

In the name of God



COVID 19 MANAGEMENT IN CHILDREN

A. Sanaei

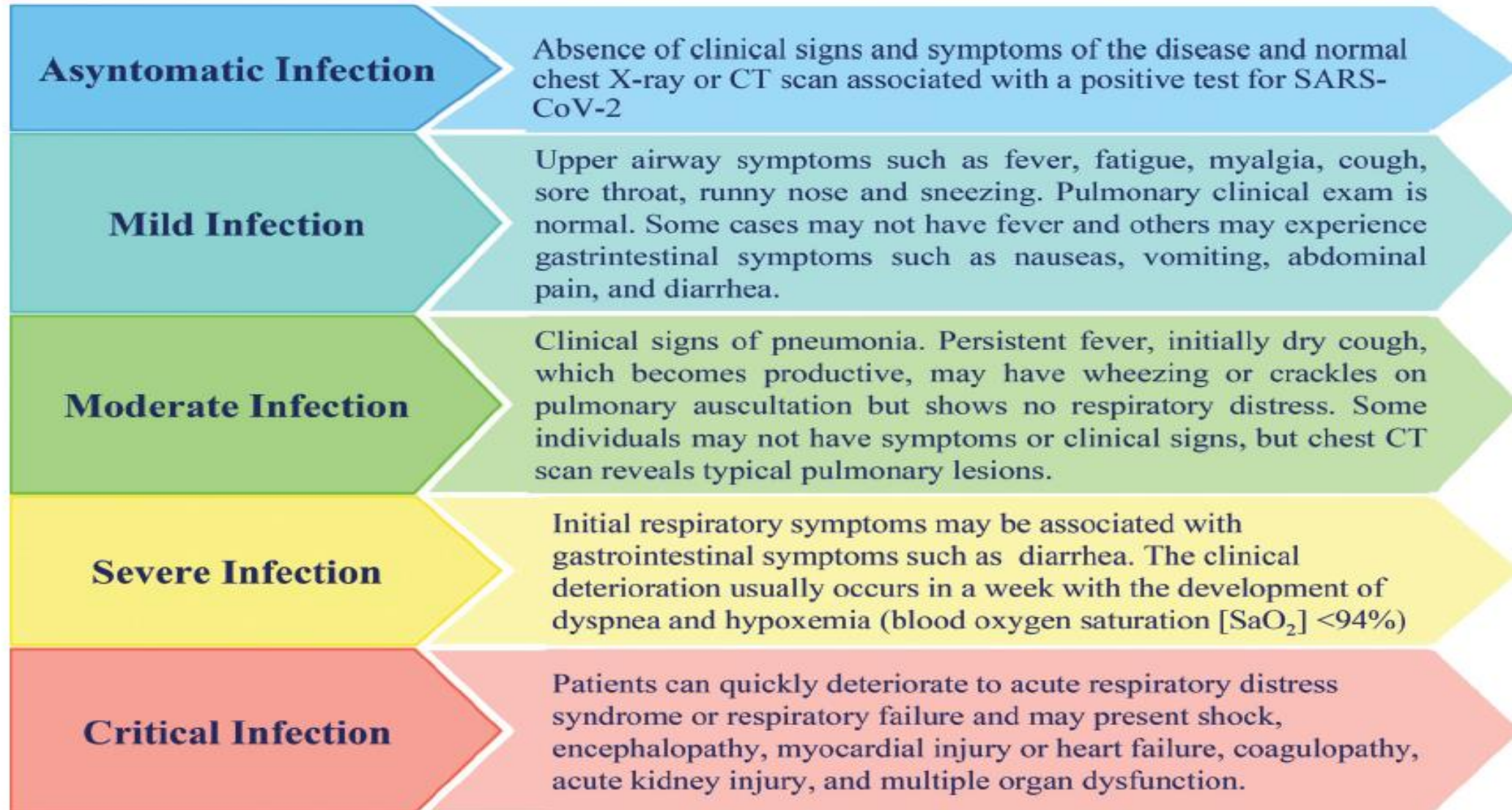
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Clinical Presentation of Covid-19



**Not Hospitalized
or
Hospitalized but Does Not Require
Supplemental Oxygen**

**Hospitalized and Requires
Supplemental Oxygen
(but Does Not Require Oxygen Delivery
Through a High-Flow Device,
Noninvasive Ventilation, Invasive
Mechanical Ventilation, or ECMO)**

**Hospitalized and Requires Oxygen
Delivery Through a High-Flow Device
or Noninvasive Ventilation**

**Hospitalized and Requires Invasive
Mechanical Ventilation or ECMO**

General measures of management

- ✓ اکسیژن درمانی مهمترین اقدام است و باید با نظارت دقیق انجام شود.
- ✓ هر یک ساعت ارزیابی صورت گیرد و در صورت عدم پاسخ بیمار، برای بهبود وضعیت اکسیژن رسانی به بیمار تصمیم گیری شود.

General measures of management

- children with mild illness **do not require fluid restriction** .
- In **respiratory compromise** consider fluid restriction : reduce the risk of ARDS.
- Tachypnea: increased insensible losses.
- **Diuretics** considered in **worsening respiratory failure requiring CPAP or NIV,** particularly if **pulmonary edema** on chest x-ray.
- Paracetamol is the first line antipyretic. Avoid ibuprofen .
- children should receive **low flow nasal cannula (LFNC) oxygen if they are hypoxic, rather than high flow nasal cannula (HFNC).**
- If children are hypoxic despite LFNC, then HFNC can be tried: not routinely be used as a method of reducing work of breathing in children who are otherwise saturating adequately

Corticosteroids

- The **RECOVERY trial** in COVID-19 (+) adults revealed a reduction in 28-day mortality in those receiving invasive mechanical ventilation or oxygen in combination with dexamethasone.
- Dexamethasone should NOT be used in COVID-19 (+) patients who are Otherwise healthy and do not require respiratory support
- *Dexamethasone should be considered in covid-19 (+) patients with respiratory support (oxygen or invasive mechanical ventilation)*

<p><u>Corticosteroids (IV/PO)</u></p> <ul style="list-style-type: none"> • <i>Dexamethasone-Preferred</i> • Alternatives: <ul style="list-style-type: none"> ▪ Breastfeeding/Pregnant: Prednisolone or methylprednisolone ▪ Preterm infant: Corrected GA < 40 weeks: Hydrocortisone <p><u>Should only be used in patients with:</u></p> <ol style="list-style-type: none"> a) Respiratory support: oxygen or invasive mechanical ventilation b) Continuation for underlying condition requiring chronic steroid treatment c) Additional diagnosis where steroid therapy is appropriate 	<table border="1" data-bbox="970 215 1760 786"> <thead> <tr> <th>Preferred Drug</th> <th>Dose³³⁻³⁴</th> </tr> </thead> <tbody> <tr> <td>Dexamethasone</td> <td>0.15mg/kg once daily (Max: 6 mg)</td> </tr> <tr> <th>Alternative Drugs</th> <th>Dose³³⁻³⁴</th> </tr> <tr> <td>Prednisolone</td> <td>1 mg/kg once daily (Max: 40 mg)</td> </tr> <tr> <td>Methylprednisolone</td> <td>0.8 mg/kg once daily (Max: 32 mg)</td> </tr> <tr> <td>Hydrocortisone</td> <td>0.5 mg/kg q12h X 7 days 0.5 mg/kg daily X 3 days</td> </tr> </tbody> </table> <p>Duration: up to 10 days</p>	Preferred Drug	Dose ³³⁻³⁴	Dexamethasone	0.15mg/kg once daily (Max: 6 mg)	Alternative Drugs	Dose ³³⁻³⁴	Prednisolone	1 mg/kg once daily (Max: 40 mg)	Methylprednisolone	0.8 mg/kg once daily (Max: 32 mg)	Hydrocortisone	0.5 mg/kg q12h X 7 days 0.5 mg/kg daily X 3 days	<p>Adverse events:</p> <ul style="list-style-type: none"> • Hypertension • Hyperglycemia
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➤ **Dexamethasone**

➤ **The best time for prescription**

➤ **<7 days from symptom onset** , **Optimal clinical timing: days 4–7 of symptoms**
when ferritin > 500

Corticosteroid therapy can be considered in children with COVID-19 **ARDS** and for patients with **fluid- and catecholamine-refractory septic shock**.

If used, intravenous methylprednisolone is recommended with the following dose/schedule for ARDS and septic shock; modifications to weaning schedule can be considered based on clinical course.

	mg/kg/dose	Interval
Days 1-5	1	Every 12 hours
Days 6-10	0.5	
Days 11-12	0.25	
Days 13 -14	0.125	

- **CDC : Hypercoagulability and COVID-19**
- **increased risk for venous and arterial thrombosis of large and small vessels.**
- **thrombocytopenia**
- **Increased D-dimer levels**
- **Increased fibrin degradation products**
- **Prolonged prothrombin time**
- **pulmonary embolism**
- **Microvascular thrombosis of the toes**
- **Clotting of catheters**
- **Myocardial injury with ST-segment elevation**
- **Large vessel strokes**

Anticoagulation

- **prophylaxis or therapeutic anticoagulation should be considered unless contraindicated.**

Bleeding Risk Factors

- **Not Recommended**

- Intracranial hemorrhage
- Active bleed
- abnormal PT or APTT is not a contraindication.
- platelet count less than 25,000;
- monitoring advised in severe renal impairment
- If LMWH contraindicated due to renal failure (Creatinine Clearance $<30\text{mL/min}$), UFH can be used as an alternative.

- **consider with caution**

- Intracranial mass
- Lumbar puncture w/in 24 hours
- Coagulopathy
- Neurosurgical procedure w/in 24 hours

Absolute contraindications to anticoagulation

Intracranial hemorrhage
Acute stroke/brain ischemia
Ongoing and uncontrolled bleeding
Uncorrected coagulopathy
Incomplete spinal cord injury with suspected or known paraspinal hematoma
Allergy to UFH or enoxaparin
Platelet count < 50,000/mcl
Epidural – discuss with anesthesia prior to initiating pharmacologic prophylaxis
Patient is likely to require an invasive procedure within the next 24 hours
Congenital bleeding disorder
Uncontrolled severe hypertension
Intracranial mass

massgeneral.org

Clinical Situation	Recommendation	Notes / Considerations
All hospitalized patients	All patients should receive standard prophylactic anticoagulation with LMWH in the absence of any contraindications ⁸	For pregnant patients ≥ 20 weeks gestation, UFH is preferred to LMWH.

Venous thromboembolism (VTE) management in different COVID states.

**Exposed (pre-symptomatic), Asymptomatic case, and mild phenotype:
VTE prophylaxis not recommended.**

moderate cases : thromboprophylaxis

For Any age:

*If normal renal function and no contraindications

Chemoprophylaxis (Enoxaparin)

- <2 mo:
 - 0.75 mg/kg/dose SC q12 h
- ≥ 2 mo:
 - Wt <40 kg:
 - 0.5 mg/kg/dose SC q12 h
 - Wt ≥40 kg:
 - 40 mg SC qd
 - Titrate to Anti-Xa 0.2-0.4 units/mL

* If renal impairment (CrCl < 30 mL/min) consider unfractionated heparin (UFH) †

Severe cases:

- Switch to intensified dose thromboprophylaxis
- If D-dimer is >500 (5ng/ml) and Ferritin > 500 ng/ml and those with the worsening clinical situation.

Table 2. Intensified dose thromboprophylaxis

For Any age:

*If normal renal function and no contraindications

Chemoprophylaxis (Enoxaparin)

- <2 mo:
 - 1 mg/kg/dose SC q12 h
- ≥ 2 mo:
 - **Wt <40 kg:**
 - **0.75 mg/kg/dose SC q12 h**
 - **Wt ≥ 40 kg:**
 - **40 mg q12 h**
 - Titrate to Anti-Xa 0.4-0.8 units/mL

* If renal impairment (CrCl < 30 mL/min) consider unfractionated heparin (UFH) †

Critically ill cases:

- Start therapeutic dose anticoagulation if D-Dimer > 2500 ng/ml, Platelet count > 450 x10⁹/L and CRP elevation > 100 mg/dL.

Table 3. Therapeutic dose anticoagulation

High-risk of VTE:

-critically ill

*Normal renal function
and

No contraindications

- Anticoagulation with therapeutic dose
 - Consider Enoxaparin:
 - < 2 mo: 1.5 mg/kg/dose SC q12 h
 - **≥ 2 mo:**
 - **Wt < 40 kg:**
 - **1 mg/kg/dose SC q12 h**
 - **Wt ≥ 40 kg:**
 - **40 mg q12 h**
 - Titrate to Anti-Xa 0.6-1.1 units/mL Titrate to Anti-Xa 0.6-1.1 units/mL

* If renal impairment (CrCl < 30 mL/min) consider unfractionated heparin (UFH)[†]

On Discharge:

- **At least two weeks** of prophylactic or therapeutic anticoagulation

Remdesivir

- an investigational antiviral drug originally developed to treat Ebola.
- works by inhibiting RNA-dependent RNA polymerase :
inhibit COVID-19, MERS, and SARS in-vitro and in animal models.
- *approved by FDA*

- **CDC Guidelines**

OUTDATED

- July 24, 2020

- Remdesivir

- remdesivir be prioritized for use in hospitalized patients with COVID-19 who require supplemental oxygen but who are not on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO .
- using remdesivir for 5 days or until hospital discharge, whichever comes first

Update recommendation

Hospitalized and Requires Supplemental Oxygen

(but Does Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO)

Remdesivir 200 mg IV for one day, followed by remdesivir 100 mg IV once daily for 4 days or until hospital discharge, whichever comes first **(AI)**^{b,c,d}

or

Remdesivir (dose and duration as above) plus **dexamethasone**^e 6 mg IV or PO for up to 10 days or until hospital discharge, whichever comes first **(BIII)**^f

If **remdesivir** cannot be used, **dexamethasone**^e may be used instead **(BIII)**

Remdesivir

Exclusion criteria
Evidence of multi-organ failure
Vasopressor requirement
ALT levels $> 5 \times$ ULN
CrCl < 30 mL/min, dialysis or CVVH
Concomitant use of other antiviral

Remdesivir : in the first 4 days of admission

Remdesivir

Dosing & Duration	Comments									
<p>Adult dosing:</p> <ul style="list-style-type: none">• 200 mg load, then 100 mg q24h <p>Pediatric dosing*:</p> <table border="1" data-bbox="129 715 835 882"><thead><tr><th>Weight</th><th>LD (once)</th><th>MD (q24h)</th></tr></thead><tbody><tr><td><40 kg</td><td>5 mg/kg</td><td>2.5 mg/kg</td></tr><tr><td>≥40 kg</td><td>200 mg</td><td>100 mg</td></tr></tbody></table> <p>LD-Loading Dose, Max =200 mg MD-Maintenance Dose, Max= 100 mg</p> <p>Duration:</p> <ul style="list-style-type: none">• 5-10 days	Weight	LD (once)	MD (q24h)	<40 kg	5 mg/kg	2.5 mg/kg	≥40 kg	200 mg	100 mg	<p>Requires:</p> <ul style="list-style-type: none">• Gilead's expanded access program required OR• FDA issued Emergency Use Authorization (EUA) As of 5/1/20, distributed to hospitals via Virginia Department of Health <p>Adverse events:</p> <ul style="list-style-type: none">• Increased liver enzymes• Infusion related hypotension• Drug-drug interactions CYP450• Avoid use with acetaminophen• QT prolongation (possible TdP Risk)
Weight	LD (once)	MD (q24h)								
<40 kg	5 mg/kg	2.5 mg/kg								
≥40 kg	200 mg	100 mg								

- Discontinue remdesivir if ALT \geq 5 time ULN
- Discontinue remdesivir if eGFR $<$ 30 mL/min/1.72m²

Adverse Events: generally well tolerated

- ALT/AST increase (onset 5-25 days, resolution 3-4 days)
- Infusion-related hypotension, Phlebitis
- Constipation , Dyspepsia, Nausea,
- Extremity pain, Headache, rare QT prolongation (possible Torsades de pointes risk)

- **Remdesivir therapy may be extended to up to 10 days if no substantial clinical improvement is seen at Day 5.**
- **The combination of remdesivir and dexamethasone has not been studied in clinical trials; however, there are theoretical reasons for combining these drugs.**

Favipiravir dosing is in patients ≥ 12 months of Age & body weight ≥ 10 kg

Body weight	Favipiravir 200 mg Tablet
10-15 kg	Loading Dose: One tablet PO BID for One day Maintenance from Day2: Half tablet (100 mg) PO BID
16-21 kg	Loading Dose: Two tablets PO BID One day Maintenance from Day2: One Tablet PO BID
22-35 kg	Loading Dose: 3 Tablets PO BID for One day Maintenance from Day2: One tablet PO TID
36-45 kg	Loading Dose: Four tablets PO BID for One day Maintenance from Day2: Two tablets PO BID
46-55 kg	Loading Dose: Five tablets PO BID for One day Maintenance from Day2: Two tablets qAM, three Tablets qPM
For >55 kg	Can use adult dosing if age ≥ 16 years, if age <16 years use dosing of 46-55 kg range

Treatment duration: 7 to 14 days

- . **Tocilizumab (IV)**
 - . **IL-6 inhibitor**

Tocilizumab:

High risk of cytokine storm

OR

Rapidly worsening gas exchange

+

Pulmonary infiltrates

+

SpO₂ ≤ 93% on RA or > 6 L/min

TOCILIZUMAB

Criteria for risk high-risk of cytokine storm¹⁰

≥ 1	Description
IL-6	$\geq 3x$ upper normal limit
Ferritin	>300 ug/L with doubling in 24 hr
Ferritin + LDH	>600 ug/L at presentation >250
D-dimer	Elevated

<p>Adult Dosing (≥ 18 years):</p> <ul style="list-style-type: none"> • 8 mg/kg X 1 (Max 800 mg) <p>Pediatric Dosing (<18 years):</p> <ul style="list-style-type: none"> • < 30 kg: 12 mg/kg X 1 (Max 800 mg) • ≥ 30 kg: 8 mg/kg X 1 (Max 800 mg) <p>** Round dose to nearest full vial **</p> <p>Duration: One dose Consider additional dose 8-12 hours after if continued clinical decompensation</p>	<p>Contraindications:</p> <ul style="list-style-type: none"> • Avoid in pregnancy • Breastfeeding <p>Caution:</p> <ul style="list-style-type: none"> • Treatment with >1 biologic is not recommended • Avoid live viral vaccines • Caution converting from tocilizumab (half-life~16 days) to anakinra • CRP & IL-6 levels not reliable measurements of inflammation post tocilizumab <p>Serious adverse events:</p> <ul style="list-style-type: none"> • Gastrointestinal perforation, Anemia, Hepatitis, Infusion reaction <p>Typical response within 48-72 hrs with cessation of fevers and stabilized or improved oxygenation</p>
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* Interferon β

• اینترفرون بتا- 1 بی ($IFN \beta-1b$) ، 250 میکروگرم

بصورت تزریق زیرجلدی یک روز در میان به تعداد 5 - 7 دز

• اینترفرون بتا- 1 ای ($IFN \beta-1a$) ، 44 میکروگرم بصورت

تزریق زیر جلدی یک روز در میان به تعداد 5 - 7 دز

توجه: در مورد استفاده از بتافرون در کودکان زیر 12 سال مطالعه به اندازه کافی وجود ندارد و اثربخشی و ایمنی آن دقیقاً مشخص

نیست.

One high quality RCT compared lopinavir-ritonavir with usual care in 199 adults hospitalised with SARS-CoV-2 infection, and found no difference in the primary outcome (time to clinical improvement) or mortality (secondary outcome), but did report that length of stay, ICU duration, and risk of complications were lower (secondary outcomes)

WHO

- Data from Solidarity (including the French Discovery trial data) and the recently announced results from the UK's Recovery trial both showed **that hydroxychloroquine does not result in the reduction of mortality of hospitalised COVID-19 patients, when compared with standard of care.**
- There is currently no evidence to date that hydroxychloroquine should be use in mild disease, nor that it will reduce severe illness or mortality.

Anakinra

For patients with evidence of sHLH-like features

With ID input, [anakinra](#)
(Kineret) can be considered

Antibiotics

- *consider antibiotics* if
- They are unusually ill at admission/day
- They are not showing improvement by day 3
(particularly fever and/or still in oxygen)
- If the cough is productive .

- Routine empiric antibiotics are not recommended:**

low rates of bacterial superinfection in COVID-19 patients

Unnecessary antibiotic use increases the risk of multi-drug resistant organisms and *C. difficile*.



Does not favor antibiotics:

COVID-19 confirmed / high likelihood
CXR: Peripheral / bilateral infiltrates
Baseline PCT < 0.2
Non-ICU admission

Favor empiric antibiotics:

COVID-19 not yet established
CXR: Lobar infiltrate
Baseline PCT ≥ 0.2
ICU admission



Recommend:

Sputum GS & culture & Legionella urinary antigen
ceftriaxone 1 gm IV QD + doxycycline 100 mg PO BID
(azithromycin is alternative to doxycycline)
ICU/sepsis: consider MRSA / MDRO coverage

- **CDC**
- **Mesenchymal Stem Cells**
- A new subsection on mesenchymal stem cells was added to Immune-Based Therapy in the Blood-Derived Products Under Evaluation for the Treatment of COVID-19 section. The Panel **recommends against** the use of **mesenchymal stem cells** for the treatment of COVID-19, except in a clinical trial .
- **Adjunctive Therapy: Vitamin C, Vitamin D, and Zinc Supplementation**
- Vitamin and mineral supplements have been promoted for the treatment and prevention of respiratory viral infections; however, their roles in treating COVID-19 are yet unproven.

تجویز IVIG:

در شرایط مثل HLH، نوزادان و شیرخواران بدحال و یا هایپوگاماگلوبولینمی (IgG کمتر از 400 mg/dl) توصیه میشود. هم چنین در صورت وجود شواهد دال بر TSS؛ Kawasaki Shock Syndrome و MIS-C مصرف IVIG توصیه می شود.

❖ بیماران بسیار بدحال:

در شرایطی که برای بیمار از پروتکل پیشنهادی کشوری استفاده شده و نتیجه بخش نبوده و جان بیمار در خطر باشد برای تصمیم گیری در مورد استفاده از درمان های خاص باید از نظرات یک تیم متشکل از متخصصین عفونی، ریه و بیهوشی و سایر رشته ها حسب نیاز کمک گرفته شود و ممکن است داروها و روش های زیر کمک کننده باشد.

- ❑ High dose corticosteroids
- ❑ Hemoperfusion
- ❑ Cytosorb cytokine removal
- ❑ Plasmapheresis

در هنگام ترخیص توصیه می شود تمام معیارهای زیر وجود داشته باشد :

1. تب برای 24 تا 48 ساعت بدون دریافت تب بر قطع شده باشد.
 2. علائم تنفسی مثل سرفه در حال بهبودی باشد و علائم حیاتی پایدار باشد .
 3. اشباع اکسیژن (O2 sat) در هوای اطاق بالای 93 % بوده و یا در صورت پائین بودن آن سه روز پشت سر هم O2 sat در حد قابل قبولی ابقاء شده و افت پیدا نکند.
 4. نیاز به درمان داخل وریدی نباشد و بیمار تحمل خوراکی داشته باشد.
 5. آزمایش CBC قبل از ترخیص رو به طبیعی شدن باشد و در صورت در دسترس بودن CRP 50% و ESR 20% نسبت به قبل افت داشته باشد .
 6. در موارد شدیدی که گرافی درخواست می شود، در تصویربرداری Consolidation کاهش یافته و تعدادی از ضایعات ناپدید شده و ضایعه جدیدی ایجاد نشده باشد
 7. انجام RT- PCR جزء معیارهای پیش نیاز ترخیص نیست ولی در موارد زیر بسته به سیاست ها و شرایط جامعه و مرکز ممکن است درخواست شود :
- بیماران با نقص ایمنی
 - بیمارانی که قرار است به بخش های دیگر و یا واحدهای Long term care facility (مثل شیرخوارگاه ها) منتقل شوند

National Institute Of Health Of America

Oct 9, 2020 NIH

D Figure 1. Recommendations for Pharmacologic Management of Patients with COVID-19 Based on Disease Severity

DISEASE SEVERITY

PANEL'S RECOMMENDATIONS

(Recommendations are listed in order of preference in each category below; however, all options are considered acceptable.)

**Not Hospitalized
or
Hospitalized but Does Not Require
Supplemental Oxygen**

No specific antiviral or immunomodulatory therapy recommended
The Panel **recommends against** the use of **dexamethasone (AI)**
See the Remdesivir section for a discussion of the data on using this drug in hospitalized patients with moderate COVID-19.^a

**Hospitalized and Requires
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(but Does Not Require Oxygen Delivery
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Remdesivir 200 mg IV for one day, followed by remdesivir 100 mg IV once daily for 4 days or until hospital discharge, whichever comes first **(AI)^{b,c,d}**
or
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If **remdesivir** cannot be used, **dexamethasone^e** may be used instead **(BIII)**

**Hospitalized and Requires Oxygen
Delivery Through a High-Flow Device
or Noninvasive Ventilation**

Dexamethasone^d plus **remdesivir** at the doses and durations discussed above **(AIII)^f**
or
Dexamethasone^{d,e} at the dose and duration discussed above **(AI)**

**Hospitalized and Requires Invasive
Mechanical Ventilation or ECMO**

Dexamethasone^{d,e} at the dose and duration discussed above **(AI)**
or
Dexamethasone^e plus **remdesivir** for patients who have recently been intubated at the doses and durations discussed above **(CIII)^f**

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion

Figure 1. Recommendations for Pharmacologic Management of Patients with COVID-19 Based on Disease Severity

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discussed above **(AIII)^r**

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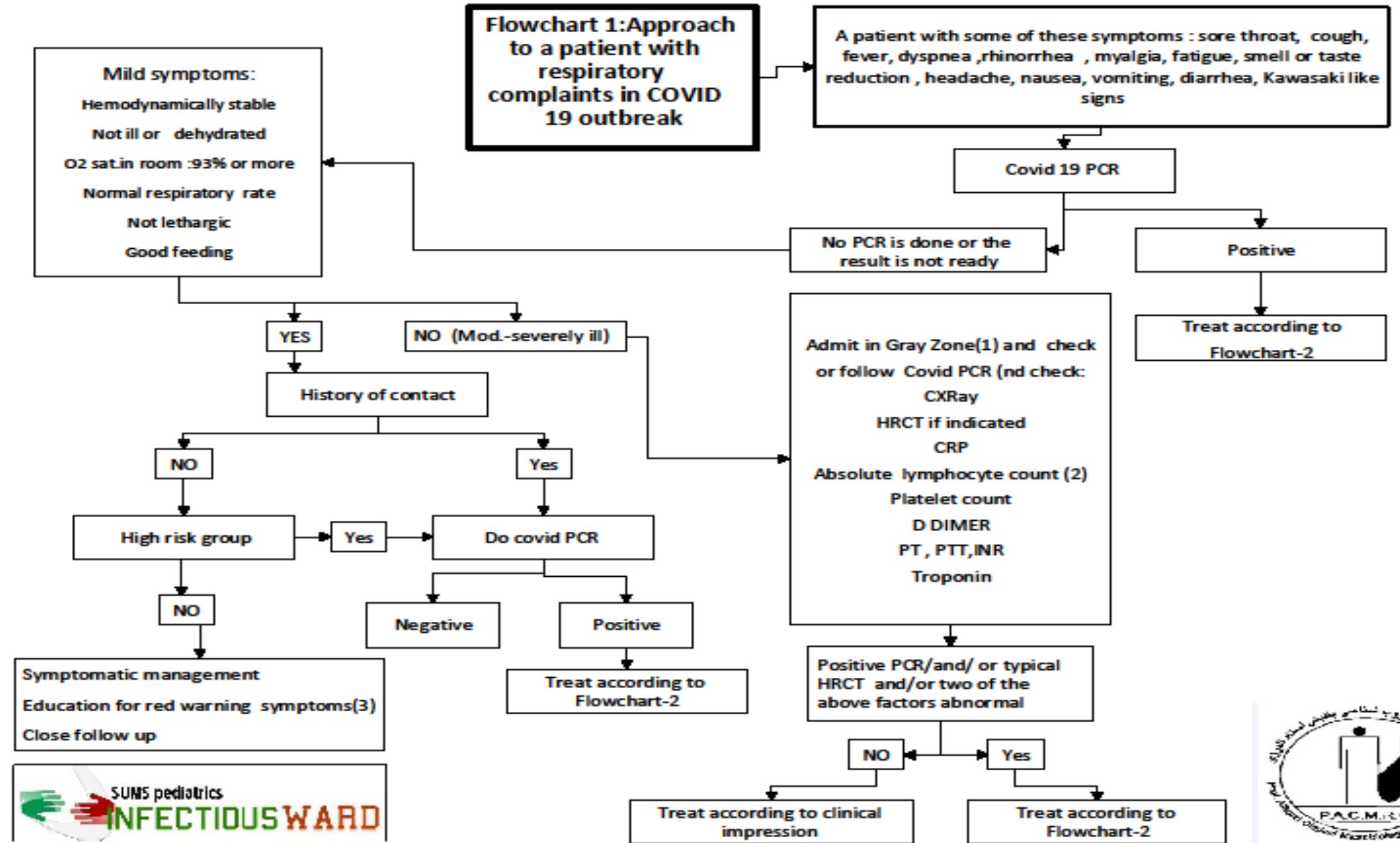
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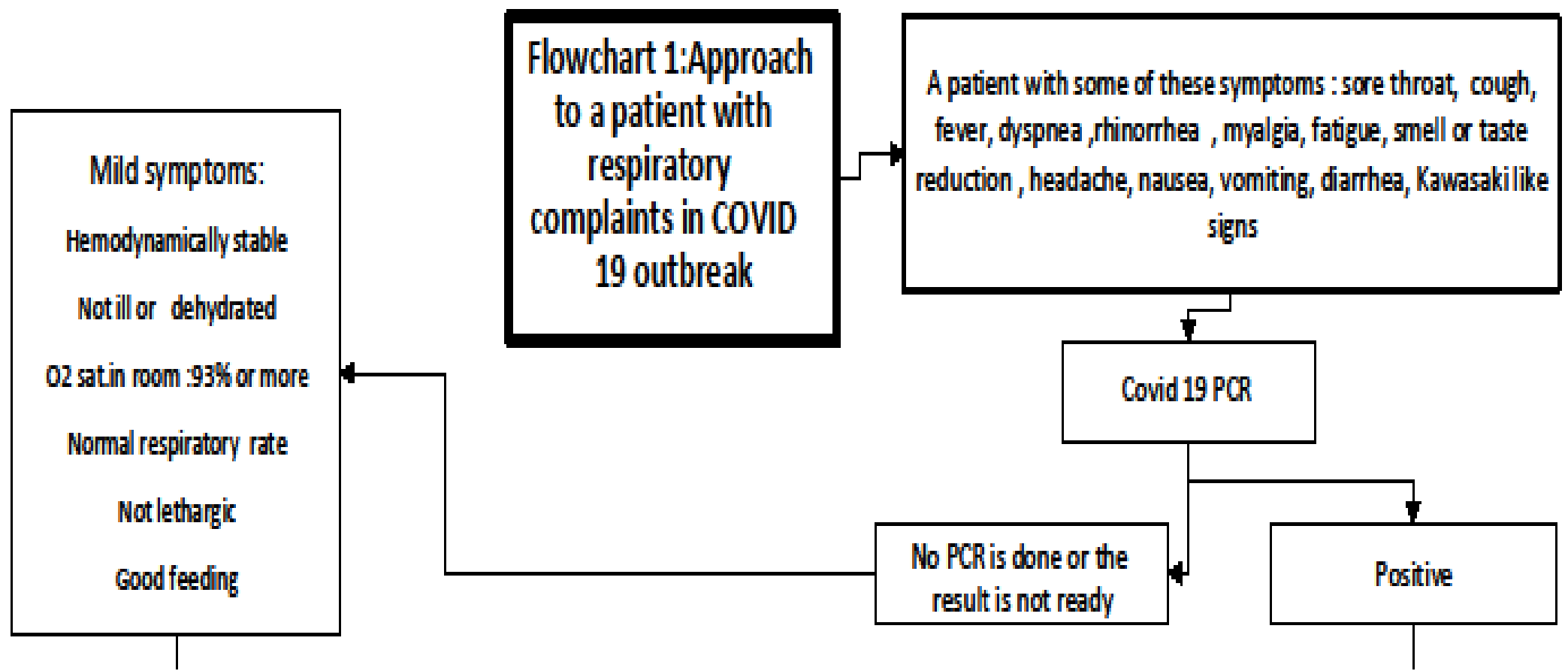
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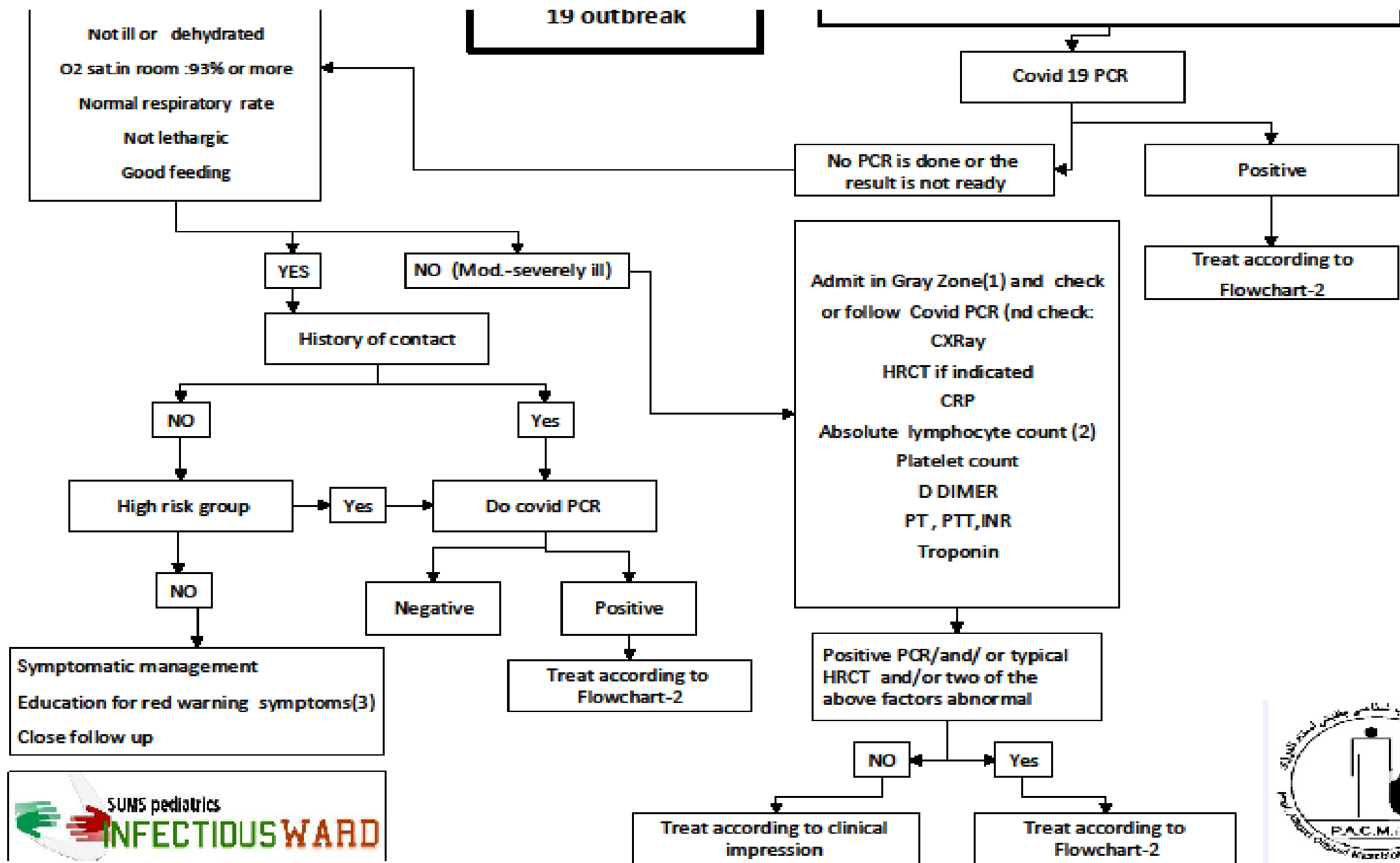
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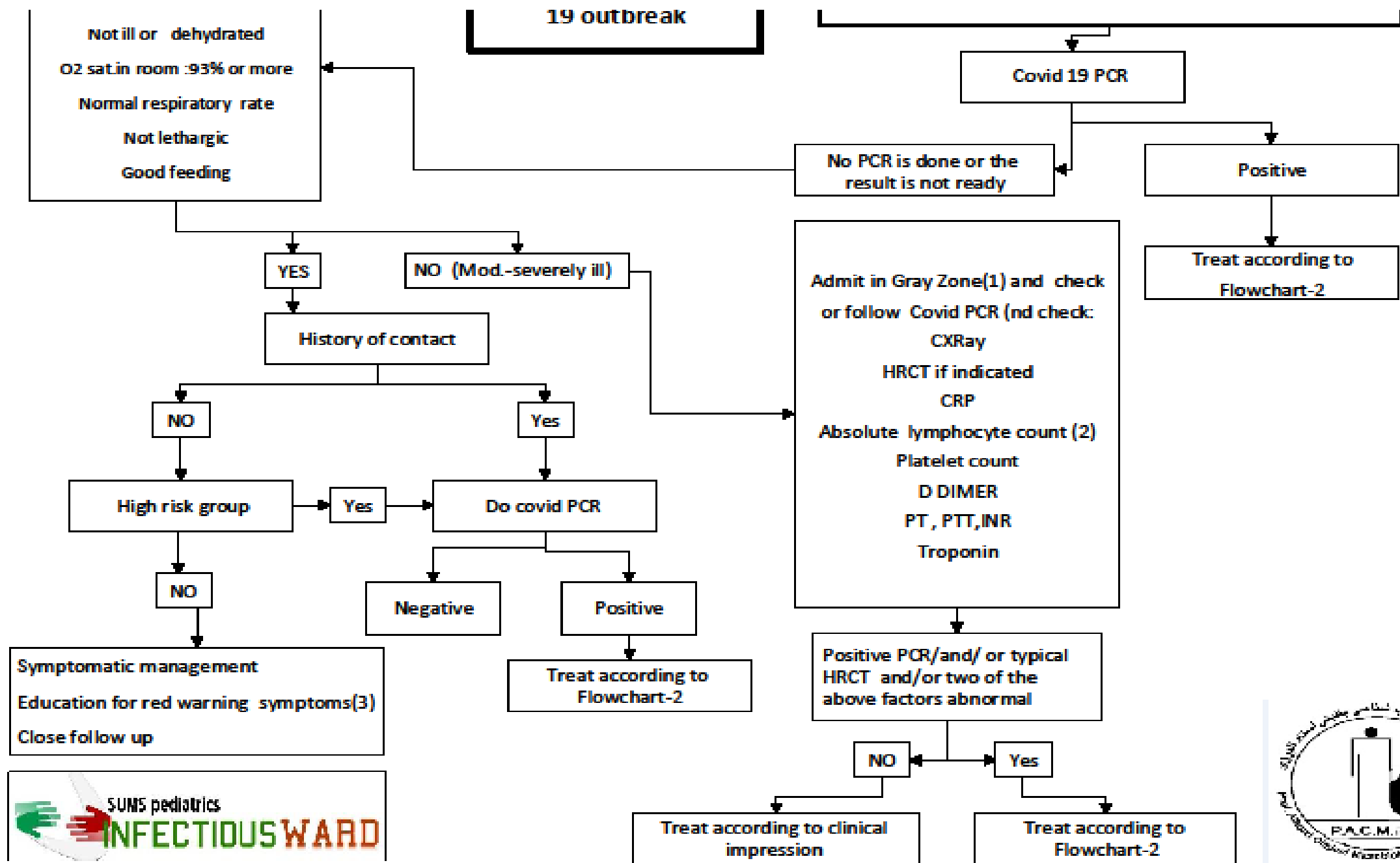
Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion

Flowchart 1: Approach to a patient with respiratory complaints in COVID 19 outbreak



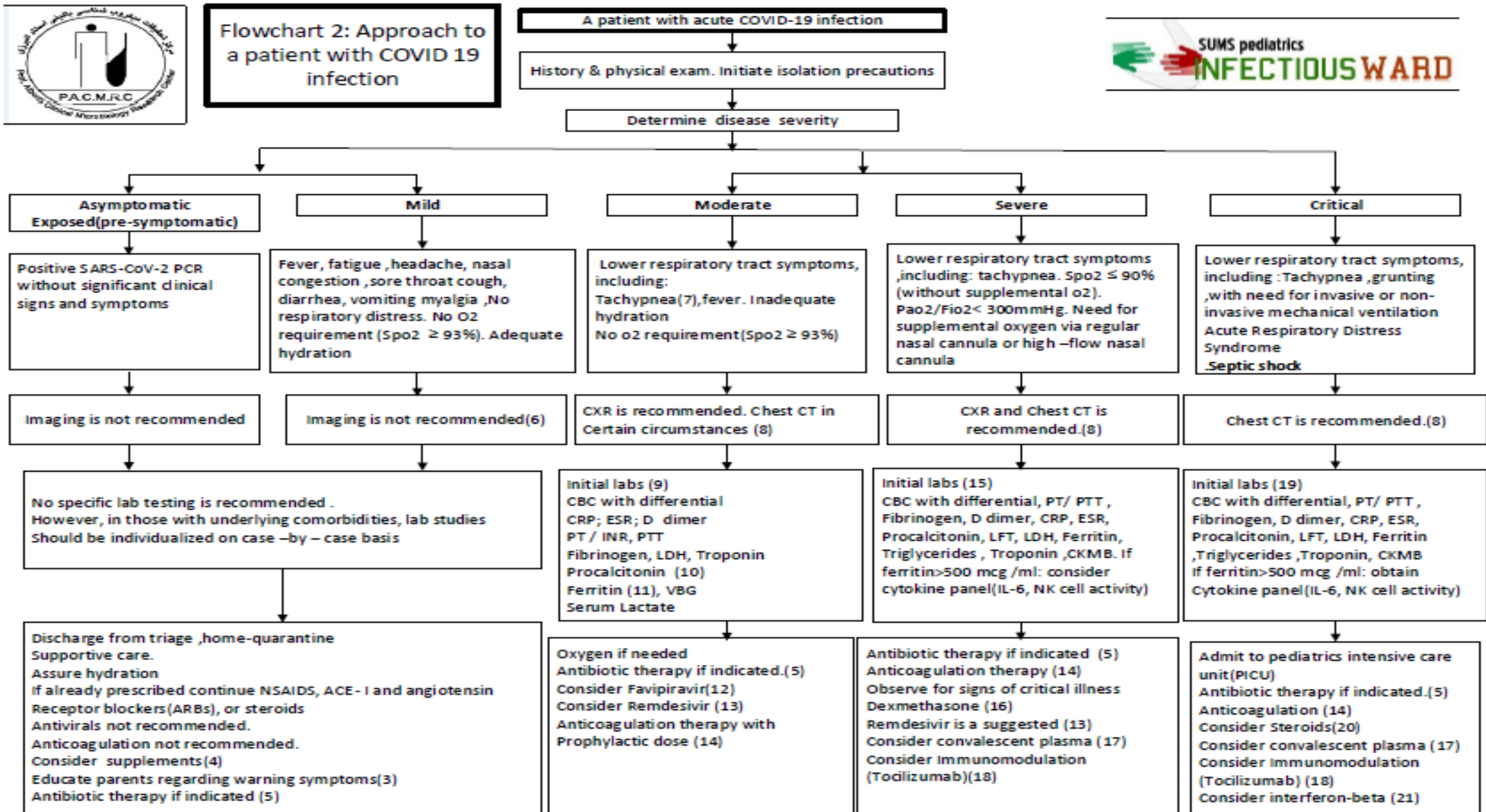


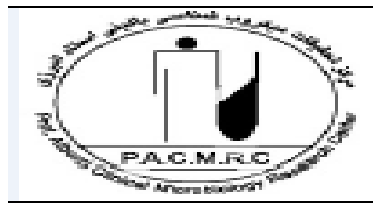






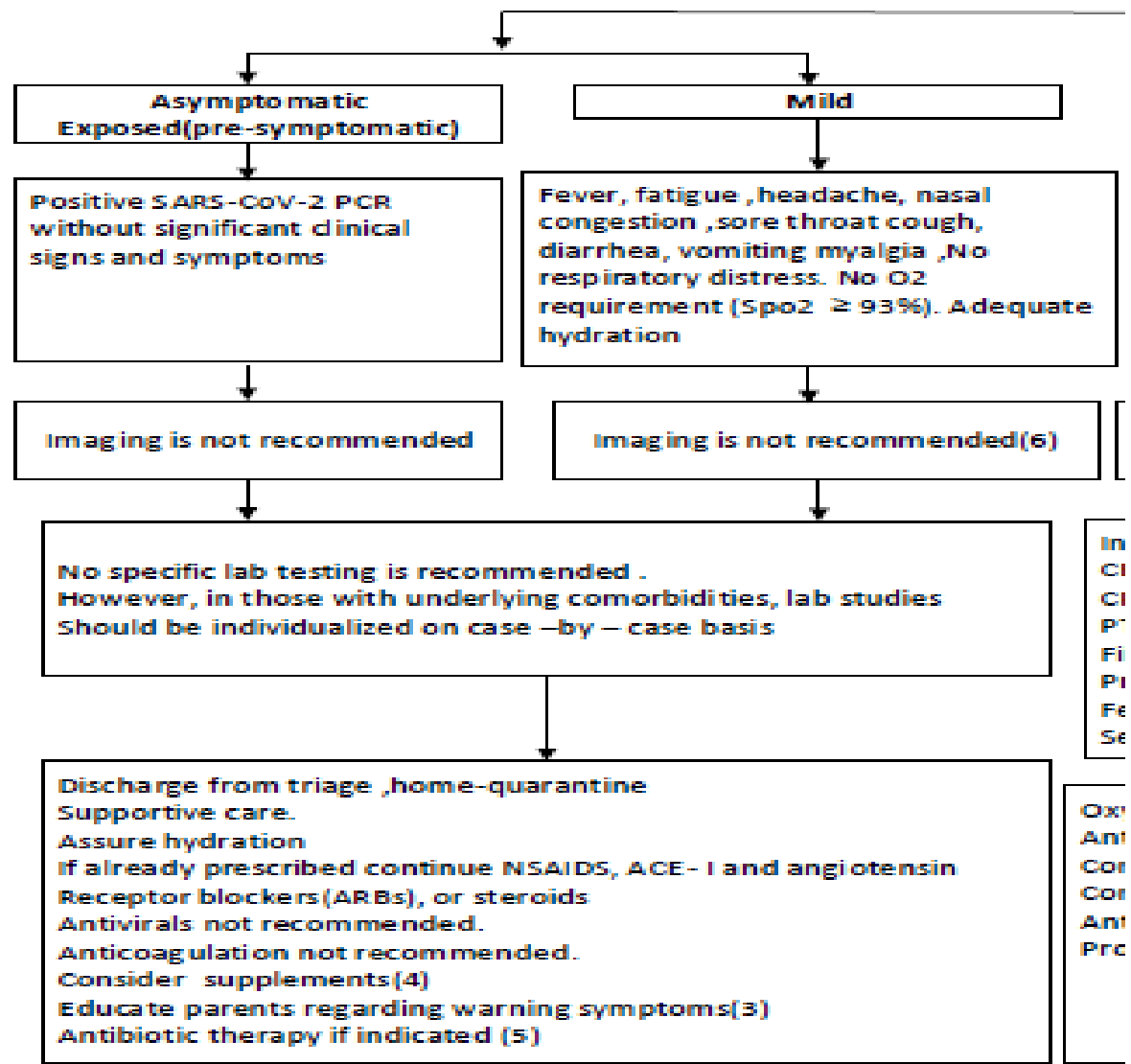
Flowchart 2: Approach to a patient with COVID 19 infection





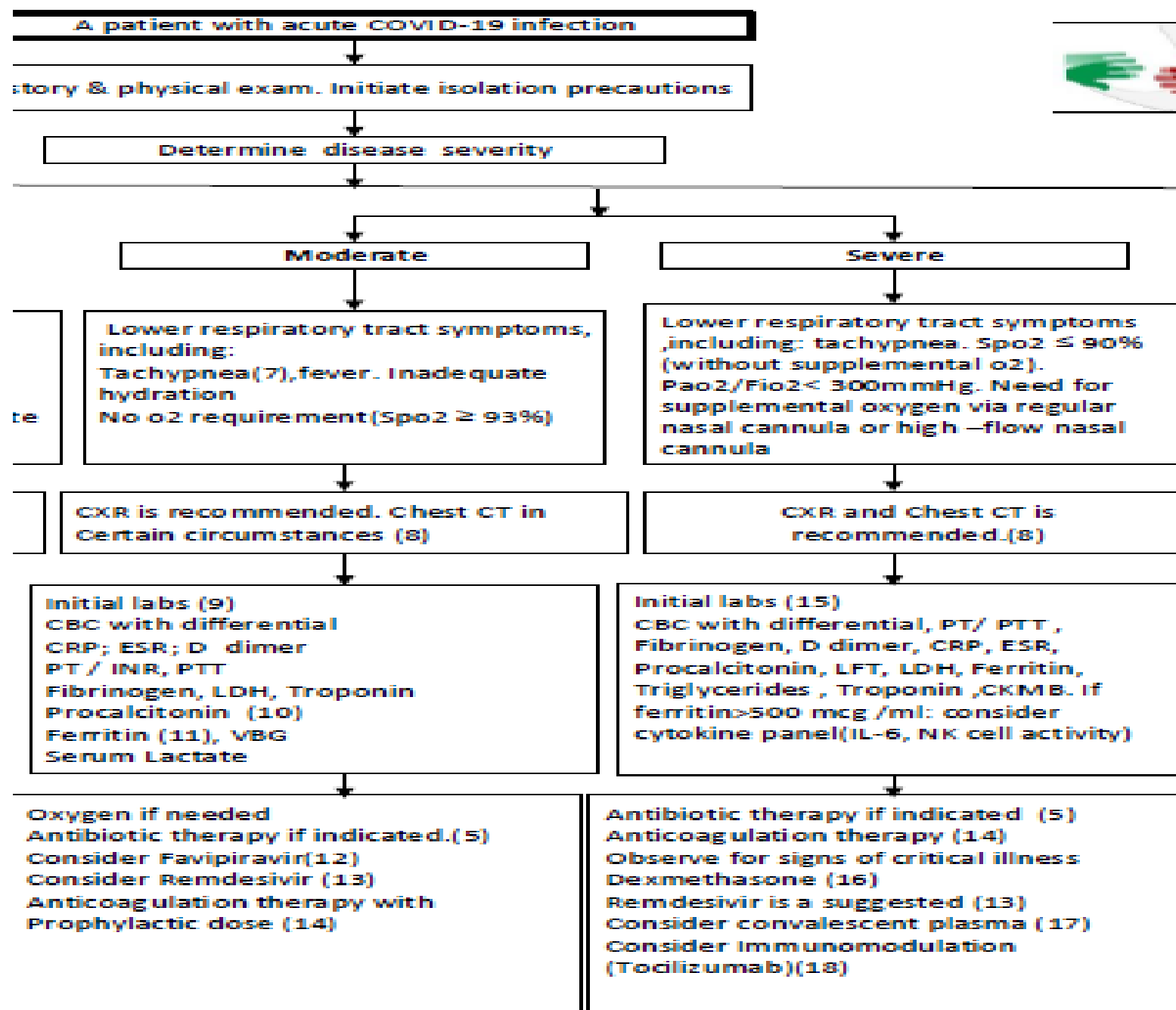
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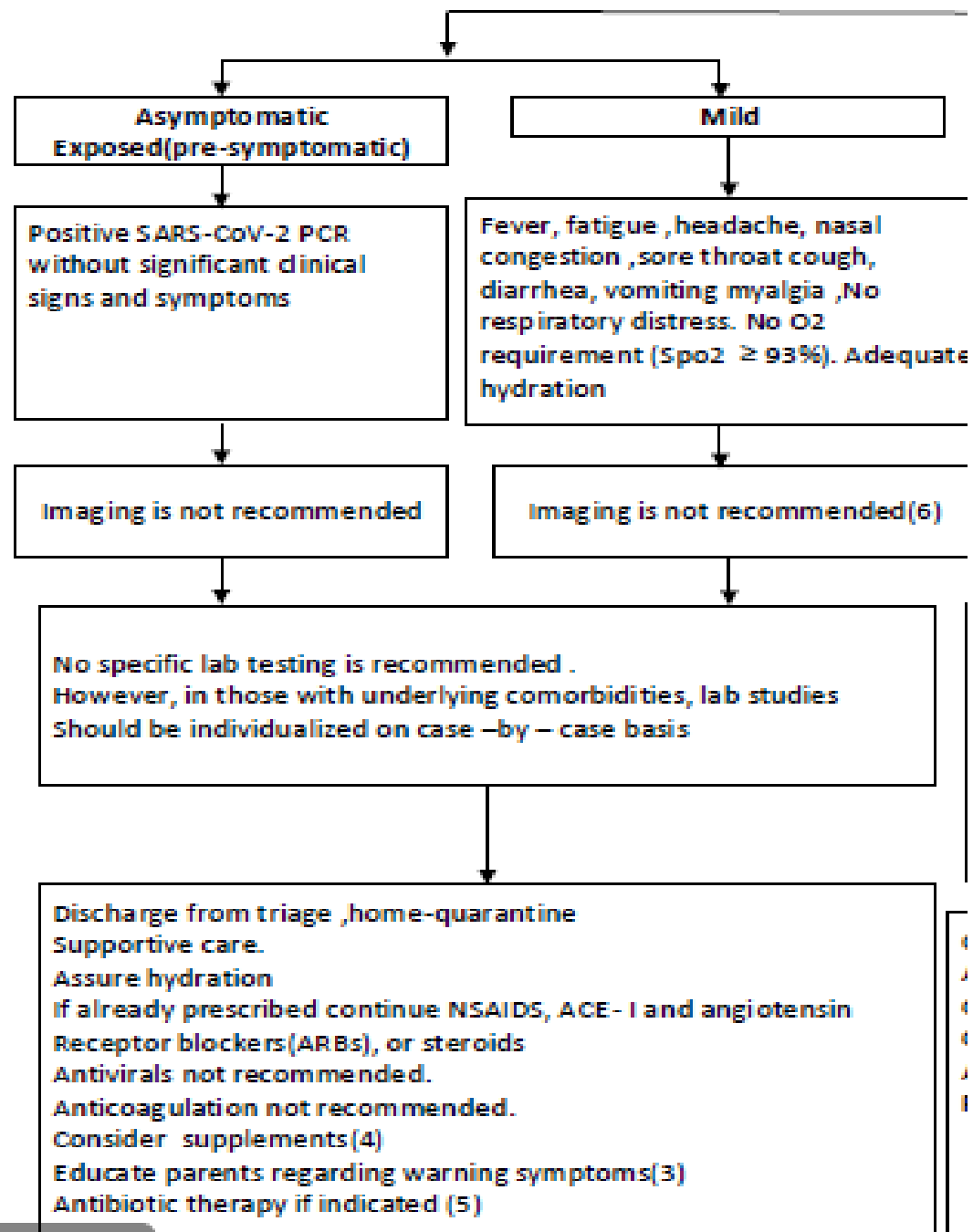
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A close-up photograph of a white flower with six petals and yellow stamens, set against a soft, blue background. The flower is in focus, while the surrounding green leaves and other buds are slightly blurred. The overall mood is serene and hopeful.

The best way to
predict the future is
to create it.

Latest update on on treatment arms

Posted on 16 October 2020

The Solidarity Trial published interim results on 15 October 2020. It found that all 4 treatments evaluated (remdesivir, hydroxychloroquine, lopinavir/ritonavir and interferon) had little or no effect on overall mortality, initiation of ventilation and duration of hospital stay in hospitalized patients.

Influenza and COVID-19

persons with COVID-19 should receive an inactivated influenza vaccine (BIII).

When Influenza Viruses and SARS-CoV-2 Are Cocirculating

Only testing can distinguish between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and influenza virus infections and identify SARS-CoV-2 and influenza virus coinfection.

When SARS-CoV-2 and influenza viruses are cocirculating, the Panel recommends testing for both viruses in all hospitalized patients with acute respiratory illness (AIII).

When SARS-CoV-2 and influenza viruses are cocirculating, the Panel recommends influenza testing in outpatients with acute respiratory illness if the results will change clinical management of the patient (BIII).

Testing for other pathogens should be considered depending on clinical circumstances, especially in patients with influenza in whom bacterial superinfection is a well-recognized complication.

Antiviral Treatment of Influenza When Influenza Viruses and SARS-CoV-2 Are Cocirculating

The treatment of influenza is the same in all patients regardless of SARS-CoV-2 coinfection (AIII).

The Panel recommends that hospitalized patients be started on empiric treatment for influenza with oseltamivir as soon as possible without waiting for influenza testing results (AII).

Antiviral treatment of influenza can be stopped when influenza has been ruled out by nucleic acid detection assay in upper respiratory tract specimens for nonintubated patients and in both upper and lower respiratory tract specimens for intubated patients.