonia and/or adult respiratory distress syndrome (ARDS) with the added advantage of ease of use at point of care, repeatability, absence of radiation exposure, and low cost. Lack of access to USS at the point of care, provision of appropriate training and inter-operator discrepancies are the major disadvantages.

Characteristic ultrasonographic features of COVID-19 pneumonia include the following:

1. Thickening of the pleural line with pleural line irregularity
2. B lines in a variety of patterns including focal, multifocal, and confluent.
3. Consolidations in a variety of patterns including multifocal small, non-translobar, and translobar with occasional mobile air bronchograms.
4. Appearance of A lines during recovery phase.
5. Pleural effusions are uncommon.

The authors recommend using USS to assess and monitor progression if a competent clinician is available to perform POCUS.

Bacteriology

If patients are able to cough sputum, a sample should be sent for microscopy, culture and sensitivity (M, C/S).

Tracheal aspirates, bronchoalveolar lavage and other specimens on regular basis if patients are persistently febrile.

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COVID-19 Admission and Discharge Criteria:

Criteria for hospital admission in COVID-19 center:

- If the oxygen saturation ≤93% at room air for the patient not known as chronic respiratory illness OR ≤91% for patient with established chronic respiratory diseases
- Respiratory rate >30/min
- If systolic blood pressure <90 cmH_2o and diastolic blood pressure <60 cmH_2o
- Heart rate >110 beat per minute
- Signs of moderate/severe respiratory distress
- Multiple co-morbidities (cardiac, respiratory, diabetic, CKD and cancer patients)

N.B Fever alone is not an indication for admission

Criteria for hospital discharge:

- Oxygen saturation >94% at room air
- Respiratory rate < 20/min
- Vitally stable
- No other deranged physiological markers

N.B Patient must be reminder to isolate him/herself at home for at least 14 days after recovery of symptoms.

Personal Protective Equipment (PPE) in COVID-19 Patients

Aerosol generating procedures:

Bronchoscopy, Upper GI Endoscopy, ENT procedures, nebulization, intubation of a patient, CPR, non-invasive ventilation, endotracheal suctioning, when obtaining nasopharyngeal or oropharyngeal swab, dental procedures, etc. in **Covid-19 suspected or confirmed** cases health personnel need to use the following protective equipment:

A. N95 mask
B. Goggles or face shield
C. Gloves
D. Disposable gown
E. Closed shoes/boots
F. Cap

Non aerosol generating procedures in covid-19 suspected or confirmed patients:

Health personnel need to use the following protective equipment:

A. Surgical mask
B. Goggles or face shield
C. Gloves
D. Disposable gown
E. Cap

*Use N-95 masks if close contact with COVID-19 suspect or confirmed case expected.

Fever/screening clinics the following PPE is recommended:

A. Surgical mask
B. Goggles or face shield
C. Gloves
D. Disposable gown
E. Cap

*Use N-95 masks if close contact with COVID-19 suspect or confirmed case expected.

Escorts or drivers, the following PPE is recommended:

A. Surgical masks
B. Gloves

If physical contact is expected, depending on circumstances, a gown PLUS goggles or face shield are also recommended, otherwise need to maintain minimum 2-meter distance from the patient.

The patient should be given surgical mask and instructed to perform hand hygiene.

For Laboratory staff; depending upon the chance of splash:

A. Surgical mask
B. Goggles or face shield (if risk of splash)
C. Gloves
D. Disposable gown

All staff, including health care workers involved in any activity that does not involve contact with COVID-19 patients and working in other areas of patient transit (e.g. wards, corridors).

No PPE required.

For Everyone:

1. Maintain 1-2 metre distance while visiting patients, if no need to touch the patient.
2. Mandatory hand-hygiene after each use of PPE and between patients.
3. Mandatory surface cleaning of bed or furniture with 0.5% Chlorine disinfectant between each patient in OPD or in an inpatient setting.

COVID-19 Case definition

Suspect case (Also known as Patient under Investigation - PUI)

A. A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath), AND a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset;
   OR
B. A patient with any acute respiratory illness AND having been in contact with a confirmed or probable COVID-19 case (see definition of contact) in the last 14 days prior to symptom onset;
   OR
C. A patient with severe acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath; AND requiring hospitalization) AND in the absence of an alternative diagnosis that fully explains the clinical presentation.

Probable case

A. A suspect case for whom testing for the COVID-19 virus is inconclusive.
   OR
B. A suspect case for whom testing could not be performed for any reason.

Confirmed case

A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.

Contact

A contact is a person who experienced any one of the following exposures during the 2 days before and the 14 days after the onset of symptoms of a probable or confirmed case:

1. Face-to-face contact with a probable or confirmed case within 1 meter and for more than 15 minutes
2. Direct physical contact with a probable or confirmed case
3. Direct care for a patient with probable or confirmed COVID-19 disease without using proper personal protective equipment
4. Other situations as indicated by local risk assessments.

*Note: for confirmed asymptomatic cases, the period of contact is measured as the 2 days before through the 14 days after the date on which the sample was taken which led to confirmation.

Reference:

Global Surveillance for human infection with coronavirus disease (COVID-2019), Interim guidance, Geneva, World Health Organization, 2020. (https://www.who.int/publicationsdetail/global-surveillance-for-humaninfection-with-novel-coronavirus-(2019-ncov).

Clinical Classifications of COVID-19

Severity	Characteristic
Mild	• Patients uncomplicated upper respiratory tract viral infection may have non-specific symptoms such as fever, fatigue, cough (with or without sputum production), anorexia, malaise, muscle pain, sore throat, dyspnoea, nasal congestion, or headache. Rarely, patients may also present with diarrhoea, nausea, vomiting and anosmia. • The clinical symptoms are mild and no pneumonia manifestations can be found in imaging.
Moderate **(pneumonia)**	• Patients have symptoms such as fever and respiratory tract symptoms, etc. and pneumonia manifestations can be seen in imaging. • Adult with no severe signs, and no need for supplemental oxygen.
Severe **(severe pneumonia)**	• Adolescent or Adults: fever or suspected respiratory infection, who meet any of the following criteria: • Respiratory rate ≥ 30 breaths/min; • Oxygen saturation ≤ 93% at a rest state; • Patients with > 50% lesions progression within 24 to 48 hours in lung imaging. • While the diagnosis is made on clinical grounds; chest imaging may identify or exclude some pulmonary pathologies.
Critical	• Respiratory failure and need for mechanical ventilation • Shock • Other organ failure needing ICU monitoring treatment.

Risk Factors for Severe Illness

- Cardiovascular disease
- Chronic lung disease
- Diabetes mellitus
- Hypertension
- Cancer (in particular hematologic malignancies, lung cancer, and metastatic disease)
- Chronic kidney disease
- Obesity (BMI ≥30)
- Smoking

Pharmacological Interventions for COVID-19

Principles of Clinical Management and Treatment for confirmed COVID 19 cases

Apply standard precautions, contact precautions, and droplet precautions with eye protection should always be used when caring for the patient

Clinical management includes prompt implementation of recommended infection prevention and control measures and supportive management of complications, including advanced organ support if indicated.

No specific treatment for COVID19 infection is currently approved for improving morbidity and mortality yet:

- Give supplemental oxygen therapy, as needed.
- Use conservative fluid management, if possible.
- Give empirical antimicrobials as indicated.
- DO NOT routinely give systemic corticosteroids for treatment of viral pneumonia or ARDS.
- Closely monitor patients for signs of clinical deterioration.
- Address co-morbid condition(s).

Laboratory and Radiological Monitoring

- Baseline tests should be done prior to treatment initiation for all patients.
- Repeat PCR test after 5 days of therapy initiation.
- IgM/IgG quantitative testing to follow up titre progression with clinical state of the patient, every 7 days.
- IgM/IgG qualitative testing may also be used to indicate serocoversion IgM to IgG.
- Repeat blood tests every 72 hours and imaging every week, earlier if clinically indicated, while on treatment.
- Repeat more frequently in critically ill patients if indicated.

Summary of Medications Used in the Management of COVID-19

Antibiotics

Empirical antibiotics should be considered as follows:-

1. For patients without risk factors for MRSA or Pseudomonas (i.e. living in community) consider 3rd generation cephalosporin, macrolide, co-amoxiclav or a respiratory quinolone.
2. In patients with risk factors for MRSA or Pseudomonas (i.e., chronic hospitalization), consider vancomycin and/or anti-pseudomonal agents (such as ceftazidime or piperacillin/ tazobactam).

Nebulised Treatment

- **If COVID-19** is not confirmed nor suspected use nebulizers.
- **If COVID-19** is confirmed or suspected in **non-intubated patients:**
    - **Metered Dose Inhalers (MDIs),** with a spacer should be used for management of chronic conditions.
    - Usage of **Nebulized Medications** should preferably be avoided for **COVID-19** suspect/diagnosed patients due to increased risk of aerosolization leading to potential transmission.

- Nebulised bronchodilator therapy should be reserved for acute bronchospasm, patients should be kept in negative pressure isolation room (if available) and all airborne infection control precautions should be adopted by the nurse/doctor monitoring the patient. If negative pressure rooms are not available, isolation rooms should be well ventilated and cleaned in between patients. Rooms (in out-patient clinics, triage areas, emergency departments, medical and respiratory wards) should be made available in sufficient numbers.

- **If COVID-19** is confirmed or suspected **in intubated patients**, we recommend, an in-line nebulizer container as part of a closed ventilator circuit, whilst patients are on strict airborne precautions in a negative-pressure room (where available).

Usage of inhalers (Controller medications for Asthma& COPD) during COVID-19

- People with **asthma & COPD** should continue to use their inhaled controller medications, there is no scientific evidence to support that inhaled corticosteroids should be avoided for asthma & COPD patients.
- **Stopping inhaler treatment increases the risk of exacerbations.**

Airway clearance

- Management principles
  - Airway clearance should be used only in selected ventilated patients (closed-circuit) with extremely thick secretions, to avoid mucus plugging.
  - Secretion thinning by Normal (0.9%) saline nebulizer 4 times daily.
  - Avoid N-acetylcysteine due to bronchospasm and frequent dosing requirements. However, it may be considered to support treatment of cytokine storm syndrome.
  - **Mechanical airway clearance is not routinely recommended**

Systemic corticosteroids

Corticosteroids ARE NOT RECOMMEND for COVID-19 as it may prolong viral shedding.

Indications:

1. Asthma or COPD exacerbation, treat with 40mg prednisone PO or 30mg methylprednisolone IV, once daily x 3-5 days. Or IV hydrocortisone 100-200mg every 8 hours.
2. In cases of refractory shock (not responding to inotropes) and macrophage activation syndrome (MAS)
3. Chronic steroid use in excess of 10mg prednisone daily, treat with 50mg hydrocortisone IV every 6 hours until improvement in shock.

REMDESIVIR (For compassionate use)

Antiviral drug found to reduce pulmonary pathology on the basis of preliminary clinical trial data it is **recommended** for the treatment of COVID-19 in hospitalized patients with **severe disease**.

Remdesivir is not approved by the Food and Drug Administration (FDA); however, it is available through an FDA emergency use authorization for the treatment of hospitalized adults and children with COVID-19.

Side effects: Hepatotoxicity

Dose: Adult: 200mg IV on day 1 (loading dose) followed by 100mg IV OD x 9 days

Tocilizumab (Actemera)

One of the most important mechanism underlying the deterioration of COVID-19 is cytokine storm characterized by elevated levels of IL6, IFN- and other cytokines, which will lead to ARDS or even multiple organ failure. Tocilizumab is a recombinant humanized monoclonal antibody binding to IL6 receptor and inhibiting its signal transduction. Tocilizumab has been used in the treatment for rheumatoid arthritis (RA). Moreover, Tocilizumab has been reported to be effective against cytokine release syndrome induced by CAR-T cell infusion against B cell acute lymphoblastic leukaemia. Tocilizumab is recommended for the immunotherapy of patients with extensive lung lesions and severe cases that show an increased level of IL6 in laboratory testing. The efficacy of Tocilizumab in COVID-19 patients still needs to be investigated.

Dose 4 – 8 mg/kg (once 400mg /day) IV x 1, max. dose 800mg if needed.

Adverse effects include increase liver enzymes, hyperlipidaemia, infusion reaction and neutropenia.

Antithrombotic Therapy in Patients with COVID-19

COVID-19 has been associated with inflammation and a prothrombotic state, with increases in fibrin, fibrin degradation products, fibrinogen and D-dimers.

The risk for thromboembolism (VTE) is markedly increased, especially in patients in the in the intensive care unit (ICU), with case series reporting prevalence of 25 to 43 % in ICU patients, often despite prophylactic dose anticoagulation.

Recommendations:

- Patients who are receiving anticoagulant or antiplatelet therapies for underlying conditions should continue these medications if they receive a diagnosis of COVID-19
- D-dimer results could be used to guide LMWH (e.g. enoxaparin), see table below:

D-Dimers	Body Weight	Dose
<1000 ng/ml	<100 kg 100-150 kg >150 kg	Enoxaparin 4000 IU 1x1 Enoxaparin 4000 IU 1x2 Enoxaparin 6000 IU 1x2
1000-3000 ng/ml	<100 kg 100-150 kg >150 kg	Enoxaparin 4000 IU 1x2 Enoxaparin 8000 IU 1x2 Enoxaparin 12000 IU 1x2
>3000 ng/ml	<100 kg	Tinzaparin 175units/kg 1x1

Management of COVID-19 According to Severity

1. Mild illness without any risk factors/Co-morbidities
   - If admitted, patients should be isolated at COVID centres in single room with good ventilation.
   - Droplet & contact precautions.
   - Negative pressure rooms are not required unless aerosol generating procedures.
   - Symptomatic treatment only.

2. Mild illness with Co-morbidities
   - Consider admission for further monitoring
   - Symptomatic treatment
   - We do not recommend any specific treatment for mild illness.

3. Moderate Illness
   - Admit to an isolation room, for the purpose of close monitoring.
   - Uptitrate O2 using nasal cannula, venture masks, humidified O2 masks and non-rebreathing (reservoir) masks according to O2 saturations.
   - Consider empirical antibiotics to treat bacterial pneumonia.
   - Routine use of Azithromycin is not recommended, but may be used if considering treatment for bacterial infection.
   - Routine use of other specific treatment is not recommended.

4. Severe Illness
   - Initiate/continue treatment plan for moderate illness (if not given before).
   - We recommend using High Flow Nasal Cannula or Non-Invasive Ventilation (HFNC/NIV) taking adequate precautions to reduce aerosolization.
   - Awake proning can be tried as a rescue measure
   - We recommend using Remdesivir for patients with severe illness.
   - Anti-virals (HAART), can be initiated on a compassionate basis, as no proven benefit (Better to start before clinical deterioration). Options include: Lopinavir/Ritonavir, Darunavir/Cobicistat, Darunavir/Ritonavir and Atazanavir.
   - Anticoagulation.

5. Critical Illness
   - Continue IV antibiotics and supportive care.
   - Rule out ventilator associated pneumonia/catheter related infections and other secondary bacterial/viral/ fungal infections.
   - Always remember to rule out differentials of non–resolving pneumonia (organising pneumonia).
   - Tocilizumab can be considered for COVID-19 patients with persistent fever, elevated inflammatory markers, and signs of cytokine release syndrome (CRS) or macrophage activation syndrome (MAS). Must check IL-6 level prior to starting Tocilizumab. Consider methylprednisolone (2mg/kg/day for 5 days) if suspecting CRS/MAS, but IL6 measurement or treatment is not available.
   - Steroids: Not indicated. Use only in case of refractory shock, CRS or MAS.

- Convalescent plasma may be considered, if available. It was shown to improve symptoms, PaO2/FiO2, end-organ damage and reduce viral load.
- Anticoagulation
- Refractory or progressive cases in ICU: Interferon beta B1 can be considered, however it should be combined with an anti-viral (Lopinavir/Ritonavir) and Hydroxycholorquine.

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Bronchoscopy Guidelines (Precautions and Indications)

Principles

- Deciding the need for bronchoscopy during COVID-19 pandemic is tricky. Bronchoscopists should be wise enough in choosing any procedure (Risk versus Benefit ratio should be considered). Bronchoscopy being an aerosol generating procedure has the potential to transmit infection to others. Need for all procedures should be reviewed case by case basis and if not an urgent one it should be rescheduled based on clinical priorities
- Bronchoscopy is not considered as a diagnostic modality for COVID-19. Being an aerosol generating procedure performing bronchoscopy has got a high potential for transmission of infection
- Primary/preferred method for diagnosing COVID-19 is evaluation of nasopharyngeal/ oropharyngeal swab and sputum analysis
- All bronchoscopic procedures (COVID-19) should be performed in negative pressure isolation rooms.
- Minimize the staff for all bronchoscopic procedures and avoid training your fellows, since it increases the procedure duration.
- All essential personal protective equipment (PPE) should be used by health care professionals performing any bronchoscopic procedure.
- Donning & doffing protocols of PPE should be strictly followed Standard disinfection protocols should be followed for cleaning your flexible/rigid bronchoscopes, electrosurgical equipment and video monitors.
- Rigid Bronchoscopic procedures carries maximum risk of transmission of infection and hence it should be performed only by a highly skilled individual (shortens the procedure duration)
- Powered Air purifying Respirators (PAPR) kit is the ideal PPE while performing any rigid Bronchoscopic procedure (prolonged) as it avoids breathing resistance/suffocation and moisture build up associated with using N95 mask alone.
- Bronchoscopy is not considered as a diagnostic modality for COVID-19.
- Being an aerosol generating procedure performing bronchoscopy has got a high potential for transmission of infection Primary/Preferred method for diagnosing COVID-19 is evaluation of nasopharyngeal/oropharyngeal swab and sputum analysis.
- Be wise in choosing any bronchoscopic procedure (e.g. with goggles/face shield). Be wise in choosing any bronchoscopic procedure.

Patient selection and PPE (Figure 2)

1. When patients with suspected or confirmed COVID-19 infection are undergoing bronchoscopy, we suggest that health care workers in the procedure and recovery rooms use a N95 respirator, gown, gloves, eye protection and apron.

2. In patients suspected of having COVID-19 infection, we suggest that a nasopharyngeal specimen be obtained first. In the setting of severe or progressive disease requiring intubation, if additional specimen is needed to establish a diagnosis of COVID-19 or other diagnosis that will change clinical management, lower respiratory specimens from endotracheal aspirate or bronchoscopy with bronchoalveolar lavage (BAL) can be performed.

3. Prior to performing bronchoscopy in asymptomatic patients in an area where community transmission of COVID-19 infection is present, we suggest testing for COVID-19 infection

4. When asymptomatic patients present for bronchoscopy in an area where community spread of COVID-19 is present, we suggest that health care workers in the procedure room wear N-95 respirators, as opposed to surgical masks.

5. When bronchoscopy is indicated to diagnose, stage, or characterize a known or suspected lung cancer in an area where community transmission of COVID-19 is present, we suggest that bronchoscopy be performed in a timely and safe manner, by a proficient bronchoscopist.

6. In patients with confirmed COVID-19 infection who recover and need a routine bronchoscopy, we suggest that the timing of the procedure be customized based on the indication for the procedure, the severity of the COVID-19 infection and time from symptom resolution.

Figure (2) various indications for bronchoscopy.

Indications for Emergency Bronchoscopic procedure *(To be performed on same day)*	
1	Symptomatic central airway obstruction: • Mass • Foreign body • Mucous plug
2	Massive Haemoptysis
3	Symptomatic Tracheal stenosis
4	Migrated stent (Silicon/metallic)
Indications for Semi urgent Bronchoscopic procedure *(can wait for 2 to 4 days, preferably send a swab to rule out COVID-19 infection)*	
1	Evaluation of lung mass or nodule (Diagnosis/staging)
2	Evaluation of Mediastinal lymphadenopathy
3	Whole lung lavage
4	Suspected pulmonary infection in immunocompromised patients
5	Post lung transplant recipients – Evaluation of Bronchiolitis obliterans syndrome
6	Suspected pulmonary infection in bone marrow/solid organ transplant
7	Evaluation of lobar atlectasis
Indication for Elective Bronchoscopy (Re-schedule till your locality is free of COVID-19)	
1	Bronchial Thermoplasty
2	Tracheobronchomalacia evaluation
3	Cryobiopsy for histopathological confirmation of etiology of DPLD
4	Bronchoscopic lung volume reduction procedures
Indications for Bronchoscopy in COVID-19 suspected/confirmed cases	
1	**Relatively contraindicated**
2	For swab and sputum negative patients who are strong clinical suspects
3	For patients who are on mechanical ventilator: Mucous plug clearance
4	Evaluation for alternative infection
5	To rule out differentials of non –resolving pneumonia
6	Massive haemoptysis – airway interventions

The Latest Research on COVID-19 Treatments and Medications

1) Remdesivir

Remdesivir is a brand-new antiviral that has not been approved by the FDA for use, and is being tested in randomized controlled studies. It was previously shown to have some effect against SARS, MERS, and Ebola in cell and animal models. In a recent *in vitro* study, remdesivir prevented human cells from being infected with SARS-CoV-2.

Early results from a large U.S. study of 1,063 patients showed that people who got remdesivir recovered faster compared to those who got a placebo (11 days vs. 15 days, respectively). The death rate in the remdesivir group (8%) was also lower than the placebo group (11%). More details from this study, sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), are expected to be shared soon.

Based on the positive reports from these two studies, the FDA issued an emergency use authorization (EUA) for remdesivir on May 1, 2020. The EUA does not mean that the FDA has approved remdesivir for the treatment of COVID-19. Rather, the intent of the EUA is to make it easier for doctors to get remdesivir for hospitalized patients with severe COVID-19 symptoms.

2) Hydroxychloroquine and chloroquine

Hydroxychloroquine or chloroquine, often in combination with a second-generation macrolide, are being widely used for treatment of COVID-19, despite no conclusive evidence of their benefit. Although generally safe when used for approved indications such as autoimmune disease or malaria, the safety and benefit of these treatment regimens are poorly evaluated in COVID-19. Besides the antiviral activity, chloroquine has an immune-modulating activity, which may synergistically enhance its antiviral effect.

HCQ contraindicated in epilepsy and porphyria.

Side effect of HCQ: Bone marrow suppression, retinopathy, QT – segment prolongation and risk of TORSADES DE POINT, especially if in combination with macrolide or other QTc prolonging agent.

Loading dose of Hydroxycholorquine 400 mg PO BID on first day, followed by 200 mg BID for 5 days. May extend up to 10 days depending on clinical response.

The authors do not recommend using this drug, until further evidence emerges to support its use in COVID-19.

3) Azithromycin

Azithromycin is a macrolide antibiotic commonly used to treat bacterial infections. It has been shown to have some *in vitro* activity against viruses like influenza A and Zika, but did not work against the coronavirus that causes MERS.

One research group looked at azithromycin in combination with Hydroxycholorquine for COVID-19. They reported that 93% of patients cleared the virus after 8 days in their case series, as there was no control group. Adverse effects include cardiotoxicity and ototoxicity.

The authors do not recommend using this drug, until further evidence emerges to support its use in COVID-19.

4) Convalescent plasma

On March 24, 2020, the FDA issued an Emergency Investigational New Drug (eIND) application for the use of convalescent plasma to treat people with COVID-19. Convalescent plasma is collected from people who have recovered from COVID-19. It is then transfused into patients with active COVID-19. It is thought that antibodies found in the convalescent plasma can help fight the infection.

The procedure is not widely available, and studies are underway to assess its effectiveness in treating COVID-19.

5) Actemra (tocilizumab)

Tocilizumab is an anti-IL6 disease-modifying anti-rheumatic drug (DMARD) approved for rheumatoid arthritis and juvenile idiopathic arthritis. Whilst the authors do recommend using Tocilizumab for patients with CSR/MAS, it is important to recognize that, in addition to Tocilizumab (Actemra), other DMARDS are also being tested for COVID-19. These include:

Calquence (acalabrutinib), Xeljanz (tofacitinib), Jakafi (ruxolitinib), Olumiant (baricitinib), Kineret (anakinra), Ilaris (canakinumab), Otezla (apremilast), Mavrilimumab, Kevzara (sarilumab).

6) Kaletra (lopinavir/ritonavir)

Kaletra is a Highly Active Anti-Retroviral Treatment (HAART), containing a combination of two lopinavir and ritonavir. Data for using Kaletra in COVID-19 is limited.

In one randomized study of 199 people hospitalized with COVID-19, there was no difference between using Kaletra and not using it in terms of how long it took for patients to improve. Another small study of 127 people with mild COVID-19 symptoms looked at Kaletra alone compared to Kaletra in combination with interferon beta-1b and ribavirin. They found that the group who got all three medications improved sooner and cleared the virus faster (7 days) than those who only got Kaletra (12 days). However, this study assumes the gold standard to be Kaletra, which is not the case, as it could be argued that patient may have cleared the virus in 6 days if they were given nothing.

7) Tamiflu (Oseltamivir)

Oseltamivir is indicated to for the treatment of influenza (flu). Results from a hospital in Wuhan, China were not promising. Of 138 hospitalized patients, 124 got Tamiflu along with other medications. By the end of the study, 85 patients (62%) were still hospitalized and 6 had died. Nonetheless, several clinical trials are currently looking at Tamiflu in combination with other medications for coronavirus.

8) Avigan (favipiravir) and other antiviral medications

Favipiravir (also known as Avigan) is an antiviral approved in Japan and China for the flu. *In vitro* studies have shown that high doses of favipiravir were able to prevent human cells from being infected with SARS-CoV-2.

Two studies in China looked at how favipiravir worked in comparison to other antivirals. In a study of 240 patients in China with mild COVID-19 symptoms, 71% of patients given favipiravir recovered after 7 days compared to 56% who were given umifenovir (Arbidol). Another small study in China looked at 80 patients with mild COVID-19 symptoms and saw that that favipiravir helped to clear the virus faster than Kaletra (4 days vs. 11 days, respectively). The patients who took favipiravir also showed greater

improvements in their lungs based on chest images. The first U.S. clinical trials for favipiravir were recently approved to start in Boston.

Other antivirals being tested for COVID-19 include umifenovir and galidesivir:

- Umifenovir (Arbidol) is a flu medication that is used outside the U.S. As mentioned above, it was not as good as favipiravir in helping patients recover in a study from China. Another study of 81 patients looked at how long it took from when patients first had symptoms to when they tested negative for the coronavirus, and it found that there was no difference between people who got umifenovir and those who did not. However, it seems to be better than Kaletra at helping patients with COVID-19 clear the virus. In a small study of 50 people, the virus was not detected in any patients who had received umifenovir after 14 days. The virus was still present in almost half of the patients who got Kaletra.
- Galidesivir is a new drug that is currently being developed for a variety of viral infections; it has not yet been approved for human use. Clinical trials for galidesivir are starting in Brazil.

9) Colcrys (colchicine)

Colchicine is used for gout. It works in many different ways, including activating anti-inflammatory processes and interfering with cells involved in inflammation. It is thought to work similarly to Tocilizumab in COVID-19 patients in that it might be helpful in cytokine storm syndrome. A large clinical trial is currently studying the efficacy of colchicine, when given soon after a COVID-19 diagnosis, in lowering rates of hospitalization and death.

10) Ivermectin

Ivermectin is an oral anti-parasitic. It is also available as a lotion or cream to treat lice and rosacea. A recent *in vitro* study found that Ivermectin can stop SARS-CoV-2 from replicating. More research is needed to see if the doses studied would be safe and effective against the virus in humans.

Coronavirus Vaccines Currently in Development

Ten vaccines are currently being tested in human clinical trials. While some trials are in phase II, it could still be many months before we know whether any of these vaccines will protect people against COVID-19.

Institutions	Country	Type of vaccine	Status
CanSino Biological and the Beijing Institute of Biotechnology	China	Non-replicating viral vector	Phases I and II
Moderna and the National Institute of Allergy and Infectious Diseases	U.S.	RNA	Phases I and II
Inovio Pharmaceuticals	U.S.	DNA	Phase I

Institutions	Country	Type of vaccine	Status
Beijing Institute of Biological Products and Sinopharm	China	Inactivated	Phases I and II
Wuhan Institute of Biological Products and Sinopharm	China	Inactivated	Phases I and II
Sinovac	China	Inactivated	Phases I and II
University of Oxford/AstraZeneca/Serum Institute of India	United Kingdom	Non-replicating viral vector	Phases I and II
BioNTech/Fosun Pharma/Pfizer	U.S. and Europe	RNA	Phases I and II
Institute of Medical Biology and the Chinese Academy of Medical Sciences	China	Inactivated	Phases I
Novavax	U.S.	Protein subunit	Phases I and II

COVID-19 Admission and Management for Critical Care in Adults

Principles

- Among patients hospitalized with coronavirus disease 2019 (COVID-19), up to one-quarter require intensive care unit (ICU) admission.
- Profound hypoxemic respiratory failure from acute respiratory distress syndrome (ARDS) is the dominant finding in critically ill patients. Common complications include acute kidney injury (AKI), elevated liver enzymes, and the late development of cardiac injury, including sudden cardiac death. Sepsis, shock, and multi-organ failure are less common.
- For most critically ill patients with COVID-19, we prefer the lowest possible fraction of inspired oxygen (FiO_2) necessary to meet oxygenation goals, ideally targeting a peripheral oxygen saturation between 90 and 96%.
- We recommend using High flow O2 support (HFNC/NIV) taking adequate precautions to reduce aerosolization.
- In patients with COVID-19 who have acute hypoxemic respiratory failure and higher oxygen needs, we suggest selective use of non-invasive measures rather than routinely proceeding directly to intubation. As an example, we might trial HFNC in younger patients without comorbidities who can tolerate nasal cannula. In contrast, we may proceed directly to early intubation in patients at higher risk (elderly patients and patients with comorbidities or risk factors for progression).
- It should be noted that High Flow Nasal Cannula is indicated for severe acute hypoxaemic respiratory failure, and it should not be used to treat patients with hypercapneic respiratory failure, such as acute exacerbations of COPD. Also, patients with obstructive sleep apnoea, obesity hypoventilation syndrome should be treated with non-invasive ventilation (NIV).
- For patients with COVID-19 who receive HFNC or NIV, vigilant monitoring is warranted for progression with frequent clinical and arterial blood gas evaluation every one to two hours to ensure efficacy and safe ventilation. The threshold to intubate such patients should be low. Attempting prone positioning is also indicated.
- It is important to insert a radial Arterial Line in all patients admitted to critical care with severe or critical severity COVID-19, to allow for closer monitoring of BP, ABGs and regular blood tests.
- For critically ill patients with COVID-19, intubation should **not** be delayed until the patient acutely decompensates since this is potentially harmful to both the patient and healthcare workers. There should be a low threshold to intubate those who have:
    - Rapid progression over a few hours
    - Failure to improve despite HFNC >40 L/min and FiO_2 >0.6
    - Development of hypercapnia
    - Hemodynamic instability or multiorgan failure
- Intubation is a high risk procedure for aerosol dispersion in patients with COVID-19 and attention should be paid to donning full personal protective equipment (PPE) with airborne precautions as

well using equipment that minimizes dispersion (e.g. video laryngoscopy) and the development of local protocols for the procedure

- Use low tidal volume ventilation (LTVV) targeting ≤6 mL/kg predicted body weight (PBW) (range 4 to 8 mL/kg PBW that targets a plateau pressure ≤30 cm H_2O and applies positive end-expiratory pressure (PEEP) according to the strategy outlined in the table For patients with COVID-19 who fail LTVV, prone ventilation is the preferred next step
- Several procedures, including the collection of respiratory specimens, bronchoscopy, extubating, tracheostomy, and cardiopulmonary resuscitation are aerosol-generating and should be avoided or minimized, if possible. All procedures should be grouped when possible.
- Patients with COVID-19 pneumonia who are mechanically ventilated for ARDS should receive the usual daily surveillance, and supportive care including conservative fluid management (unless patients have sepsis or volume depletion). Measurement of surveillance cardiac troponins and a low threshold to perform transthoracic echocardiography is appropriate for the early detection of cardiac injury.
- No role for administering glucocorticoids.
- For acute bronchodilation, we prefer the use of in-line metered dose inhalers (MDIs) rather than administration via a standard nebulizer due to the lower risk of aerosolization associated with MDIs.
- For patients with COVID-19 who develop ARDS, the prognosis is poor with mortality ranging from 52 to 67 percent. The highest rates of death occur in those ≥64 years
- A greater level of anxiety and trauma among patients and families should be anticipated and combatted with clear communication strategies and early palliative care involvement.
- Precautions should continue if the patient continues to test positive for COVID-19.
- Several measures should be adopted to accommodate a surge in COVID-19 cases including included expanding ICU care into non-ICU spaces, utilizing non-critical care trained staff to participate in delivering critical care, and innovative approaches to obtain, conserve, and increase the efficiency of physical equipment (eg, PPE and mechanical ventilators).
- The national early warning score (NEWS) can be used on wards as a decision support tool for monitoring, responding to an escalation of care for COVID-19 patients to critical care. Chart 2 with key demonstrates its utilisation.

Chart (1A) summarizes a decision support system for patient assessment

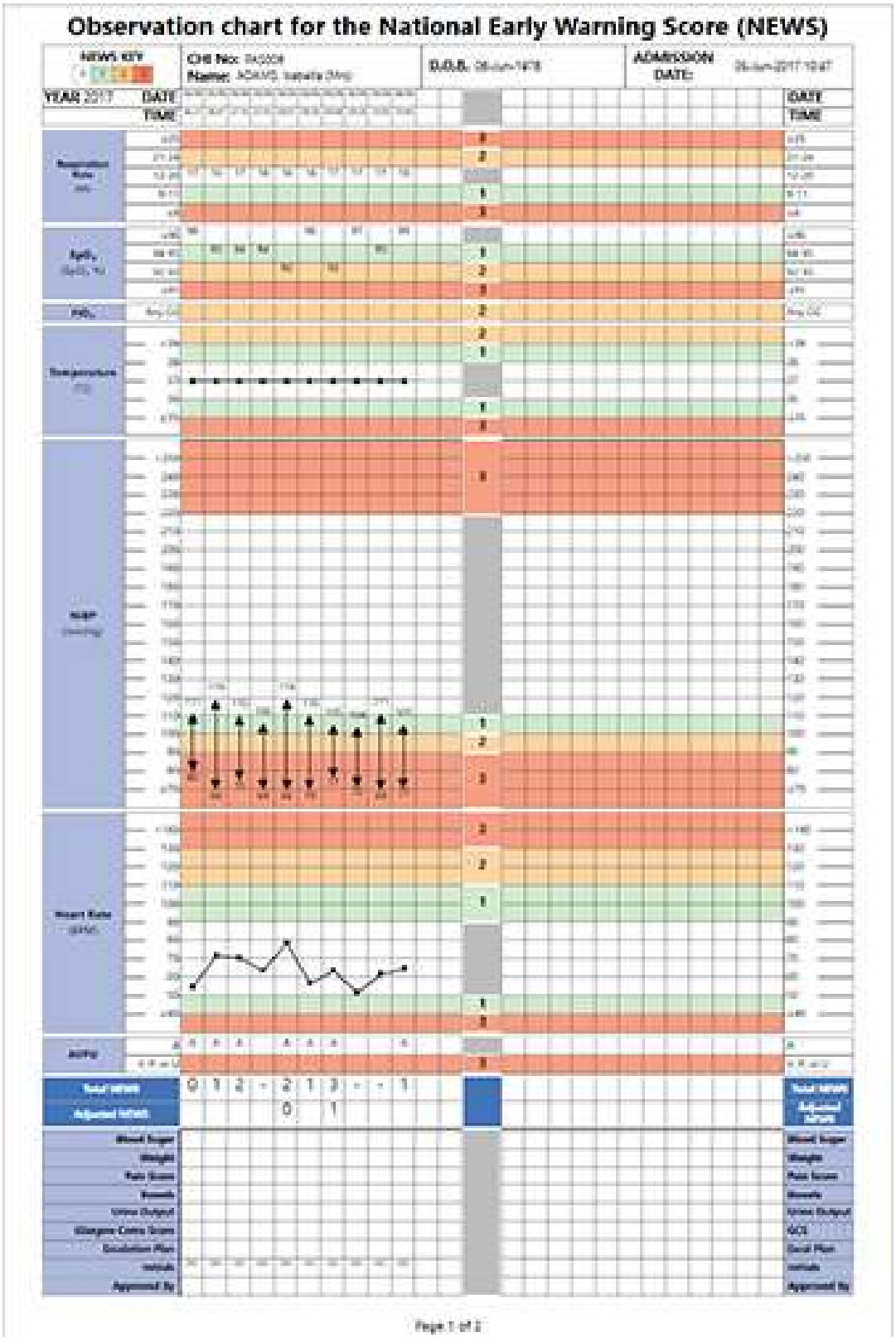

Chart (1B) summarizes a decision support system for patient assessment

Outline Clinical Response to NEWS Triggers

NEWS SCORE	FREQUENCY OF MONITORING	CLINICAL RESPONSE
0	Minimum 12 hourly	• Continue routine NEWS monitoring with every set of observations
Total: 1-4	Minimum 4-6 hourly	• Inform registered nurse who must assess the patient; • Registered nurse to decide if increased frequency of monitoring and / or escalation of clinical care is required;
Total: 5 or more **or** **3 in one parameter**	Increased frequency to a minimum of 1 hourly	• Registered nurse to urgently inform the medical team caring for the patient; • Urgent assessment by a clinician with core competencies to assess acutely ill patients; • Clinical care in an environment with monitoring facilities;
Total: 7 or more	Continuous monitoring of vital signs	• Registered nurse to **immediately** inform the medical team caring for the patient – this should be at least at Specialist Registrar level; • Emergency assessment by a clinical team with critical care competencies, which also includes a practitioner/s with advanced airway skills; • Consider transfer of Clinical care to a level 2 or 3 care facility, i.e. higher dependency or ITU;

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