

Supplement Table 1. Criteria for Presence of Acute Infection(s) and SARS-CoV-2 and Non-SARS-CoV-2 Sepsis

Determining the presence of acute infection(s)			
SARS-CoV-2	Present		Positive SARS-CoV-2 PCR between -30 days from admission to discharge and any symptoms of any kind during hospitalization, including mild or atypical symptoms, which were not more likely due to an alternative explanation
Non-SARS-CoV-2	Present	Definite	Compatible clinical syndrome and pathologic diagnosis of infection, or operative recovery of pus, or positive cultures from a normally sterile site, or positive cultures from a normally non-sterile site via a high quality sample consistent with infection
		Possible	Did not meet criteria for definite non-SARS-CoV-2 infection but had a compatible clinical syndrome and at least one objective finding consistent with other infection (e.g. imaging consistent with bacterial infection or elevated procalcitonin); the patient was treated with antibiotics and improved, and a non-SARS-CoV-2 infection was at least as likely to explain the syndrome as any alternative diagnosis
	Absent	No	Clear alternative diagnosis (non-infectious or SARS-CoV-2 infection) that accounted for the patient's clinical syndrome and no evidence of an additional concurrent infectious process
Determining whether organ dysfunction episodes, if present, were related to SARS-CoV-2 and/or non-SARS-CoV-2 infection(s)			
SARS-CoV-2	Present	Definite/Probable	Organ dysfunction equivalent to ≥ 2 SOFA points relative to baseline which was clearly associated with SARS-CoV-2 infection and either no other obvious contributors to organ dysfunction OR other factors may have contributed but SARS-CoV-2 was the primary driver
		Possible	Organ dysfunction equivalent to ≥ 2 SOFA points relative to baseline which was associated with SARS-CoV-2 infection but COVID-19 was not clearly the primary driver OR organ dysfunction was not clearly associated with SARS-CoV-2 infection
	Absent	No	No organ dysfunction equivalent to ≥ 2 SOFA points relative to baseline OR organ dysfunction was clearly due to another cause (e.g. bacterial infection or non-infectious process)
Non-SARS-CoV-2	Present	Definite/Probable	Organ dysfunction equivalent to ≥ 2 SOFA points relative to baseline which was clearly associated with a non-SARS-CoV-2 infection and either no other obvious contributors to organ dysfunction OR other factors may have contributed but a non-SARS-CoV-2 infection was the primary driver
		Possible	Organ dysfunction equivalent to ≥ 2 SOFA points relative to baseline which was associated with a non-SARS-CoV-2 infection but for which it was not clearly the primary driver OR organ dysfunction was not clearly associated with the non-SARS-CoV-2 infection
	Absent	No	No organ dysfunction equivalent to ≥ 2 SOFA points relative to baseline OR organ dysfunction was clearly due to another cause (e.g. SARS-CoV-2 infection or non-infectious process)
Determining whether SARS-CoV-2 and Non-SARS-CoV-2-related sepsis episodes were separate or concurrent/mixed			

SARS-CoV-2 AND non-SARS-CoV-2	Temporally Separate	Patient experienced least 2 separate periods of organ dysfunction, each equivalent to ≥ 2 SOFA points compared to pre-hospital baseline if sepsis was present on admission or compared to earlier in hospitalization if sepsis was hospital-onset, AND one episode was definitely/probably or possibly due to SARS-CoV-2 alone while the other was definitely/probably or possibly due to non-SARS-CoV-2 alone.
	Concurrent/Mixed	Patient experienced one episode of organ dysfunction equivalent to ≥ 2 SOFA points which was definitely, probably, or possibly due to SARS-CoV-2 AND a non-SARS-CoV-2 infection; episode may be prolonged and/or have multiple phases, but there was no period during which an acute clinical change potentially consistent with new infection (e.g. new consolidation on chest x-ray or purulent sputum) coincided with worsening organ dysfunction equivalent to ≥ 2 SOFA points.

Supplement Table 2. Representative sample of definite/probable and possible sepsis due to SARS-CoV-2 and non-SARS-CoV-2 infections

Pathogen	Sepsis Determination	Case Summary
SARS-CoV-2 Only	Definite/Probable (n=44)	<p>A patient with history notable for HIV on antiretrovirals and recent outpatient positive SARS-CoV-2 PCR presented with dyspnea and hypoxemia. The patient required 6L nasal cannula but had no other organ dysfunction on admission. The patient developed worsening hypoxemia requiring intubation and mechanical ventilation. Chest X-rays and chest CT were consistent with severe COVID-19 without evidence of bacterial pneumonia. Multiple blood and endotracheal aspirate cultures were negative, urine strep and legionella antigens were negative, procalcitonin was normal, and the patient had no other evidence of bacterial infection. Laboratory results were consistent with COVID including lymphopenia and d-dimer >4,000. Sputum was non-purulent. The patient was nonetheless treated empirically with broad-spectrum antibiotics throughout hospitalization, without improvement. The patient’s respiratory failure worsened despite paralysis, prone positioning, and inhaled epoprostenol. The patient also had gradually worsening kidney injury, thrombocytopenia, and shock requiring 3 vasopressors. The patient was terminally extubated per wishes documented prior to admission and expired shortly thereafter while in the ICU.</p> <p><i>Definite SARS-CoV-2-related sepsis based upon respiratory dysfunction; additional organ dysfunctions may have been related to SARS-CoV-2 or non-infectious causes such as medication effects, but there was no evidence of a contributing non-SARS-CoV-2 infection.</i></p> <p>A young patient with previously undiagnosed diabetes mellitus and obesity presented with shortness of breath. The patient was hypoxemic requiring high flow nasal cannula on admission. COVID-19 PCR was positive. Chest X-ray showed bilateral diffuse opacities without focal consolidation. The patient was treated with remdesivir and dexamethasone, as well as empiric ceftriaxone and azithromycin. All cultures, urine strep and legionella antigens, and procalcitonin levels were normal. Cough was non-productive. The patient’s oxygen requirement improved rapidly and they were discharged home without supplemental oxygen.</p> <p><i>Definite SARS-CoV-2-related sepsis based upon respiratory dysfunction; treated for superimposed bacterial pneumonia, however there was no evidence of a non-SARS-CoV-2 infection.</i></p>
	Possible (n=2)	<p>A patient with heart failure, cirrhosis, monoclonal gammopathy of undetermined significance, and recent admission for COVID-19 requiring dexamethasone and remdesivir presented from rehab with acutely worsening dyspnea and hypoxemia. The patient required up to 15L supplemental oxygen compared to 0-2L at time of discharge 2 weeks earlier. A CT chest showed interval increase in diffuse consolidative and nodular opacities. Repeat COVID PCR was positive. The patient received vancomycin, meropenem, and levofloxacin without improvement. Infectious disease consult recommended repeat courses of steroids and remdesivir for possible SARS-CoV-2 recrudescence vs re-infection. Organizing pneumonia was also high on the differential diagnosis. The patient’s oxygen requirement rapidly improved and they were discharged back to rehab on 1L of oxygen. During a subsequent readmission 1 month later, repeat imaging showed significant improvement in opacities which in turn revealed new diffuse nodules concerning for metastases with unknown primary. The patient was discharged to hospice.</p> <p><i>Possible SARS-CoV-2-related sepsis based upon respiratory dysfunction and worsening pulmonary opacities; however, inflammatory organizing pneumonia and lung metastases may also have contributed. No evidence of bacterial</i></p>

		<i>pneumonia beyond the initial equivocal chest imaging and the patient did not improve with antibiotics alone, therefore no non-SARS-CoV-2-related sepsis.</i>
Both SARS-CoV-2 & Non-SARS-CoV-2	Mixed episode(s) (n=12)	A patient with hypertension and coronary artery disease presented with several days of fatigue, diarrhea, and worsening shortness of breath. SARS-CoV-2 PCR was positive. Chest X-ray showed diffuse bilateral opacities. Labs were notable for WBC 17 and d-dimer >75,000. The patient was intubated and mechanically ventilated. A tracheal aspirate sample had many polys and grew abundant <i>Staphylococcus aureus</i> . The patient was treated empirically with dexamethasone, remdesivir, vancomycin, cefepime, and metronidazole (later narrowed to cefazolin). The hypoxemia improved and the patient was extubated and discharged to a long-term acute care facility. <i>Definite SARS-CoV-2-related sepsis and definite non-SARS-CoV-2-related sepsis (single, mixed episode) as respiratory failure was likely due to both COVID-19 and Staphylococcal pneumonia.</i>
	Separate episodes (n=5)	A patient with obesity, hypertension, and insulin-dependent diabetes mellitus presented five days after COVID-19 diagnosis with worsening cough, fever, and shortness of breath. The patient was intubated for severe hypoxemia and required cannulation for extracorporeal membrane oxygenation (ECMO) early in hospital week 2. ECMO course was complicated by acute kidney injury and ischemic colitis requiring colectomy and end ileostomy. Several weeks into the hospitalization, the patient had escalating pressor requirements and worsening kidney dysfunction requiring initiation of renal replacement therapy. The WBC and procalcitonin level rose precipitously. Blood, tracheal aspirate, and peritoneal washings all grew <i>Klebsiella pneumoniae</i> . Goals of care were changed to focus on comfort and the patient expired in the ICU. <i>Definite SARS-CoV-2-related sepsis on admission based on respiratory dysfunction; later developed a separate episode of sepsis based upon new vasopressor requirement and kidney dysfunction due to disseminated Klebsiella infection.</i>
Non-SARS-CoV-2	Definite/Probable (n=1)	A patient with a history of mild COVID-19 managed as an outpatient 2 weeks prior to admission presented with 3 days of fever and severe nausea, vomiting, and diarrhea. In the ED the patient was given 9L of crystalloid and low dose norepinephrine for hypotension. CT abdomen showed diffuse enteritis. The patient had tested negative for COVID by antigen test 2 days prior to presentation, but was positive by PCR in the ED with a high cycle threshold. Infectious work up was otherwise notable for one blood culture positive for Staph epidermidis (deemed a contaminant and not treated); a urinalysis, <i>C.difficile</i> assay, and norovirus tests were all negative. The patient was weaned off norepinephrine over 48 hours and had no other organ dysfunctions including no hypoxemia. All symptoms rapidly resolved and the patient was discharged home. <i>Probable non-SARS-CoV-2-related sepsis due to an infectious enteritis; the absence of respiratory symptoms, recent negative antigen test, and high cycle threshold value make COVID-related enteritis unlikely.</i>
	Possible (n=1)	A patient with severe peripheral arterial disease was admitted for an above knee amputation. The patient had been diagnosed with COVID-19 as an outpatient two weeks prior with mild symptoms which had improved. Post-operatively there were multiple episodes of hypotension requiring an ICU transfer for brief vasopressor support. The patient was treated empirically with broad spectrum antibiotics for “urosepsis” based on a markedly elevated procalcitonin (>5 ng/mL) and pyuria. Urine culture grew mixed flora and the procalcitonin level remained elevated but began decreasing

post-operatively before broad-spectrum antibiotics were started. Her hypotension did not resolve until after antibiotics were started and she was fluid resuscitated.

Possible non-SARS-CoV-2 sepsis given some evidence of bacterial infection (elevated procalcitonin) and clinical improvement in hypotension after antibiotic administration, but with a feasible non-infectious explanation for the syndrome (peri-operative inflammation, hypovolemia); COVID-19 infection was not relevant to the hospital course.