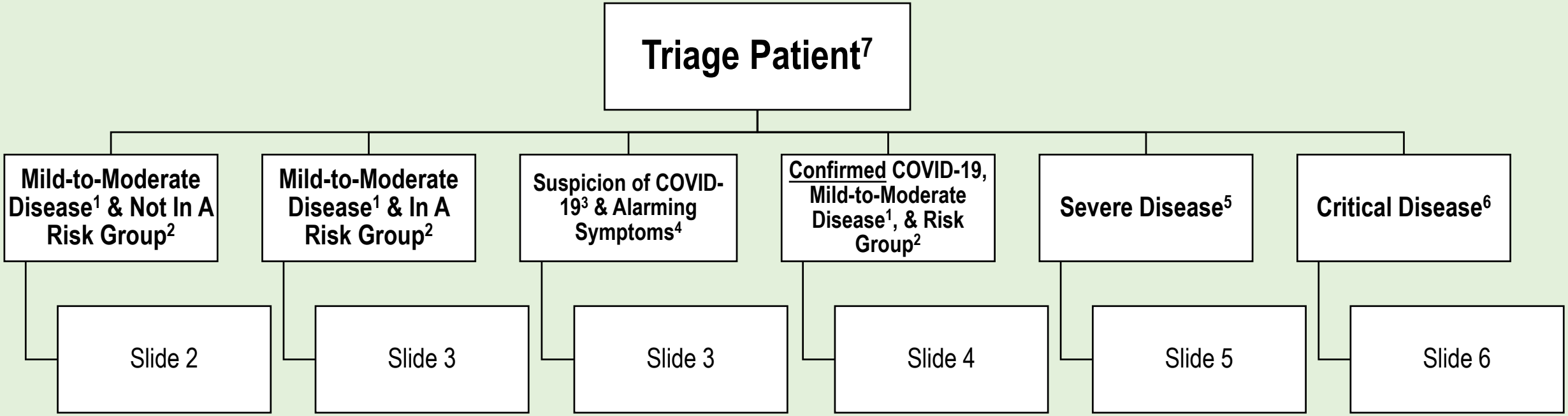


[1] Mild-to-Moderate Disease defined as moderate symptoms, no dyspnea, no oxygen required, no evidence of pneumonia. China refers to this group as "Mild".

[2] Risk Group: Age > 65 years old AND/OR underlying end organ dysfunction, diabetes, coronaropathy, COPD, or arterial hypertension. Note that China does not appear to triage based on risk group—uses symptoms to place a patient into Mild, Moderate, Severe, or Critical

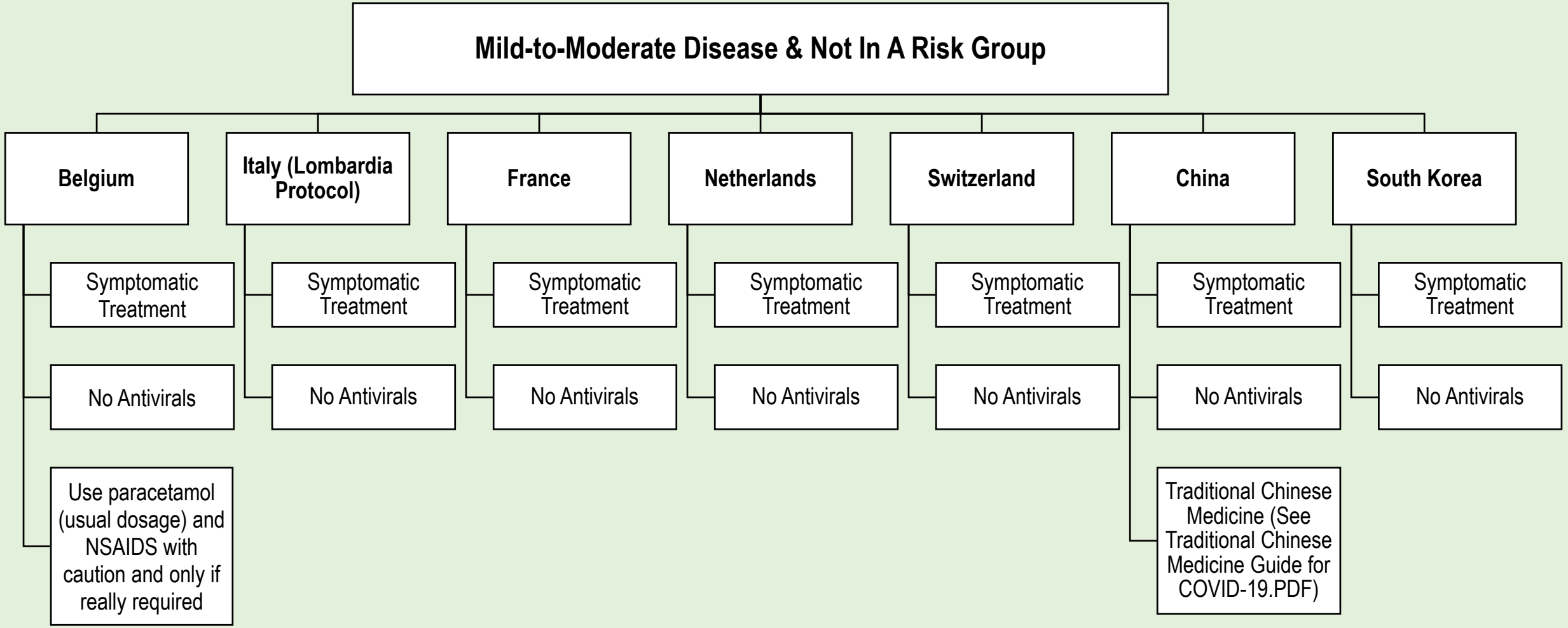
[3] Suspicion of COVID-19 based on likelihood of exposure or being infected area

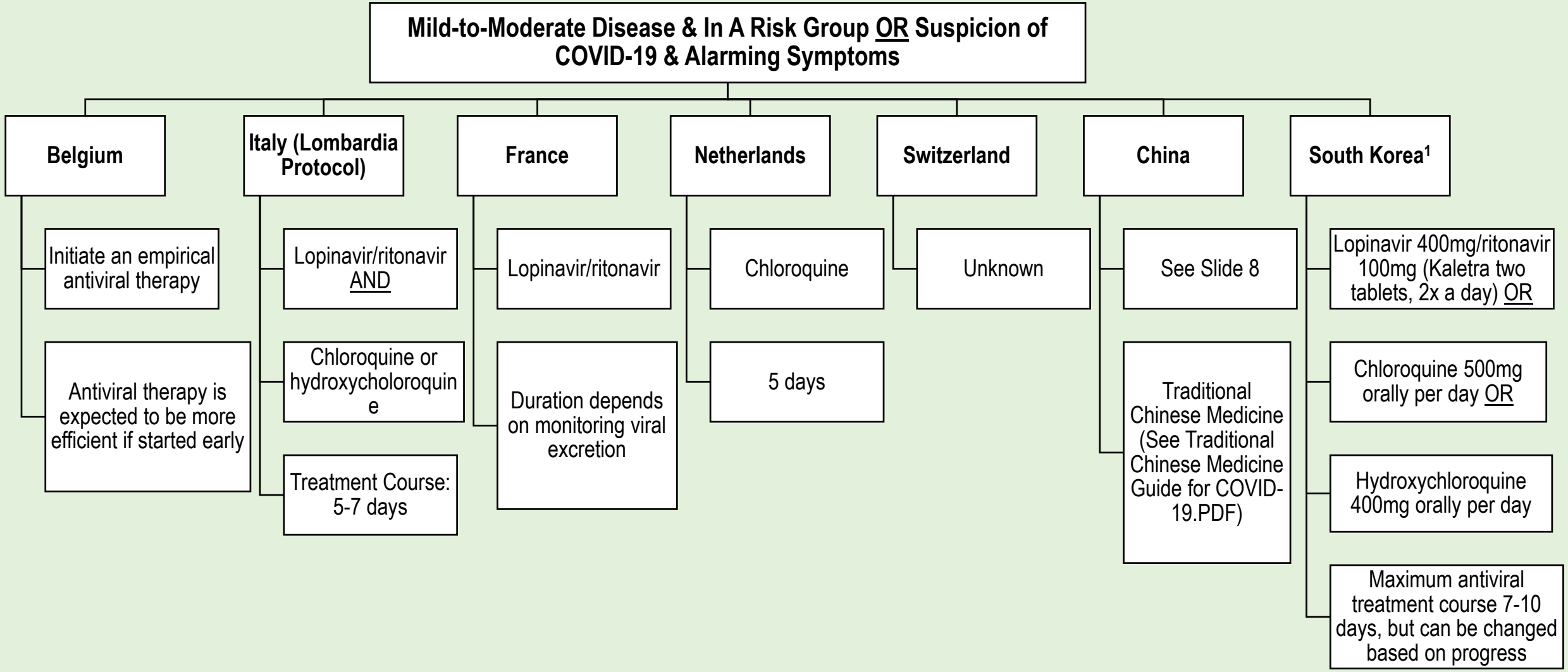
[4] Alarming symptoms include dyspnea (short or labored breathing). China likely to refer to this group as Moderate, requiring fever, respiratory symptoms and radiological findings of pneumonia.

[5] Severe disease defined as one or more of the following: 1) Respiratory rate is ≥ 30/min (adults), ≥ 40/min (children <5), 2) blood oxygen saturation ≤ 93%, PaO2/FiO2 ratio < 300, and/or 3) lung infiltrates > 50% of the lung field within 24-48 hours. China's criteria is largely the same, except: arterial partial pressure of oxygen (PaO2)/ fraction of inspired oxygen (FiO2)≦300mmHg and in high-altitude areas (at an altitude of over 1,000 meters above the sea level), PaO2/ FiO2 shall be corrected by the following formula: PaO2/ FiO2 x[Atmospheric pressure (mmHg)/760]

[6] Critical disease defined as one or more of the following: 1) acute respiratory distress syndrome, 2) sepsis, 3) altered consciousness, and/or 4) multi-organ failure. China requires: 1) respiratory failure and requiring mechanical ventilation, 2) shock, and/or 3) with other organ failure that requires ICU care.

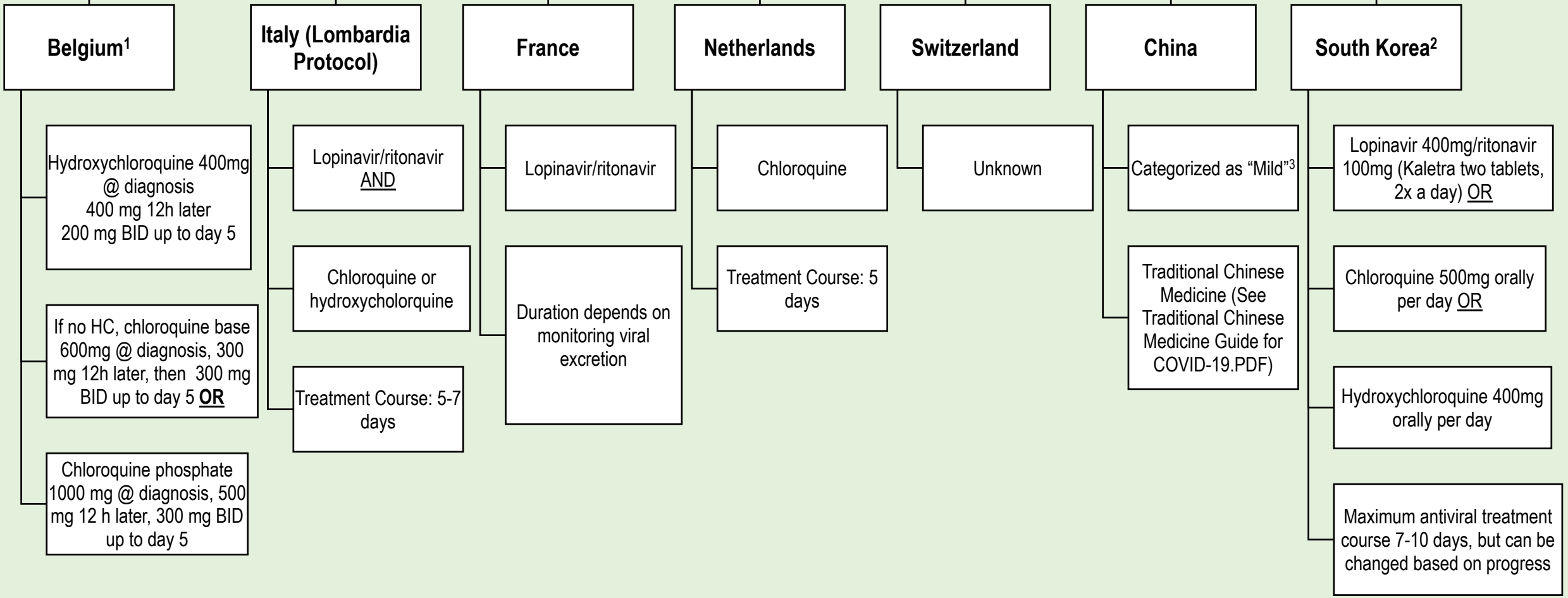
[7] Triage framework from Interim Clinical Guidance for Patients Suspected Of/Confirmed With COVID-19 In Belgium


Mild-to-Moderate Disease & Not In A Risk Group
Belgium
Italy (Lombardia Protocol)
France
Netherlands
Switzerland
China
South Korea
Symptomatic Treatment
No Antivirals
Use paracetamol (usual dosage) and NSAIDS with caution and only if really required
Traditional Chinese Medicine (See Traditional Chinese Medicine Guide for COVID-19.PDF)



[1] South Korea Task Force believes combining lopinavir/ritonavir with chloroquine or hydroxychloroquine could cause serious arrhythmias and drug interactions due to the increased QT interval and does not recommend it. Also, do not recommend the use of ribavirin or interferon as the first-line treatment because of side effects (only use if lopinavir/ritonavir or chloroquine or hydroxychloroquine do not work.

Confirmed COVID-19, Mild-to-Moderate Disease, & In A Risk Group



[1] Contra-indications: a) QTc > 500 msec, b) check drug interactions, c) myasthenia gravis, d) porphyria, e) retinal pathology, and f) epilepsy. Pregnancy is not a contra-indication as such (large safety experience with chloroquine). Perform ECG daily if initial QTc 450-500 msec, and biochemistry according to underlying disease.

[2] See Footnote 1 on slide 3.

[3] Because China triages based on symptoms (not just based on COVID-19 diagnosis or risk group), this group would probably be considered "Mild" and not "Moderate", which is discussed in slide 3. Mild cases would be treated as per slide 2.

Severe Disease

Belgium[1]

- Hydroxychloroquine 400mg @ diagnosis 400 mg 12h later 200 mg BID up to day 5
- If no HC, chloroquine base 600mg @ diagnosis, 300 mg 12h later, then 300 mg BID up to day 5 **OR**
- Chloroquine phosphate 1000 mg @ diagnosis, 500 mg 12 h later, 300 mg BID up to day 5

Italy (Lombardia Protocol)

- Remdesivir AND
- Chloroquine or hydroxycholorquine
- Treatment Course: 5-20 days
- If no remedesivir, maintain lopinavir/ritonavir

France

- Remdesivir
- Duration depends on monitoring viral excretion

Netherlands

- Chloroquine D1 600-300 mg D2-D5 300 mg BID
- Lopinavir/ritonavir second option (10-14 days)

Switzerland

- Lopinavir/ritonavir
- Atazanavir/ritonavir second option

China

- See Slide 8
- Traditional Chinese Medicine (See Traditional Chinese Medicine Guide for COVID-19.PDF)

South Korea

- Lopinavir 400mg/ritonavir 100mg (Kaletra two tablets, 2x a day) OR
- Chloroquine 500mg orally per day OR
- Hydroxychloroquine 400mg orally per day
- Maximum antiviral treatment course 7-10 days, but can be changed based on progress

[1] Contra-indications: a) QTc > 500 msec, b) check drug interactions, c) myasthenia gravis, d) porphyria, e) retinal pathology, and f) epilepsy. Pregnancy is not a contra-indication as such (large safety experience with chloroquine). Perform ECG daily if initial QTc > 450 msec, and biochemistry according to underlying disease. Avoid quinolones and macrolides if possible, or monitor closely the QT if these antibiotics are needed.

Critical Disease

Belgium

- Remdesivir1 200 g loading dose (IV, within 30 minutes) 100 mg OD for 2-10 days
- If remdesivir unavailable: (hydroxy)chloroquine, crushed in nasogastric tube, at same dosage (eplace with remdesivir if it becomes available)
- Consider dexamethasone, tocilizumab

Italy (Lombardia Protocol)

- Remdesivir AND
- Chloroquine or hydroxycholorquine
- Treatment Course: 5-20 days
- If no remedesivir, maintain lopinavir/ritonavir

France

- Remdesivir
- Duration depends on monitoring viral excretion
- Lopinavir/ritonavir second option

Netherlands

- Remdesivir for 10 days AND
- Chloroquine for 5 days

Switzerland

- Remdesivir for 10 days
- Lopinavir/ritonavir second option (add hydroxychloroquine if <65 & no comorbidity)
- Tocilizumab in case of multiple organ failure and inotropic support

China

- See Slide 8
- Traditional Chinese Medicine (See Traditional Chinese Medicine Guide for COVID-19.PDF)

South Korea

- Lopinavir 400mg/ritonavir 100mg (Kaletra two tablets, 2x a day) OR
- Chloroquine 500mg orally per day OR
- Hydroxychloroquine 400mg orally per day
- Maximum antiviral treatment course 7-10 days, but can be changed based on progress

[1] Very restricted availability of remdesivir and very strict criteria inclusion/exclusion criteria: Inclusion: a) ICU, b) PCR confirmation of SARS-Cov-2, 3) Mechanical ventilation; Exclusion: a) evidence of multiple organ failure, b) need of inotropic agents, c) creatinine clearance < 30 ml/min, dialysis, or hemofiltration, d) transaminases > 5X ULN, and e) concomitant use of lopinavir/ritonavir drug. *This means that most (if not all) patients in ICU will not be eligible.*

Discharge Criteria[1]

- Body temperature is back to normal for more than three days; and
- Respiratory symptoms improve; and
- Pulmonary imaging shows decrease in inflammation; and
- Nuclei acid tests negative twice consecutively on respiratory tract samples such as sputum and nasopharyngeal swabs (sampling interval being at least 24 hours).

[1] From China's Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 6)

General Treatment Guidelines for China's Moderate to Critical Cases

- Alpha-interferon (5 million U each time for adults, add 2ml of sterilized water, atomization inhalation twice daily) or lopinavir/ritonavir (200 mg/50mg per pill for adults, two pills each time, twice daily, ≤10 days)
- Ribavirin 500 mg each time for adults, 2-3x IV injection daily, ≤10 days) and/or umifenovir (200 mg tid for adults, ≤10 days) Note: Using three or more antiviral drugs at the same time is not recommended.
- Chloroquine phosphate (500 mg bid for adults, ≤10 days)
- Improve microcirculation by using vasoactive drugs and use hemodynamic monitoring
- Possibly include tocilizumab 400 mg once through IV drip

<u>For Severe/Critical Cases:</u>

- Convalescent plasma for patients with rapid disease progression
- Blood purification system including plasma exchange, absorption, perfusion and blood/plasma filtration can be used for the treatment of severe and critical cases in the early and middle stages of cytokine storm.
- Glucocorticoids can be used in a short period of time (three to five days). Should not exceed the equivalent of methylprednisolone 1-2 mg/kg/day (larger dose will delay removal of coronavirus due to immunosuppressive effects).

Protocol Notes and Variants

- Protocols have a heavy dependence on lopinavir /ritonavir but Chu 2004 shows weak efficacy against SARS-CoV-1 and Chen 2020 showed negative results against SARS-CoV-2, although China's Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (6th interim edition) (China Tx Protocol) includes lopinavir.
- European protocols have a heavy dependence on remdesivir, but it is scarce and exclusion criteria is very limiting.
- On-going clinical trial for the inclusion of tocilizumab into the China Treatment Protocol (400 mg once through IV drip). See Xu 2020. Kevzara also the subject of an on-going clinical trial.
- Corticosteroids are controversial, but the subject of a COVID-19 clinical trial (methylprednisolone 40 mg q12h for 5 days). Cautiously incorporated into the China Treatment Protocol.
- On-going clinical trial for the combination of a nucleoside Inhibitor and protease inhibitor: (1) lopinavir 400 mg/ritonavir 100 mg orally twice daily, plus (2) ribavirin 2.4 g orally as a loading dose followed by 1.2 g orally every 12 hours. Duration of treatment up to 10 days. Case study: ribavirin 600mg 2x day and lopinavir + ritonavir 1000mg 1x day. WHO 2020.
- On-going clinical trial for the combination of an antiretroviral and protease inhibitor. Used with low doses of cobicistat to increase bioavailability and half life: Darunavir 800 mg/Cobicistat 150 mg QD. WHO 2020.
- On-going clinical trial for the combination of a non-nucleoside reverse transcriptase inhibitor and nucleotide reverse transcriptase inhibitor: emtricitabine + tenofovir (no dosing available). WHO 2020.
- On-going clinical trial for myelofibrosis and polycythaemia vera treatment: ruxolitinib (no dosing available). WHO 2020.
- Theorized benefits for the infusion of Vitamin C, use of JAK inhibitors (Baricitinib, 4 mg per day, can be reduced to 2 mg per day when disease under control). WHO 2020.
- Favipiravir (Avigan) has been shown effective but may just be comparable to lopinavir/ritonavir with limited efficacy in critically ill patients. Guardian 2020

Sources

- Interim Clinical Guidance for Patients Suspected of/Confirmed With COVID-19 in Belgium (https://epidemio.wiv-isp.be/ID/Documents/Covid19/COVID-19_InterimGuidelines_Treatment_ENG.pdf)
- See Xu et al., “Effective Treatment of Severe COVID-19 Patients with Tocilizumab” (http://www.chinaxiv.org/abs/202003.00026)
- Gao et al., “A 49-year-old Woman Co-infected with SARS-COV-2 and Mycoplasma – A Case Report” (https://www.researchsquare.com/article/rs-16376/v1),
- Chu CM, Cheng VCC, Hung IFN, Wong MML, Chan KH, Chan KS, *et al.* Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax* 2004; 59:252–256 (https://www.ncbi.nlm.nih.gov/pubmed/14985565)
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- Korea Biomedical Review, “Physicians Work Out Treatment Guidelines for CoronaVirus” (http://www.koreabiomed.com/news/articleView.html?idxno=7428)
- Ministry of Health of the People’s Republic of China, Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 6)
- Guardian, “Japanese flu drug 'clearly effective' in treating coronavirus, says China”, Mar. 18, 2020 (https://www.theguardian.com/world/2020/mar/18/japanese-flu-drug-clearly-effective-in-treating-coronavirus-says-china)