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Recognition and management of respiratory coinfection and secondary bacterial pneumonia in patients with COVID-19

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■ ABSTRACT

The pathophysiology of COVID-19 is not fully known. Respiratory infection caused by more than one viral pathogen (viral co-infection) or both viral and bacterial pathogens (combined viral and bacterial pneumonia) have been described. Secondary bacterial pneumonia can follow the initial phase of viral respiratory infection or occur during the recovery phase. No obvious pattern or guidelines exist for viral coinfection, combined viral and bacterial pneumonia, or secondary bacterial pneumonia in the context of SARS-CoV-2. Based on existing clinical data and experience with similar viruses such as influenza and SARS-CoV, the management approach in the context of COVID-19 should, ideally, take into consideration the overall presentation as well as the trajectory of illness.

■ RESPIRATORY INFECTION AND COVID-19

Even as severe acute respiratory syndrome coronavirus type-2 (SARS-CoV-2), the etiological agent of coronavirus disease 2019 (COVID-19), spreads across the globe, the pathophysiology of the disease remains incompletely understood. Respiratory infection caused by more than one viral pathogen (viral coinfection) or both viral and bacterial pathogens (combined viral and bacterial pneumonia) have been well-described. Secondary bacterial pneumonia can follow the initial phase of viral respiratory infection or occur during the recovery phase.¹ Data on SARS-CoV-2 is limited, but thus far, the overall incidence of viral co-infection has varied widely from 0% to 15% in different case

series,^{2–7} and combined viral and bacterial pneumonia rates appear to be low.^{3,8–10} There is also a dearth of data on the predisposing factors and causative organisms.

Combined viral and bacterial pneumonia and secondary bacterial pneumonia by *Staphylococcus aureus* and other common community-acquired pneumonia pathogens have been best studied in seasonal² and pandemic^{2,3} influenza and contribute significantly to morbidity and mortality. Secondary bacterial pneumonia with severe acute respiratory syndrome virus (SARS-CoV) infection occurred as ventilator-associated pneumonia in 25% of patients at a single center of which methicillin-resistant *Staphylococcus aureus* was the causative organism in 47% of cases, although there was significant concern for cross-transmission.⁷

Because no obvious pattern or guidelines exist for viral coinfection, combined viral and bacterial pneumonia, or secondary bacterial pneumonia in the context of SARS-CoV-2, the following commentary is based on existing clinical data and experience with similar viruses such as influenza and SARS-CoV. With what we know so far, the approach in the context of COVID-19 would, ideally, take into consideration the overall presentation as well as the trajectory of illness.

All patients presenting with symptoms of respiratory infection should be tested for influenza with polymerase chain reaction (PCR)-based assay in addition to SARS-CoV-2. Polymerase chain reaction assays can be performed for other respiratory viruses if available.

Regardless of disease severity, all patients with influenza A/B viral coinfection should be treated with oseltamivir or an alternative agent.¹¹ Empiric treatment for influenza viral coinfection can be considered while waiting for test results if an obvious exposure or risk factor is present. If viral coinfection with another respiratory virus such as respiratory syncytial virus is identified, treatment options are limited and effective

The statements and opinions expressed in COVID-19 Curbside Consults are based on experience and the available literature as of the date posted. While we try to regularly update this content, any offered recommendations cannot be substituted for the clinical judgment of clinicians caring for individual patients.

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TABLE 1**Key points for laboratory and imaging findings****Co-infection and secondary bacterial infection**

- Viral co-infection incidence varies based on case series (0% to 15%)^{2–7}
- Combine bacterial and viral infection is rare in COVID-19 patients^{3,8–10}
- Secondary bacterial infection is not uncommon and leads to significant morbidity and mortality, especially in the elderly^{4,9,16}

Procalcitonin

- Detectable in 2 to 4 hours, peaks at 12 to 24 hours, and has a half-life of 25 to 30 hours
- Levels are normal (< 0.5 µg/L) in COVID-19 patients with mild disease and may be elevated (≥ 0.50 µg/L) in patients with severe disease^{10,14}
- Elevated levels are correlated to a nearly 5-fold higher risk for severe SARS-CoV-2 infection¹⁷
- Elevated levels are not specific to bacterial infection because they can also be raised in patients with acute respiratory distress syndrome, end-stage renal disease, cardiogenic shock, and multi-organ failure¹⁸
- A normal level makes bacterial infection less likely and can guide antibiotic discontinuation^{19,20}
- In bacterial infection, levels may be less affected by IL-6 inhibitors than C-reactive protein (CRP)^{21–23}

CRP, Erythrocyte sedimentation rate (ESR)

- CRP and ESR are non-specific inflammatory markers. Both are generally elevated in COVID-19 and are therefore not helpful in differentiating this from bacterial infection
- Tocilizumab rapidly reduces CRP and leukocytosis and may suppress fever^{24–26}

Typical radiographic features**COVID-19**

- Chest radiography: Bilateral, peripheral, lower-zone predominant air-space disease²⁷
- Computed tomography: Bilateral, predominantly peripheral ground glass opacities, crazy-paving and consolidation²⁸; findings vary based on stage/phase of the disease

Bacterial pneumonia

- Chest radiography: Lobar or segmental air-space opacification ± air bronchograms
- Computed tomography: Segmental or lobar focal dense consolidation ± ground-glass opacities

nia or secondary bacterial pneumonia with COVID-19 requires a high index of suspicion. Some characteristics of bacterial infection may still be identifiable despite a significant overlap of viral and bacterial symptomatology (**Table 1**). Neutrophilic leukocytosis is the hallmark of bacterial pneumonia, whereas COVID-19 patients typically present with a normal white blood cell count with lymphopenia.^{5,8,14,15}

Procalcitonin is neither sensitive nor specific in differentiating the etiology of community-acquired pneumonia.¹¹ However, several reported series of COVID-19 have consistently reported normal (low) procalcitonin levels in isolated SARS-CoV-2 infection leading to its widespread, albeit unvalidated, use to “rule out” combined viral and bacterial pneumonia, although the exact cut-off remains to be determined. This observation highlights the need to consider all variables in the context of the clinical scenario.

In patients with **mild- to-moderate respiratory failure** consistent with the presentation of COVID-19 and without obvious signs of bacterial infection, the likelihood of combined viral and bacterial pneumonia is low, and antibiotics can be safely held off. In this case, *gradually* worsening respiratory failure within the first week of presentation is more likely to be from progression of COVID-19 than from a new superimposed secondary bacterial pneumonia. This includes patients who are started on non-invasive forms of supplemental oxygen support and then ultimately require invasive mechanical ventilation.

In the absence of supporting evidence of bacterial pneumonia, antibiotics should not be initiated despite progression of respiratory distress. If, however, a patient was to develop *new or acutely worsening* respiratory failure, sepsis, or both after an initial phase of consistent improvement (considered to be days), then nosocomial acquisition of secondary bacterial infection is likely unless proven otherwise—either secondary bacterial pneumonia in the form

only in specific scenarios such as immunosuppression and/or hypogammaglobulinemia.^{12,13} Infectious disease consultation is strongly recommended to determine the benefits of such treatment in light of the potential risk for exacerbating COVID-19–related organ failure and the potential adverse effects of the medication(s).

Recognizing combined viral and bacterial pneumo-

of hospital-acquired pneumonia and/or at another extrapulmonary site.

While COVID-19 by itself can cause acute respiratory decompensation, data regarding secondary bacterial pneumonia playing a role in such decompensation is limited; therefore, guideline-driven empiric antibiotic use may be reasonable until this secondary infection is ruled out. Supportive evidence for secondary bacterial pneumonia include one or more of the following: new or recrudescent fever, new onset or change in the character of sputum, new leukocytosis and/or new neutrophilia, new relevant imaging findings, and new or increasing oxygen requirements. It is also important to consider all other sources of hospital-acquired infections in these patients such as indwelling central venous catheters or urinary tract catheters and treat accordingly.

For a **critically ill** patient admitted with severe respiratory failure, empiric treatment for all possible etiologies upfront is essential. This is especially important because procalcitonin levels can be falsely elevated in patients with multi-organ failure,^{29,30} and imaging studies may be limited in differentiating bilateral infiltrates of acute respiratory distress syndrome from obscured consolidation of bacterial infection.

Empiric therapy for community-acquired pneumonia should be based on the Infectious Diseases Society of America/American Thoracic Society guidelines, host risk factors, and prior microbiological data.¹⁹ Respiratory samples (tracheal aspirate in mechanically ventilated patients is preferable to sputum) and blood cultures should be sent for all patients, ideally prior to starting antibiotics. *Streptococcus pneumoniae* urine antigen should be tested in all patients presenting with severe community-acquired pneumonia. *Legionella pneumophila* urine antigen and *Mycoplasma pneumoniae* IgM and IgG antibodies can be sent based on clinical context and epidemiology.

In the absence of signs of bacterial pneumonia, a positive respiratory culture can represent colonization, especially in those with prior pneumonia with the same organism or altered airway anatomy. Laboratory markers, radiologic features (see **Table 1** and above) as well as quantitative and/or semi-quantitative culture methods can help in making this distinction.¹⁹

Secondary bacterial pneumonia in a patient on **invasive mechanical ventilation** has a similar presentation to that of hospital-acquired pneumonia but warrants the aggressive use of empiric broad-spectrum antibiotics with coverage for methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and possibly other multi-drug resistant organisms in

accordance with the Infectious Diseases Society of America/American Thoracic Society guidelines.¹⁹ It is also important to consider the side effects of antibiotics and institutional antibiograms.

Patients with ventilator-associated tracheobronchitis often lack the classical signs of secondary bacterial pneumonia, may have increased secretions and low-grade fevers, and can be difficult to wean from ventilatory support. The evidence to support antibacterial therapy for this clinical entity is limited and warrants a judicious case-based analysis.

The **duration of antibacterial therapy** is generally 5 to 7 days for community-acquired pneumonia³¹ and 7 days for hospital-acquired pneumonia and ventilator-associated pneumonia¹⁹ in the absence of complications. Consider shortening the duration if patients demonstrate signs of clinical stabilization, especially if adverse effects are seen. Checking the procalcitonin level at presentation will help in the de-escalation of antibiotics based on the trend of procalcitonin levels in 24 to 48 hours.³² If a microbiological source is not identified within 48 hours of testing and the procalcitonin level is < 0.5 µg/L and/or decreases by ≥ 80% from peak concentration, it is reasonable to discontinue all antibiotics.¹⁹

The use of interleukin 6 (IL-6) inhibitors such as tocilizumab for COVID-19–related cytokine activation syndrome presents a unique challenge because it suppresses common signs of sepsis. The risk of serious bacterial infections has been consistently reported to be higher with tocilizumab use for rheumatological diseases.^{33–36} C-reactive protein (CRP) and other acute phase reactants including white blood cell count may be unreliable acute phase reactants and may not rise in response to a secondary bacterial infection after tocilizumab use.^{34,37,38} Exactly how long this effect lasts with 1 or 2 doses is unclear. Procalcitonin may be less affected by IL-6 inhibitors,^{21–23} but the data to differentiate bacteria from viral pneumonia in this context is limited and should be further evaluated.

Lastly, **invasive pulmonary aspergillosis** has been described in critically ill patients with seasonal^{39,40} as well as pandemic⁴¹ influenza and is associated with high morbidity and mortality rates. Invasive pulmonary aspergillosis was also reported on post-mortem lung pathology in 2 of 20 patients with SARS-CoV-1 infection.⁴² This complication should be considered in high-risk individuals such as those with immune compromising conditions, precedent or concomitant influenza viral co-infection, clinical deterioration despite appropriate antibiotics, and those with positive fungal markers such as galactomannan on cul-

ture. If invasive pulmonary aspergillosis is suspected, treatment with broad antifungal agents such as voriconazole should be initiated promptly in consultation with infectious disease colleagues.

REFERENCES

- van der Sluijs KF, van der Poll T, Lutter R, Juffermans NP, Schultz MJ. Bench-to-bedside review: bacterial pneumonia with influenza—pathogenesis and clinical implications. *Crit Care* 2010; 14(2):219. doi:10.1186/cc8893
- Pongpirul WA, Mott JA, Woodring JV, et al. Clinical characteristics of patients hospitalized with coronavirus disease, Thailand. *Emerg Infect Dis* 2020; Apr 8. doi:10.3201/eid2607.200598 https://wwwnc.cdc.gov/eid/article/26/7/20-0598_article. Accessed April 24, 2020.
- Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. *JAMA* 2020; Mar 19. doi:10.1001/jama.2020.4326
- Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020; Mar 13. doi:10.1001/jamainternmed.2020.0994
- Ding Q, Lu P, Fan Y, Xia Y, Liu M. The clinical characteristics of pneumonia patients infected with 2019 novel coronavirus and influenza virus in Wuhan, China. *J Med Virol* 2020; Mar 20. doi:10.1002/jmv.25781
- Khodamoradi Z, Moghadami M, Lotfi M. Co-infection of coronavirus disease 2019 and influenza a: a report from Iran. *Arch Iran Med* 2020; 23(4):239–243. doi:10.34172/aim.2020.04
- Touzard-Romo F, Tapé C, Lonks JR. Co-infection with SARS-CoV-2 and human metapneumovirus. *R I Med J* (2013) 2020; 103(2):75–76. PMID:32192233
- Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; 395(10223):507–513. doi:10.1016/S0140-6736(20)30211-7
- Wang L, He W, Yu X, et al. Coronavirus disease 2019 in elderly patients: characteristics and prognostic factors based on 4-week follow-up. *J Infect* 2020; Mar 30. doi:10.1016/j.jinf.2020.03.019
- Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; 395(10229):1054–1062. doi:10.1016/S0140-6736(20)30566-3
- Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical practice guidelines by the Infectious Diseases Society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza. *Clin Infect Dis* 2019; 68(6):e1–e47. doi:10.1093/cid/ciy866
- Beaird OE, Freifeld A, Ison MG, et al. Current practices for treatment of respiratory syncytial virus and other non-influenza respiratory viruses in high-risk patient populations: a survey of institutions in the Midwestern Respiratory Virus Collaborative. *Transpl Infect Dis* 2016; 18(2):210–215. doi:10.1111/tid.12510
- Beigel JH, Nam HH, Adams PL, et al. Advances in respiratory virus therapeutics—a meeting report from the 6th Isriv Antiviral Group conference. *Antiviral Res* 2019; 167:45–67. doi:10.1016/j.antiviral.2019.04.006
- Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* 2020; Mar 3. doi:10.1007/s00134-020-05991-x
- Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020. doi:10.1016/S2213-2600(20)30079-5
- Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395(10223):497–506. doi:10.1016/S0140-6736(20)30183-5
- Lippi G, Plebani M. Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): a meta-analysis. *Clin Chim Acta* 2020; 505:190–191.
- Rule JA, Hynan LS, Attar N, et al. Procalcitonin identifies cell injury, not bacterial infection, in acute liver failure. *PLoS One* 2015; 10(9):e0138566. doi:10.1371/journal.pone.0138566
- Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med* 2019; 200(7):e45–e67. doi:10.1164/rccm.201908-1581ST
- Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. <http://www.chinaxiv.org/abs/202003.00026>. Accessed April 24, 2020.
- Bloomfield M, Parackova Z, Cabelova T, et al. Anti-IL6 autoantibodies in an infant with CRP-less septic shock. *Front Immunol* 2019; 10:2629. doi:10.3389/fimmu.2019.02629
- Gaensbauer JT, Press CA, Hollister JR, Asturias EJ. Procalcitonin: a marker of infection not subverted by treatment with interleukin-6 receptor inhibition. *Pediatr Infect Dis J* 2013; 32(9):1040. doi:10.1097/INF.0b013e318295a3d0
- Sato H, Tanabe N, Murasawa A, et al. Procalcitonin is a specific marker for detecting bacterial infection in patients with rheumatoid arthritis. *J Rheumatol* 2012; 39(8):1517–1523. doi:10.3899/jrheum.111601
- Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: a single center experience. *J Med Virol* 2020; Apr 6. doi:10.1002/jmv.25801
- Michot JM, Albiges L, Chaput N, et al. Tocilizumab, an anti-IL6 receptor antibody, to treat COVID-19-related respiratory failure: a case report. *Ann Oncol* 2020; Apr 2. doi:10.1016/j.annonc.2020.03.300
- Wong HYF, Lam HYS, Fong AH, et al. Frequency and distribution of chest radiographic findings in COVID-19 positive patients. *Radiology* 2019; March 27. doi:10.1148/radiol.202001160
- Kanne JP, Little BP, Chung JH, Elicker BM, Ketat LH. Essentials for radiologists on COVID-19: an update-radiology scientific expert panel. *Radiology* 2020; Feb 27. doi:10.1148/radiol.20200527
- Pan F, Ye T, Sun P, et al. Time course of lung changes on chest CT during recovery from 2019 novel coronavirus (COVID-19) pneumonia. *Radiology* 2020; Feb 13. doi:10.1148/radiol.20200370
- Giamarellos-Bourboulis EJ, Mega A, Grecka P, et al. Procalcitonin: a marker to clearly differentiate systemic inflammatory response syndrome and sepsis in the critically ill patient? *Intensive Care Med* 2002; 28(9):1351–1356. doi:10.1007/s00134-002-1398-z
- Hui L, Zhang X, An X, et al. Higher serum procalcitonin and IL-6 levels predict worse diagnosis for acute respiratory distress syndrome patients with multiple organ dysfunction. *Int J Clin Exp Pathol* 2017; 10(7):7401–7407. PMID:31966582
- Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis* 2016; 63(5):e61–e111. doi:10.1093/cid/ciw353. e111
- Lam SW, Bauer SR, Fowler R, Duggal A. Systematic review and meta-analysis of procalcitonin-guidance versus usual care for antimicrobial management in critically ill patients: focus on subgroups based on antibiotic initiation, cessation, or mixed strategies. *Crit Care Med* 2018; 46(5):684–690. doi:10.1097/CCM.0000000000002953
- Campbell L, Chen C, Bhagat SS, Parker RA, Östör AJ. Risk of adverse events including serious infections in rheumatoid arthritis patients treated with tocilizumab: a systematic literature review and meta-analysis of randomized controlled trials. *Rheumatology (Oxford)* 2011; 50(3):552–562. doi:10.1093/rheumatology/keq343
- Chiu YM, Chen DY. Infection risk in patients undergoing treatment for inflammatory arthritis: non-biologics versus biologics. *Expert Rev Clin Immunol* 2020; 16(2):207–228. doi:10.1080/1744666X.2019.1705785
- Yamamoto K, Goto H, Hirao K, et al. Longterm safety of tocilizumab: results from 3 years of followup postmarketing surveillance of 5,573 patients with rheumatoid arthritis in Japan. *J Rheumatol* 2015; 42(8):1368–1375. doi:10.3899/jrheum.141210
- Calderón-Goercke M, Loricera J, Aldasoro V, et al. Tocilizumab in giant cell arteritis. Observational, open-label multicenter study of 134

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- patients in clinical practice. *Semin Arthritis Rheum* 2019; 49(1):126–135. doi:10.1016/j.semarthrit.2019.01.003
37. **Nguyen MT, Pødenphant J, Ravn P.** Three cases of severely disseminated *Staphylococcus aureus* infection in patients treated with tocilizumab. *BMJ Case Rep* 2013; Jan 2. doi:10.1136/bcr-2012-007413
38. **Bari SF, Khan A, Lawson T.** C reactive protein may not be reliable as a marker of severe bacterial infection in patients receiving tocilizumab. *BMJ Case Rep* 2013; Oct 31. doi:10.1136/bcr-2013-010423
39. **Vanderbeke L, Spriet I, Breynaert C, Rijnders BJ, Verweij PE, Wauters J.** Invasive pulmonary aspergillosis complicating severe influenza: epidemiology, diagnosis and treatment. *Curr Opin Infect Dis* 2018; 31(6):471–480. doi:10.1097/QCO.0000000000000504
40. **Schauwvlieghe AFAD, Rijnders BJA, Philips N, et al.** Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: a retrospective cohort study. *Lancet Respir Med* 2018; 6(10):782–792. doi:10.1016/S2213-2600(18)30274-1
41. **Yu Z, Gu Q, Zhang B, et al.** Clinical features of fatal pandemic influenza A/H1N1 infection complicated by invasive pulmonary fungal infection. *Mycopathologia* 2020; 185(2):319–329. doi:10.1007/s11046-019-00421-z
42. **Hwang DM, Chamberlain DW, Poutanen SM, Low DE, Asa SL, Butany J.** Pulmonary pathology of severe acute respiratory syndrome in Toronto. *Mod Pathol* 2005; 18(1):1–10. doi:10.1038/modpathol.3800247