PAKISTAN CHEST SOCIETY

PAKISTAN
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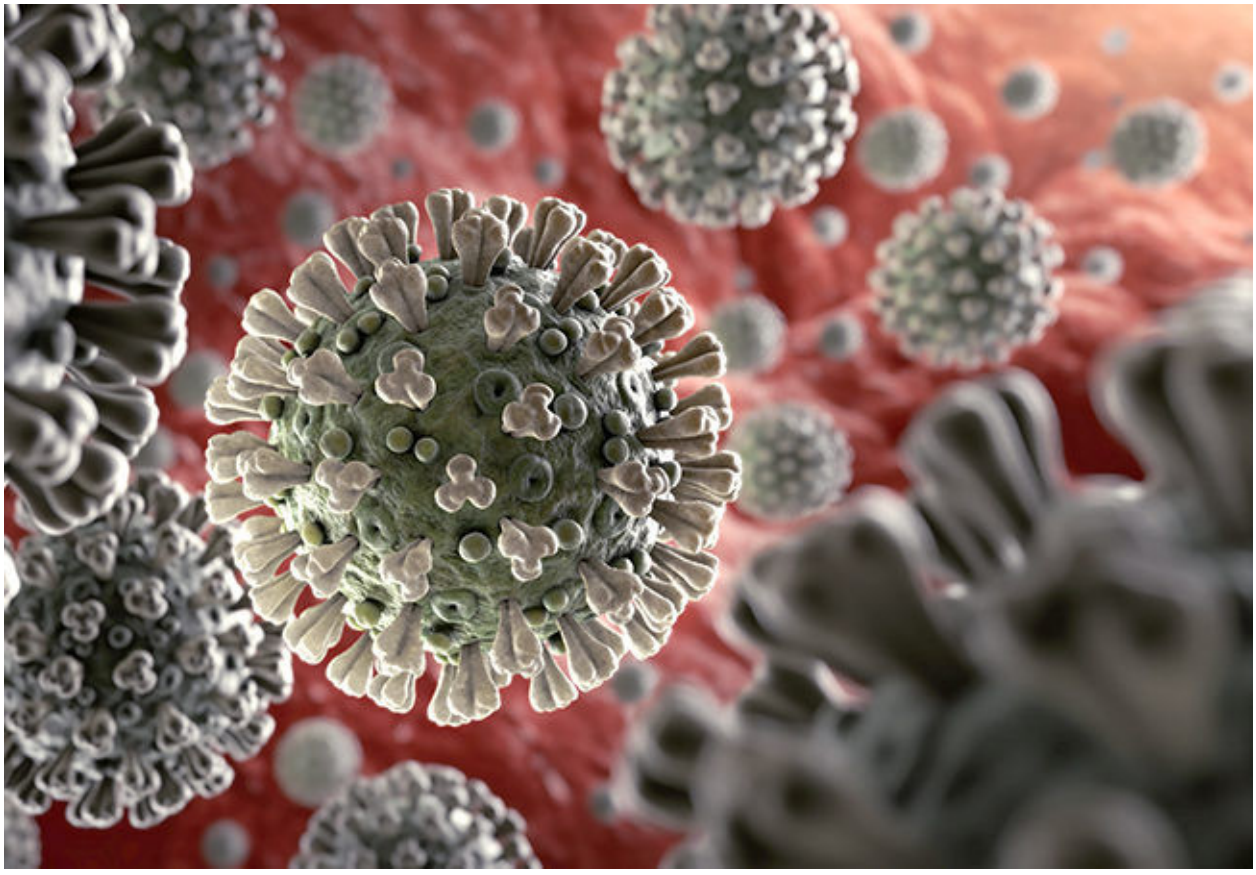
STRIVING FOR PULMONARY CARE

COVID-19
Management Guidelines



Second Edition July 2020

Message by President Pakistan Chest Society

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic in Pakistan is ongoing since 26th February 2020. Though the number of cases has reduced significantly but we should be vigilant as there is a chance of second wave- the same wave will change its amplitude. Due to blessing of God we had significant low death rate around 2% in comparison to global average of 4%.

Now we know more about the virus and its dynamics. Till date no specific treatment is available but supportive one. A number of treatment options have been tried with some encouraging results. There is still a need to follow preventive strategies like smart lockdown, physical distancing, hand washing, droplet and contact precautions etc.

Exact three month ago, PCS guideline committee took the lead and developed COVID-19 guidelines in very short period of time. Now I am happy to see that the members of the said committee have again shown their enthusiasm in updating the COVID-19 guidelines for that I would like to congratulate them for such prompt and comprehensive update.

I am sure that this updated guideline will help our health care workers involved in the management of patients suffering from COVID-19. It will also help our under and postgraduate students and the nursing staff to manage their patients well.

PROFESSOR DR. NISAR AHMED RAO

President,
Pakistan Chest Society

31 July 2020

Guidelines on Management of Patients with COVID-19
Second Edition July 2020
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Preface

The world is now a different place- the upsurge of coronavirus infectious pandemic brought the change of compulsion for the general public to cover the face with any kind of cloth mask. While writing the preface for the first edition of PCS guidelines, haziness, confusion and unknown fears about the rising pandemic prevailed across Pakistan. The cause being limited and dismal knowledge on the precise management of the strange novel viral disease that the world had never seen before. Though progress has been made, we still lack acute insight on its exact pathological features, quick diagnosis and a cost effective standard pharmacological therapy.

As mentioned in the preface of our March 2020 edition, this globally detrimental phenomenon has left us with no other choice but to join heads and come up with strategies to help the ailing humanity. The naïve world shared success experiences and lessons, resources, cooperation, and started to know what to avoid and what to adopt regardless of nationalities; the world including ourselves have learnt to fight and win this battle to a greater extent. We acknowledge that while the health-care sector and facilities served as a battlefield where the medical staff worked diligently and fought like soldiers, we lost some precious lives. The nation will always remember their services and sacrifice. Although great lives were lost during the pandemic's spread across Pakistan, our mortality rate is lower than that of our neighbors including China and India. Almighty Allah has and had been kind enough to burden our shoulders with as much as we could handle. On the other hand, our immunity, BCG status, less prevalence of HIV, acclimation to overcrowding and difficult unopened access to alcohol are additional factors that we, as a nation, fought COVID-19 better than Europeans and Americans.

COVID-19 has shown itself in various forms including, but not limited to, its asymptomatic nature at one extreme to mild, moderate, severe and critical illness on the other end; extra pulmonary features like diarrhea, loss of smell and taste, thrombotic potential, strokes and sometimes pseudo-autoimmune features. It is debated whether it should still be called a disease or named a syndrome since it holds the propensity to cause multisystem inflammatory involvement that may predispose an unlucky individual to guarded prognosis.

In our homeland, when COVID-19 units including HDUs, ICUs and wards were loaded in March and April 2020, peaks and plateaus were observed in May and June 2020 and, fortunately, descended in July 2020. Now we stand on the brink of marking this pandemic as a historical incident. At this point in time, we are unsure whether the world will witness recurrent COVID-19 outbreaks — like influenza — or whether this evil will perish from the face of the Earth.

This updated version of this precise guideline remains a quick review for all concerned specialties.

Very sincerely,
Professor Talha Mahmud
On behalf of PCS Guidelines Working Group

Contents

Dedicated

to

the Sweet Memories and Martyrdom

of Our Dear Colleagues

Professor
Naeem Agha

Professor
Khalid Chaudhary

in the line of duty

(Rest in Peace)

Introduction:

COVID-19 is a viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The infection became a pandemic few months after it started in China in December 2019. It can cause a range of respiratory problems from simple flu like symptoms to pneumonia and acute respiratory syndrome. In Pakistan it has infected more than 278305 and has claimed about 5951 lives so far till 31 July 2020.

The guidelines for diagnosis and management of COVID-19 were published by Pakistan Chest Society (PCS) in March, 2020. Since the start of pandemic, the knowledge about the disease and its management is evolving. With each passing day, evidence is growing thus adapting the change in practice mandatory. PCS therefore updates its recommendations for the disease and presents the new guidelines based on current evidence.

Definitions (WHO):

Suspect Case:

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 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) 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:

- Face-to-face contact with a probable or confirmed case within 1 meter and for more than 15 minutes;

- Direct physical contact with a probable or confirmed case;
- Direct care for a patient with probable or confirmed COVID-19 disease without using proper personal protective equipment;
  OR
- Other situations as indicated by local risk assessments.

Clinical Features of COVID-19:

Incubation Period:

Incubation period varies from 2 to 14 days after exposure with most of the patient experiences symptoms on 5th day.

Spectrum of Disease Severity:

Clinical spectrum of disease ranges from asymptomatic to mild symptoms such as cough, fever, myalgias to pneumonia, acute respiratory distress syndrome, and sepsis with septic shock to multi-organ failure.

Most of the cases are self-limiting (80%), however, elderly and patients with co morbidities tend to have more severe disease.

Frequently occurring presenting symptoms are:

- Fever > 100 ^{o}F 44-98%
- Dry cough (new or worsening) 46- 82%
- Shortness of breath (new or worsening) 14-31%
- Myalgia or fatigue 11-52%

Less common symptoms are:

- Sputum production
- Headache
- Sore throat
- Hemoptysis
- Rhinorrhoea

Gastrointestinal symptoms such as nausea & diarrhea may be seen in some as presenting symptom. **Anosmia** (loss of smell) and **altered taste** are also recognized as presenting symptoms. Besides these symptoms, data is emerging for atypical presentation such as meningitis, pulmonary edema and bradycardia; clinicians should be alert especially in patients having comorbidities or immunocompromised status.

Clinical Classification of COVID-19 Patients:

According to signs & symptoms, these patients can be categorized into asymptomatic, mild, moderate, severe and critically ill.

Asymptomatic

SARS Co-V 2 infection with no symptoms.

Mild Disease

Presence of any one or combination of symptoms as given above, usually:

- An upper respiratory tract viral infection
- Low grade fever, cough, malaise, rhinorrhea, sore throat without any hemodynamic compromise, with normal Chest x-rays and oxygen saturation above 94%

Moderate Disease

- Shortness of breath with respiratory rate > 25
- High grade fever > 100 ^{o}F for more than 3 days
- Hemoptysis (possible)
- Gastro-intestinal symptoms: Nausea, vomiting, diarrhea
- Without change in mental status (i.e., confusion, lethargy)
- With or without comorbidities and chest X-rays suggestive of some infiltrates. Patient is usually hypoxic, saturation <93 percent but they don`t recognize and not usually worried (happy hypoxia)

Severe Disease (14%)

Patients usually have signs of pneumonia (fever, cough) along with:

- Respiratory rate > 30/min
- Quick Sequential Organ Failure Assessment (qSOFA) score 2 or more
- SpO_2- <90%
- Confusion, agitation, restlessness
- Bilateral lung infiltrates, involving >50% of lung fields on chest radiograph

Critically ill (5%)

These patients can present in any three of the following forms as critical:

a. Respiratory failure / ARDS

- Onset is within one week of insult (e.g pneumonia) or worsening
- Chest X-rays or CT Scan showing bilateral opacities, not explained by fluid overload (normal echocardiography) with impaired oxygenation
    - **Mild ARDS:** PaO_2/FiO_2: >200 mmHg and ≤ 300 mmHg
    - **Moderate ARDS:** PaO_2/FiO_2 ≤ 200 mmHg and >100 mmHg
    - **Severe ARDS:** PaO_2/FiO_2 ≤ 100 mmHg

b. **Septic shock**

   Persistent hypotension despite volume resuscitation, requiring vasopressors to maintain MAP > 65mmHg & serum lactate >2mmol/L

c. **Multi organ dysfunction syndrome (MODS)**

   Dysregulated host response to suspected or confirmed viral or bacterial infection resulting in acute life threatening organ dysfunction.

   Signs may comprise of altered mental status, weak pulse, cold extremities, fast heart rate, low blood pressure, low urinary output, labored breathing or tachypnea, low oxygen saturation, skin mottling, lab evidence of coagulopathy, acidosis, thrombocytopenia and deranged liver functions.

Asymptomatic and mild disease can be managed at home, provided having social support at home and ability to recognize worsening of symptoms or early warning signs such as difficulty in breathing, persistent high fever, chest pain, new onset confusion, inability to wake, bluish discoloration of lips and face and able to act promptly.

Epidemiological risk factors for severity of disease:

- Older Age
- Male gender
- Chronic pulmonary disease
- Chronic structural lung disease
- Cardiovascular disease
- Chronic kidney disease
- Chronic liver disease
- Diabetes Mellitus

Cytokine Release Syndrome (CRS) is defined as ANY of the following in the presence of moderate, severe or critical disease:

a. Ferritin >1000 mcg/L and rising in last 24 hours
b. Ferritin >2000 mcg/L in patient requiring high flow oxygen or ventilation
c. Lymphopenia <800 cells/ml, or lymphocyte percentage < 20% or neutrophil to lymphocyte ratio of > 5 and two of the following:
   - Ferritin >700 mcg/mL and rising in the last 24 hours
   - LDH > 300 IU and rising in the last 24 hours
   - D-Dimer >1000ng/mL (or >1mcg/ml) and rising in the last 24 hours
   - CRP >70 mg/L (or >10 hrs CRP) and rising in the last 24 hours, in absence of bacterial infection
   - If any 3 present on admission no need to document rise

Table 1. Laboratory Features Associated with Severe COVID-19.

Abnormal Laboratory Parameter	Possible threshold
Lymphopenia: **Absolute lymphocyte count**	<800/microL (normal range for age ≥21 years: 1800 to 7700/microL)
D-dimer	>1000 ng/mL (normal range: <500 ng/mL)
CRP	>100 mg/L (normal range: <8.0 mg/L)
LDH	>245 units/L (normal range: 110 to 210 units/L)
CPK	>2× the upper limit of normal (normal range for troponin T high sensitivity: females 0 to 9 ng/L; males 0 to 14 ng/L)
Ferritin	>500 mcg/L (normal range: females 10 to 200 mcg/L; males 30 to 300 mcg/L)
Troponin	>2× the upper limit of normal (normal range: 40 to 150 units/L)

CRP: C-reactive protein; LDH: lactate dehydrogenase; CPK: creatine phosphokinase

Diagnosis of COVID-19:

Ideally, there should be an available system for non-emergency patients with suspected COVID-19 to have telephonic consultation prior to presenting to a health care facility for evaluation. To reduce the risk of infection spread in community, many patients can be evaluated over the phone regarding the need for COVID-19 testing, and be offered collection of diagnostic specimen at home. If possible, all symptomatic individuals with suspected COVID-19 should undergo testing; the diagnosis cannot be definitively made without nasopharyngeal PCR for COVID-19 testing. However, limited capacity especially in remote areas may preclude testing all patients with suspected COVID-19 and instead, compatible clinical and radiological criteria may be used in such cases especially in the setting of an exposure risk, particularly when no other cause of the symptoms is evident.

When adequate facilities and resources are available, testing should be considered in all **symptomatic individuals** including hospitalized patients with unexplained respiratory illness, health care workers, work or residence in congregate living settings (nursing homes etc), or in individuals with predisposing conditions (diabetes, hypertension, coronary heart disease and obesity etc) for severe COVID-19 disease. Some of the **asymptomatic individuals** may also be

important for public health or infection control purposes including candidates for surgical procedures/organ transplantation or aerosol-generating procedures, before giving immunosuppressive drugs, following close contact with an individual with proven COVID-19 or screening hospitalized patients at locations where community prevalence is ≥10% PCR positivity.

After initial evaluation of patients who meet the criteria for **suspect cases**, (see case definitions, clinical features and triage section) and taking decision for home care and quarantine versus hospitalization, in terms of isolation room/bay or ICU admission, the following diagnostic interventions should be considered:

1. Complete Blood Count (CBC):

- Leukopenia, leukocytosis, and lymphopenia (most common) can be seen.
- Hemoglobin and platelets count is mostly preserved.
- Thrombocytopenia and severe lymphopenia (absolute lymphocyte count <800/micro.L) have been associated with severe disease mortality.

2. Serum Biochemistry, Inflammatory Markers & Viral Serologies:

- Elevated serum **lactate dehydrogenase (LDH) and Ferritin** levels are common. LDH >245 units/L and Ferritin >500 mcg/L reflects severe disease. LDH should be repeated daily if elevated.
- **CRP** levels mirrors disease severity and >100 mg/L is a marker of severity.
- High **D-dimer levels** (>1 mcg/mL), elevated **troponin** (>2× the upper limit of normal) and elevated **creatine phosphokinase** (>2× the upper limit of normal) have been associated with higher mortality. Troponin should be repeated every two to three days if elevated.
- Serum **procalcitonin** levels are typically normal in COVID-19 at the time of hospitalization and raised levels usually reflect bacterial infection. Procalcitonin can be checked to assess the risk of secondary bacterial infection; however elevated levels have been reported as COVID-19 progresses, they may be less specific for bacterial infection later in the course of critical disease.
- **IL-6** levels may be raised in combination with other inflammatory markers like Ferritin and D-dimer especially in patients with CRS.
- Deranged **LFTs** (elevated **aminotransferase** levels) have also been described.
- Deranged **renal functions** (raised serum urea and creatinine levels, and altered electrolytes) are associated with acute kidney injury and are reflective of severe disease.
- **Coagulopathy** (elevated prothrombin time), acidosis, raised lactate and hyperbilirubinaemia may be seen in life threatening cases associated with multiorgan dysfunction/CRS.

- **HBSAg, anti HCV and HIV serology** testing should be considered in routine if previously not done.
- **Antiphospholipid antibodies** may be raised in rare cases (clinical significance is unclear).

3. SARS-CoV-2 RNA detection by Reverse-transcription Polymerase Chain Reaction (RT-PCR) - Nucleic acid amplification testing (NAAT): Can be done in any of the following respiratory specimens:

a) Nasopharyngeal swab specimen from both anterior nares (preferable as viral RNA levels may be higher in nasal compared with oral specimens).
b) Nasal or nasopharyngeal wash/aspirate can also be utilized.
c) Oropharyngeal swab can be collected but is not essential; if collected, it should be placed in the same container as the nasopharyngeal specimen.
d) Sputum collected only from patients with productive cough.
e) Tracheal aspirate/bronchial washings/bronchoalveolar lavage: Can be evaluated from patients who are admitted in critical care and require intubation. Specimen can also be utilized to diagnose concomitant infection by other viruses like influenza and respiratory syncytial virus/bacteria/fungi.

A positive RT-PCR for SARS-CoV-2 generally confirms the diagnosis of COVID-19 and no additional diagnostic testing is generally required. Assays for RT-PCR SARS-CoV-2 are highly specific tests and reported false-negative rates have ranged from < 5 to 40%, although these estimates are limited, in part because there is no perfect reference standard for comparison. In hospitalized patients (in a compatible clinico-radiological scenario), if initial PCR testing on naso/oropharyngeal swabs is negative, repeat testing should generally be performed 24-48 hours after the initial test, preferably from multiple respiratory tract sites. In such scenarios it is reasonable to maintain infection control precautions and provide counseling to patients and their families who otherwise may assume/blame that the patient with negative test is still placed in COVID-19 ward.

Sensitivity of SARS-CoV-2 PCR testing likely depends on the type and quality of the specimen obtained, the duration of illness at the time of testing, and the specific assay used. Point-of-care SARS-CoV-2 PCR assays may have less sensitivity as compared to laboratory-based tests. Lower respiratory tract specimens may have higher viral loads and be more likely to yield positive tests than upper respiratory tract specimens. In a recent study of 205 patients with COVID-19 who were sampled at various sites, the highest rates of positive viral RNA tests were reported from BAL (95%) and sputum (72%), compared with oropharyngeal swab (32%). So sputum specimen should be preferred to nasopharyngeal/oropharyngeal swab if patient is actively producing it but should be collected with caution.

The likelihood of detectable SARS-CoV-2 RNA on RT-PCR testing may also vary by the duration of illness. In an analysis of seven scientific studies that evaluated SARS-CoV-2 RNA testing by duration of first symptom onset or exposure, the estimated rates of false-negative results were 100 percent on the day of exposure, 38 percent on day 5, 20 percent at day 8, and 66 percent at day 21. On the other hand, some patients with COVID-19 may continue to have positive RT-PCR (SARS-CoV-2 RNA) on repeated nasopharyngeal testing for weeks after the onset of symptoms. Prolonged viral RNA shedding following the resolution of illness (generally more than nine days after illness onset) does not necessarily indicate infectiousness.

Sputum induction is not recommended *and droplet/aerosol and contact precautions must be followed when collecting respiratory specimen from suspected COVID-19 case. Ideally, all respiratory specimen collection procedures should be conducted in negative pressure room if available. For safety reasons, specimens from a patient with suspected or confirmed COVID-19 should* ***not*** *be submitted for* ***viral culture*** *(only considered for research purposes).*

4. Serological Testing:

Generally used to screen for previous/late infection. Large-scale serologic screening in near future may be able to provide a better sense of the scope of asymptomatic infections and inform epidemiologic analysis. For subjects who present approximately two weeks into the course of illness and have negative RT-PCR, serologic tests ([Ig]M/IgG or IgG) would be suggestive of COVID-19. The reliability of the serologic testing is also dependent on the duration of illness and the type of assay used. Serologic tests may have minimal utility for diagnosis of acute infection but may be able to detect current infection between **9 and 14 days**, but still have low positive predictive value (can cross react with other coronaviruses) in settings of low seroprevalence. Some of the serological tests received emergency approval by FDA and may have high specificity ≥99.5% however, some of the point-of-care lateral flow assays are less sensitive than ELISA or chemiluminescent immunoassays.

5. Radiology:

Chest radiograph is usually the first investigation and may be normal in initial phases and when positive mostly reveal bilateral opacities with predominance of peripheral lung involvement (figure 1). Chest CT should not be performed routinely and considered only if there is expected change in clinical management also keeping in consideration the risks of infection spread during patients' transport to radiology department.

Chest CT if considered may be helpful in making the diagnosis and can also reveal details of lung parenchymal abnormalities including presence of complications like ARDS and pleural effusions. No finding can completely rule in or rule out the possibility of COVID-19 pneumonia. Typical chest CT scans most commonly demonstrate ground-glass opacification with or without

consolidative abnormalities, consistent with viral pneumonia. The abnormalities tend to be bilateral, exhibit a peripheral distribution, and predominantly may involve the lower lobes (figure 2). Uncommon findings include pleural effusion and/or thickening, and mediastinal lymphadenopathy. A "positive" chest CT for COVID-19 carries a sensitivity of 97 percent (using the RT-PCR tests as a reference standard) and specificity is around 25 percent as other etiologies may result in similar radiological findings. Timings of occurrence of radiological abnormalities may be variable; in some patients most severe abnormalities were detected approximately 10 days after symptom onset and in some with minimal respiratory symptoms and even prior to the detection of viral RNA from upper respiratory specimens.

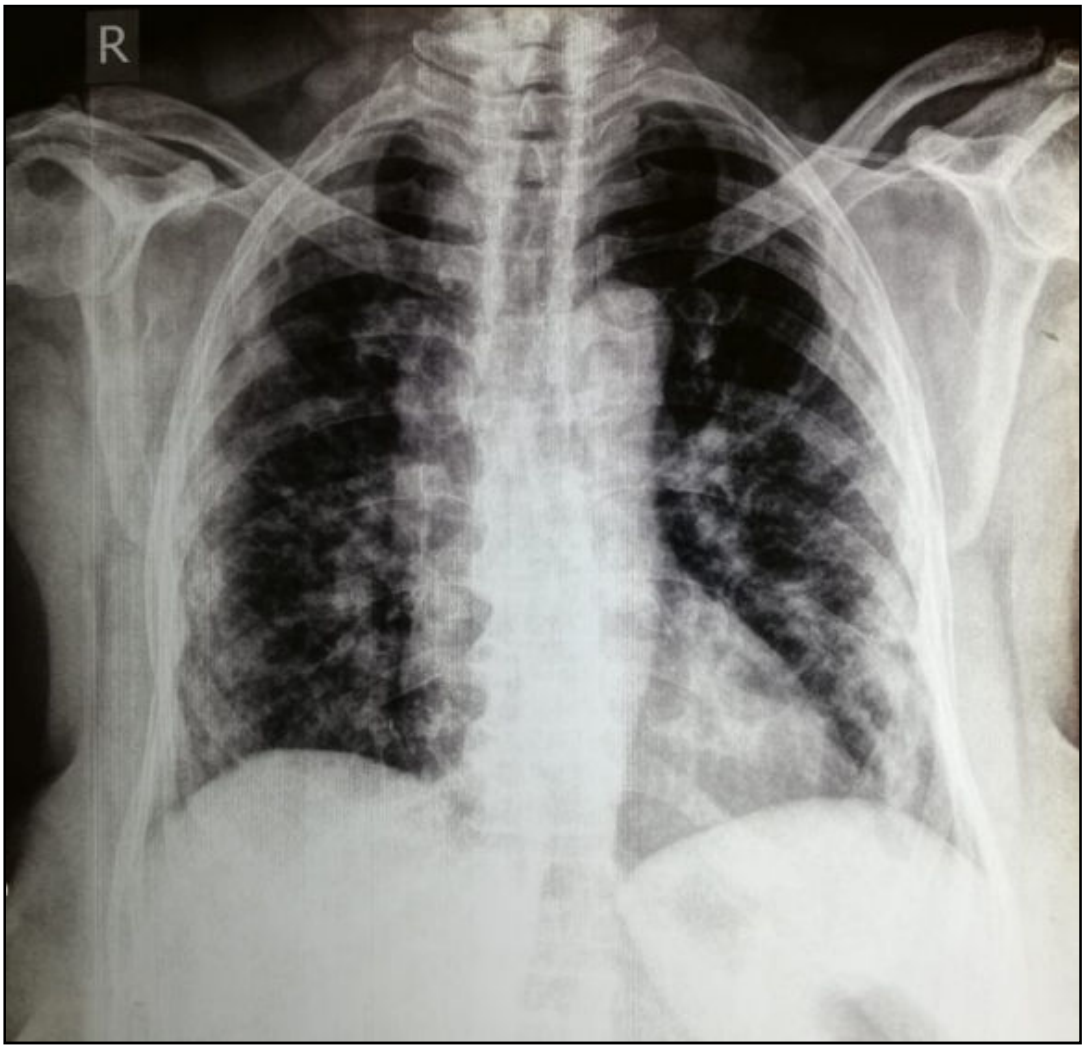

Figure 1. CXR-PA of a 68-year-old woman with respiratory failure secondary to COVID-19 pneumonia: Bilateral peripheral patchy areas of airspace consolidation with involvement of middle and lower zones dominance.
Source: Department of Pulmonology, Shaikh Zayed Hospital FPGMI Lahore.

Thoracic ultrasound (TUS) findings in COVID-19 are non-specific and the role is not well established but it can still be used as a bedside modality without any radiations risk. It has the additional advantage of avoiding transportation of infectious, hypoxemic and hemodynamically unstable suspected or established COVID-19 patients for chest CT to radiology department. TUS findings may include thickening of the pleural line with pleural line irregularity, B lines in a variety of patterns including focal, multifocal, and confluent (interstitial edema), consolidations in a variety of patterns including multifocal small, non-translobar, and translobar with occasional air bronchograms (pneumonia/ARDS), appearance of A lines during recovery phase and sometimes pleural effusions.

6. Electrocardiogram (ECG) & Echocardiography:

ECG is required for hospitalized patients to measure baseline QT interval as some subjects may require drugs like azithromycin which may cause QT interval prolongation and cardiovascular events. Pre and post drug administration ECG can help recognize subjects who can develop QT

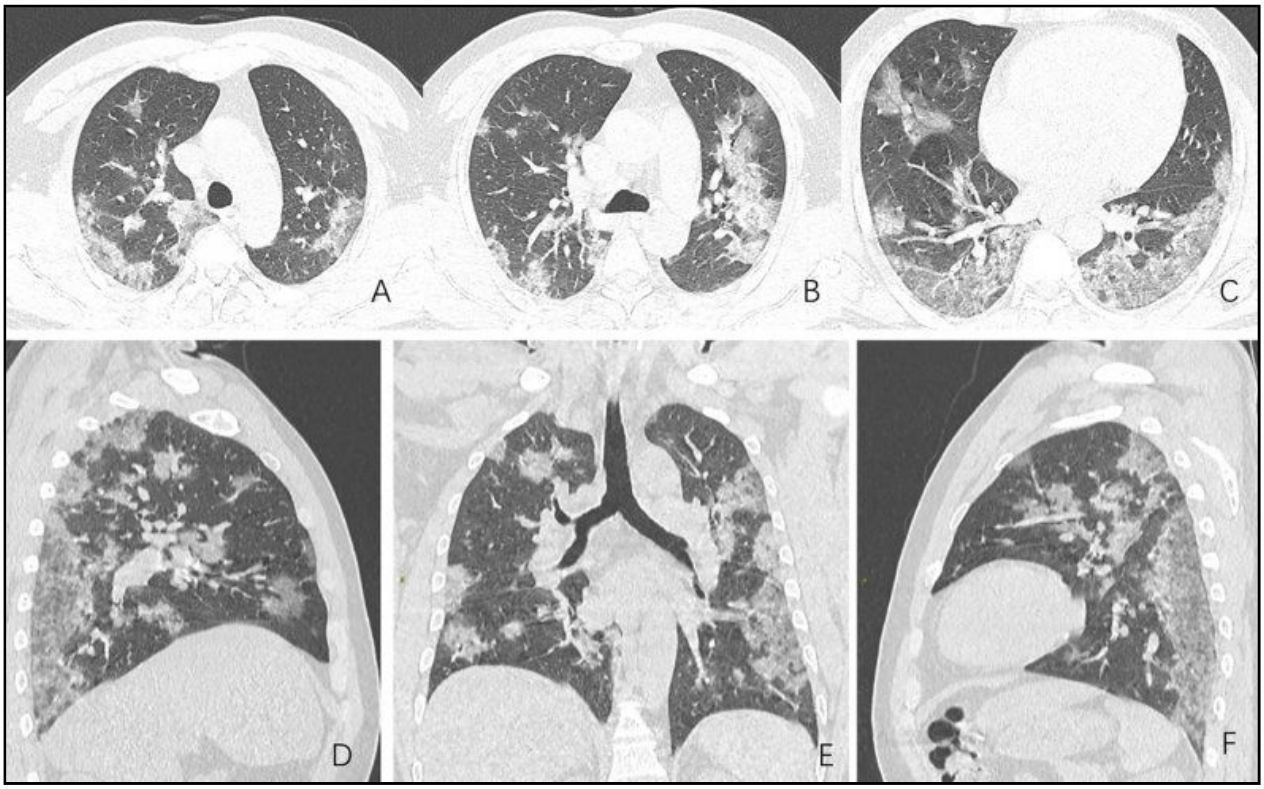

Figure 2. CT Images of a 44-year-old man with COVID-19 pneumonia.
Source: Qian L, Yu J, Shi H. Severe acute respiratory disease in a Huanan seafood market worker: images of an early casualty. Radiology: cardiothoracic imaging. DOI: 10.1148/RYCT.20202000033. Published Online February 1, 2020.

interval prolongation as an adverse event related to offending drug. On the other hand, some sick patients require serial ECGs and may also require echocardiography if there is evidence of arrhythmias, acute cardiac injury (increasing troponin levels with hemodynamic compromise) or other cardiovascular findings suggestive of cardiomyopathy and shock.

7. Blood and Sputum Bacterial Cultures:

Secondary bacterial infection has not been a frequently reported feature of COVID-19. If a patient with initial stability or with chronic symptoms over few days develop new onset clinical deterioration and chest radiological abnormalities suspected of bacterial superinfection, two sets of blood cultures and sputum Gram stain and culture should be considered.

6. Bronchoscopy:

Bronchoscopy is an aerosol-generating procedure and should only be performed when necessary and likely to change the management. Diagnostic bronchoscopy through endotracheal tube (with inline adapters for ventilated patients) likely carries less risk and should be performed in an airborne infection isolation room with full precautions. Bronchoscopy should have a limited role for the diagnosis of COVID-19 and is preferably performed when another diagnosis is being considered (eg, suspected super-infection like Pneumocystis jirovecii or invasive aspergillosis).

Therapeutic bronchoscopy is sometimes considered in critical patients for the presence of significant secretions and removal of thick muco-hematic plugs or rarely for airways stenotic complications. Rarely, therapeutic bronchoscopy may be required for life-threatening hemoptysis or post intubation airway stenosis.

7. Rapid Antigen Based Assays:

SARS-CoV-2 rapid antigen based assays are under development. Potentially, rapid antigen tests are easy to use but are typically less sensitive than PCR assays and a negative antigen test is possible and does not rule out COVID-19. Negative antigen test results should be confirmed using a sensitive RT-PCR if the clinical suspicion is high. The WHO had previously cautioned against the use of rapid tests based on antigen testing or antibody detection that have not undergone adequate validation because of concerns regarding false-positive or false-negative results.

Table 2. Management of Confirmed COVID-19 Patients.

Severity of Illness	General Management	Drugs*
Asymptomatic	• Strict isolation for a minimum of 10 days • If develops any symptoms, contact helpline • Discontinue isolation after 10 days	**Not needed**
Mild Disease	• Strict isolation at home or any healthcare facility with isolation facilities • Should be placed in a single room • Contact and droplet precautions should be instituted	• Use paracetamol for fever • Avoid NSAIDS • Oral hydration • Anti-histamines for rhinorrhea
Moderate Disease	• Should be admitted in hospital and placed in a single room • Contact and droplet precautions should be instituted • Use paracetamol for fever • Avoid ibuprofen or NSAIDs • Hydrate the patient preferably oral or IV fluid as required • Check oxygen saturation and if below 93% should administer oxygen via nasal cannula or face mask	• Use paracetamol for fever • Avoid NSAIDs • *Hydroxychloroquine alone or with azithromycin is no longer recommended** • All patients should be advised **awake proning** if they have oxygen saturation<93%. • **Anticoagulation** (prophylactic or therapeutic-See below)@ • **Remdesivir** is advised in patients with moderate disease**. • **Tocilizumab** to be given to patients who develop CRS*** • **Cortocosteroids** are indicated in early CRS^ (dexamethasone 6mg once a day or methylprednisolone 0.5-1mg/kg/day)

Severe Disease	•Admit the patient preferably in ICU (or HDU) with airborne isolation and strict PPE precautions • Hydrate the patient preferably IV according to need and hemodynamic status of patient. • Oxygen administration via facemask to keep oxygen saturation >92% • If unable to maintain saturation, manage Respiratory failure as per Fig 3 below • Regular assessment for need of endotracheal intubation and mechanical ventilation as delay in intubation is associated with unfavorable outcomes	• **Use paracetamol for fever** • **Avoid NSAIDS** • **Give empiric antimicrobials to treat pathogens according to local settings** • **All patients should be advised awake proning if they have oxygen saturation <93%.** • Anticoagulation **(prophylactic or therapeutic)**[@] • Remdesivir **is advised in patients with moderate /severe disease**[**]**(200mg first dose followed by 100mg for next 4 days)** • Tocilizumab **to be given to patients who develop CRS**[***]**(4-8mg/kg with maximum dose of 800mg) 2 doses can be given** • Cortocosteroids **are indicated in early CRS**[^]**. (dexamethasone 6 mg once a day or methylprednisolone 0.5-1mg/kg/day**
Critically ill	•Admit the patient in ICU with airborne isolation and strict PPE precautions • IV fluids according to need and hemodynamic status of patient (use conservative fluid strategy and diuresis if needed) • Manage Respiratory failure as per Fig 3 below • Use ARDSNET protocol for ventilatory management •If in shock: Norepinephrine is the vasopressor of choice. Should also rule out /consider concomitant cardiogenic shock (echo, troponins and pro-BNP)	• **Give** empiric antimicrobials **to treat pathogens according to local settings** • Anticoagulation **(preferable therapeutic- See below)**[@] • Remdesivir **is advised in patients with moderate /severe disease**[**]**(200mg first dose followed by 100mg for next 4 days)** • Tocilizumab **to be given to patients who develop CRS**[***]**(4-8mg/kg with maximum dose of 800mg) 2 doses can be given** • Cortocosteroids **are indicated in early CRS**[^] **(dexamethasone 6mg twice a day or methylprednisolone 40 mg Q 8 hourly)** • Convalescent plasma **therapy-see foot note below**[♣♣]

*__Combination of Hydroxychloroquine (HCQ) and Azithromycin__ was one of the initial few drugs that were used for the management of COVID-19. However, the emerging evidence does not favor this regimen. A recent multicentre randomised trial showed that the use of HCQ alone or with azithromycin did not improve clinical status after 15 days. A retrospective study done in New York also showed that HCQ, azithromycin or both did not lower in-hospital mortality. In fact, this combination therapy can cause prolonged QT interval and Torsades de Pointes. Hence these drugs alone or in combination are no longer recommended.

**__Remdesivir__ has recently been approved for moderate, severe and critically ill patients. A randomized double blind placebo controlled trial showed no significant clinical benefits however time to clinical improvement showed positive results. Compassionate use of remdesivir in severely-ill COVID-19 patients showed clinical improvement in 68% of patients.

***__Tocilizumab__ has shown a promising role in the treatment of CRS. A single center prospective study from Italy reported the efficacy of Tocilizumab in 100 patients. All the patients had pneumonia requiring ventilatory support. Tocilizumab was given in a dose of 8mg/kg by two consecutive IV infusions. It was noted that 77% of the patients improved or remained stable with 61% showing significant improvement in bilateral opacities and 15% being discharged. A prospective randomized double blind placebo controlled trial is underway to evaluate the safety and efficacy of tocilizumab in patients with severe COVID-19 pneumonia.

^The role of **steroids** in the management of COVID-19 was initially considered to be controversial but after the breakthrough trial known as the 'recovery trial', it was shown that dexamethasone reduces mortality in patients with COVID-19 who require oxygen support. Hence steroids are now strongly recommended for patients with moderate, severe and critically ill disease.

@Anticoagulation:

Prophylactic or therapeutic anticoagulation requires in moderate and severe cases as in COVID-19 as thrombotic complications are common.

Prophylactic anticoagulation:

- In moderate disease: standard DVT prophylaxis (enoxaparin 40 mg sub-cutaneous (S/C) once daily or rivaroxaban 10 mg once a day)
- In severe and critical disease, high dose prophylaxis (enoxaparin 60 mg S/C once daily or 40 mg every 12 hourly)

Therapeutic anticoagulation:

Indications:

- Documented presence of DVT or PE on ultrasound doppler or CTPA
- D-Dimer over 3 times normal upper limits

- Strong suspicion for thrombo-embolic disease when investigation cannot be done and patient is hypoxic

Drugs and Dosage:

Enoxaparin 1mg/kg every 12 hourly (preferred as initial treatment).

Switch to rivaroxaban on discharge. **Rivaroxaban** 15 mg twice a day for 21 days and then 20 mg once a day.

Duration: 3 months.

Dose adjustment will be required in case of renal impairment or morbid obesity (BMI ≥ 40kg/m2).

♣♣Convalescent Plasma Therapy:

Convalescent plasma (CP) therapy has been used for severe pneumonia caused by COVID-19 and has showed promising results in some studies including resolution of lung infiltrates as well as acceleration of viral clearance from body. However, it is both time dependent and not free from adverse effects. CP therapy helps in decreasing viremia and hence is beneficial in early phase of disease. Moreover, it can aggravate immune response and mechanism associated with it like CRS. A recent RCT done in Wuhan, China (although terminated early) in which convalescent plasma therapy was added to standard therapy in patients with severe and life threatening COVID-19 showed no statistically significant clinical improvement within 28 days. More clinical trials are required to evaluate the efficacy as well as side effects profile of convalescent plasma therapy.

On March 24, the American Food and Drug Administration (FDA) published a recommendation with the "COVID-19 Convalescent Plasma Research - Emergency" declaration. FDA stated that certain standards have been established for donation and that CP use is allowed for patients under certain conditions. Of note, FDA does not allow the use of CP for prophylaxis. With the "Blood Regulatory Network", WHO suggested using CP when vaccines and anti-viral drugs are not available in the treatment of critically ill patients with COVID-19.

Special Consideration:

For intubation:

- Perform in negative pressure room whenever possible
- PPE should include N95 respirator with face shield/protective eyewear (personal eyeglasses not adequate), isolation gowns (yellow gowns) for high risk aerosolizing procedures /impermeable to secretions and contact precautions. Intubate early/electively to avoid emergent intubation
- Avoid bag mask ventilation of patients

- Pre-oxygenate with nasal cannula and face masks as needed
- Use rapid sequence induction and intubation with early use of paralytics
- Ensure HEPA filters placed between ETT and CO2 detector or ETT and bag mask (if need to use)
- Consideration for shoe covers and surgical hoods or caps to avoid droplet contamination is reasonable

Noninvasive Ventilation (NIV-BIPAP and CPAP) and Hi-flow Nasal Cannula (HFNC):

- **Noninvasive ventilation** should be used with cautions because of aerosolization
    - If noninvasive ventilation cannot be avoided due to respiratory distress or obstructive sleep apnea (OSA), a Pulmonary/Critical Care consult is required for further recommendations
    - Patients on noninvasive ventilation should remain in a negative pressure room with appropriate well fit N-95/PPE
    - This includes patients being transported between facilities

- **Hi-flow nasal cannula (HFNC)** can also be used in severe hypoxic patient with caution
    - Can consider use of hi oxygen flows (60-80 l/m) in negative pressure room, with all personnel using appropriate well fitted N-95/PPE

Bronchodilators:

- Avoid nebulization on non-intubated COVID-19 patients
    - MDIs are recommended for confirmed non-intubated patients
    - MDIs will be stored in wiped-clean closed plastic bag
- Nebulization may be used on intubated COVID-19 patients if the patient was prescribed an MDI prior to intubation,
- When administering an MDI, a face shield/protective eyewear (personal eyeglasses not adequate) and N95 mask are required

Discharge Criteria:

- Improvement of respiratory symptoms.
- Afebrile for at least 3 days.
- Chest x ray shows improvement in infiltrates.
- Maintaining oxygen saturation >90% on room air.

Figure 3. Respiratory support in patients with COVID-19 Goal (SpO_2 90 to 96%)

Precautions: N95 mask, gown, gloves, eye protection; disposable stethoscope; negative pressure room for aerosol-generating procedures

Deterioration

Recovery

Oxygenation Support (non intubated patient)

Low flow nasal cannula up to 6 L/minute or non nebreathing mask up to 10 L/min

Use of High Flow Nasal Cannula (HFNC) and Non Invasive Ventilation (NIV) (aerosol generating) is controversial; early intubation may be preferred for decompensating patients

HFNC preferred over NIV, except for acute hypercapnia due to AECOPD or Acute CCF

Reassess patients on HFNC and NIV every 1 to 2 hours, or sooner if SpO_2 <90 or clinical deterioration

Mechanical Ventilation

Indications:

Signs of respiratory distress/exhaustion (eg, accessory muscle use; paradoxical abdominal breathing)

Rapid progression of disease over hours; SpO_2 sat <90% despite maximal oxygen

Evolving hypercapnea (arterial pH <7.3 with $PaCO_2$ >50)

Patient requiring >40 L/m HFNC and FiO_2 >0.6; Hemodynamic instability; multiorgan failure

Rapid Sequence Intubation:

Avoid bag mask ventilation, performed by experienced operator using in-line bacterial/viral filter

Ventilator Settings:

Lung protective strategy using low tidal volume ventilation (LTVV):

Assist Control mode, tidal volume 6 mL/kg PBW (range 4 to 8 mL/kg PBW); RR 25 to 30; goal 10 to 15 breaths/min; PEEP/FiO_2: PEEP 10 to 15 cm H_2O

(Goal pH >7.15; Plateau pressure <30 cm H_2O; PaO_2 55 to 80/SpO_2 90 to 96%)

Prone Ventilation

Indications:

Failure of LTVV (eg, PaO_2/FiO_2 [P/F] ratio <150 mmHg × 12 hours or worsening oxygenation after intubation

Duration:

12 to 16 hours/day (Effects typically seen over 4 to 8 hours)

Precautions:

Experienced staff; careful securing tracheal tube and vascular lines

Additional Interventions for Refractory Hypoxemia

Recruitment maneuvers and high PEEP strategies

Neuromuscular blockade for patients with refractory hypoxemia (eg, P/F <100 mmHg) or ventilator dyssynchrony

Trial of inhaled pulmonary vasodilators such as nitric oxide/epoprostenol

Extra Corporeal Membrane Oxygenation (ECMO) as a last resort (if available)

Prevention in Health Care Settings:

Regular Hand Washing:

The CDC recommends regular hand washing with soap and water for at least 20 seconds and if soap and water are not available, use an alcohol-based hand sanitizer with at least 60% alcohol.

Table 3. PPE Use in Different Clinical Areas:

Screening areas at the entry of health care facility	Surgical mask
Health care providers in clinics	**Gown and surgical mask**
High risk screening areas/triage **for COVID -19 suspect cases**	**Full sleeved impervious gowns, gloves, surgical mask**
Areas where COVID -19 suspected and positive patient admitted	**Full sleeved impervious gowns, gloves, N95 mask and goggles/ full face wiser**
Areas where aerosol generating procedures **are performed like bronchoscopy , suctioning and nebulizations**	**Full sleeved impervious gowns, gloves, N95 mask and goggles/ full face wiser**

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Appendix:

Advantages & Disadvantages of Various Diagnostic Interventions:

Modality	Advantages	Disadvantages	Remarks
History of travel from abroad or to areas with high prevalence or attending high density crowded gathering	Easy to collect. Helpful in picking high risk people. Helpful in limiting the spread by self-quarantine measures.	People hide travel history. May be too late to self-quarantine as the disease has already spread. Not everyone will have the disease. Only 25% of Iran Zaireen had the disease.	Data should always be collected.
Contact with positive patient	Very helpful in identifying the high risk individual. Helpful in limiting the spread by self-quarantine measures.	Unknown contacts will be missed. People recall may not lead to listing of all. All contacts may not be traced.	Data should always be collected.
Typical flu symptoms	Can help in the picking of suspected cases	Not specific as other conditions may present like this.	
CBC	Easy to perform Widely available The changes due to Covid-19 are known	It is not specific. It can be higher or lower depending on individual patients. It does not confirm the diagnosis.	Must test in all the patients.
C-reactive protein (CRP)	Easy to do Widely available Varies in relation to the severity of the disease	It is nonspecific and non-diagnostic. Can be higher in other infections as well.	Useful test in admitted patients.
HRCT	Can be positive in the early stage It can show changes in almost all the cases There is good co-relation with gold standard RT-PCR test It can show progression and improvement through serial scans	It is time consuming. Not widely available. It is non-specific as similar changes can be present in the other conditions. It will require dedicated CT scanner to prevent cross infection.	A very useful test where it can be performed safely. It can be used for follow-up in recovered COVID pneumonia and fibrosis patients

SARS-CoV-2 RNA detection by reverse-transcription polymerase chain reaction (RT-PCR)	It is a diagnostic test when positive. Serial testing can declare patient cured. It can help in rapid diagnosis compared to gene sequencing.	Require invasive means to collect specimens. High chances of cross infection. Will need to be repeated as single specimen may not be positive. Multiple specimens will need to be tested from different sites. The Turn Around Time (TAT) will be in days. It will require specialized setup for reliable testing and safety measures. Kits supply can be the limiting factor.	It is a must test and gold standard at the moment. Its sensitivity decreases with the passage of time. The test in important for clinical diagnosis and epidemiological reasons. In situations of conflicting results from 2 laboratories the positive test should be accepted as the ratio of false negatives is higher.
Serological Testing	Quick to perform. Does not require must expertise and special setups. Different types of kits and methods available.	Not reliable. Can only show infection but not the active disease.	Not recommended for diagnosis but can be useful in documenting previous or current infection. The protective effect of the antibodiesis not yet documented.

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