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The Impact of Coronavirus Disease 2019 on Viral, Bacterial, and Fungal Respiratory Infections

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KEYWORDS

• Coinfections • COVID-19 • Influenza • Respiratory syncytial virus • Social distancing • Bacterial pneumonia

KEY POINTS

- The COVID-19 pandemic impacted the trends of other common respiratory viral illnesses between 2020 and 2022.
- Implementation of social distancing, mask wearing, and other behavioral interventions for COVID impacted levels of respiratory virus spread.
- Coinfection with other respiratory viruses can occur with COVID-19 infections, with influenza and RSV being among the most common.
- Coinfection with bacterial pneumonia can occur with COVID-19 infections, including community-acquired pneumonia and hospital-acquired pneumonia.
- Ventilator-associated pneumonia is a common nosocomial infection associated with COVID-19 infections and increased mortality.

INTRODUCTION

Since the emergence of the coronavirus disease 2019 (COVID-19) pandemic in Wuhan, China, in December 2019, there has been a significant focus placed on its transmission, pathogenesis, treatment, and prevention.[1] Although COVID-19 continues to have a global impact, concerns about other respiratory infections, including those caused by viruses and bacteria, remain.

The COVID-19 pandemic has shed unique light on the epidemiologic trends of common community-acquired respiratory viruses and the impacts of nonpharmacologic practices including social distancing and mask wearing. In addition, coinfections of COVID-19 with other respiratory viruses and bacterial organisms, along with nosocomial and opportunistic fungal infections, have been observed with variable outcomes.

This article highlights epidemiologic trends of common respiratory viruses during the COVID-19 pandemic and coinfections with common respiratory viruses and other infectious agents.

EPIDEMIOLOGIC TRENDS OF COMMON RESPIRATORY VIRUSES DURING THE SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 PANDEMIC

Although there has been a primary focus on the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) respiratory virus since the COVID-19

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pandemic emerged in 2019, concern for other common community-acquired respiratory viruses remains. Community-acquired respiratory viruses include influenza, respiratory syncytial virus (RSV), paramyxoviruses, rhinovirus, and adenovirus, among others; all may have varied clinical presentations/severities depending on host factors. In the absence of laboratory testing, it may be difficult to distinguish between various respiratory viruses. Often respiratory viruses cause upper respiratory tract infections all with similar symptoms of fever, chills, myalgias, cough, and shortness of breath. However, several respiratory viruses including influenza may lead to lower respiratory tract infections with pneumonia, hypoxemic respiratory failure, and superimposed infections. Given the wide range of symptom severity, including those with asymptomatic infections, respiratory viral illnesses may be underestimated because many patients do not undergo diagnostic testing for non-COVID infections. Thus, the authors provide an overview of the epidemiologic trends in respiratory viruses during the SARS-CoV-2 pandemic and discuss recent updates and the impact of the pandemic on influenza, RSV, and other respiratory viruses.

Influenza Virus

Influenza is seasonal in North America occurring frequently in the winter but can occur year-round in tropical countries. The emergence of the H3N2 strain occurred in 1968 near Hong Kong, and since that time the origin of several antigenically diverse strains of seasonal influenza a (H3N2) has been attributed to the densely populous East, South, and Southeast Asia regions. Seasonal influenza epidemics are influenced by antigenic drift or small mutations in hemagglutinin and neuraminidase proteins, which produce closely related viruses. Antigenic shift occurs less frequently and is an abrupt change in the influenza virus that can cause pandemics due to lack of immunity in the general population to this genetic shift. Annual epidemics can result in up to 650,000 deaths worldwide according to the World Health Organization (WHO), and the last influenza pandemic was in 2009 to 2010, caused by the H1N1 virus with 284,000 deaths in more than 214 countries.[2,3] Surveillance done by WHO FluNet and Centers for Disease Control and Prevention ([CDC] FluView) include the most robust data on influenza; however, because influenza is not a reportable disease in the United States, these are compiled estimates (**Fig. 1**).

Indeed, studies early in the pandemic demonstrated that changes in population behavior were associated with both reduced transmission of SARS-CoV-2 and decreased influenza transmission.[4,5] In the United States, between September 2020 and May 2021, there was a marked reported reduction in reported influenza cases: the CDC reported that only 1899 (0.2%) of 1,081,671 clinical samples tested positive for influenza virus; influenza B comprised most of the reported cases at 62.5%.[6] In contrast to the 2020 to 2021 season, the CDC reported more than 250,000 positive influenza specimens of 1,491,430 total specimens in the 2019 to 2020 season[7] with a similar global trend.[8,9] Prediction models after the light 2020 to 2021 season anticipated a heavier compensatory season in 2021 to 2022 due to decreased immunity.[10]

Respiratory Syncytial Virus

RSV contributed substantially to the respiratory viral disease burden before the pandemic. RSV is common in the pediatric population where it causes significant mortality in children younger than 2 years due to bronchiolitis and pneumonia, although there are increasing data demonstrating significant burden in elderly, chronically ill, or immunocompromised adults.[11,12] Influenza is typically associated with more deaths than RSV in all age groups except for children younger than 1 year.[13] The CDC collects information on RSV in the United States using the National Respiratory and Enteric Virus Surveillance System (NREVSS).[14] According to the CDC, RSV contributes to 58,000 hospitalizations among children younger than 5 years and 14,000 deaths among adults older than 65 years annually.[15] RSV follows a similar seasonal trend to influenza in the United States,[16] starting in early December and peaking in February in the United States.[14] Longer infection seasons have been associated with more northern latitude.[17] Infection can be seen outside a seasonal trend in tropical countries and also when infection mitigation measures disrupt seasonal patterns as noted earlier. RSV activity can correlate with rainfall and humidity in tropical regions, as in Australia during 2020 when widespread spring RSV outbreaks extended into summer.[18] In addition, in the United States and France, RSV was reported later and extended into the spring and summer months.[14,19]

Similar to influenza, epidemiologic trends demonstrate a reduction in RSV cases across various countries from March 2020[20–23] that was also attributed to social distancing and nonpharmacologic interventions. Despite lifting social distancing restrictions in April 2020, no RSV cases were detected in western Australia until august

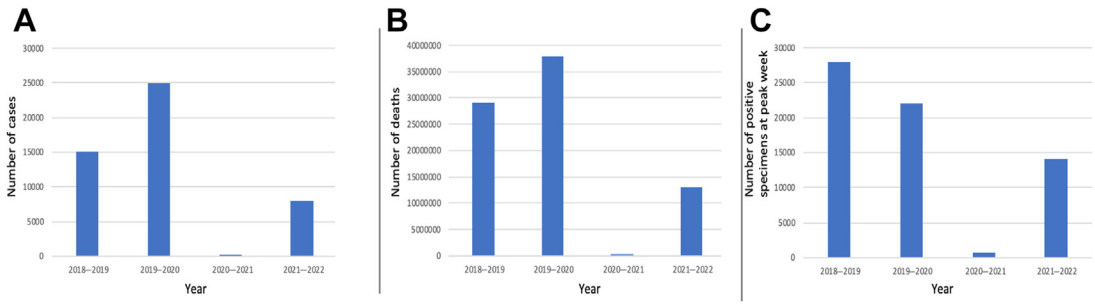

Fig. 1. Comparison of influenza seasons in the United States with compilation of data from WHO FluNet and CDC FluView between 2018 and 2022[4–8] including (*A*) total number of cases, (*B*) total number of deaths, and (*C*) total number of positive specimens at peak week.

2020, inferring that increased hygienic measures, such as hand washing, may have sustained prevention of viral transmission.[24] Another hypothesis for reduction in RSV was viral interference from SARS-CoV-2 because interferon-stimulated immunity by one virus reduces infectivity of additional viruses. In 2021 as pandemic measures were relaxed, the reemergence of RSV was noted in various regions even out of the usual seasonal trends in both northern and southern hemispheres where outbreaks began later than seasonally expected.[14,19] Another hypothesis for the reemergence of RSV was that fewer viral infections in 2020 led to lower concentrations of antibodies in pregnant women, subsequently impacting acquired immunity of infants.[25] Indeed, lack of immunity coupled with the resumption of normal societal activities is likely responsible for the surge of RSV cases in children that is overwhelming pediatric facilities in the fall of 2022.[26]

EPIDEMIOLOGIC TRENDS OF OTHER RESPIRATORY VIRUSES

Throughout the SARS-CoV-2 pandemic there remained concerns for other respiratory viruses including paramyxoviruses, respiratory adenovirus, seasonal coronavirus, and rhinovirus, among others. The NREVSS database showed that the epidemiology of non-RSV paramyxoviruses (including human metapneumovirus and parainfluenza virus) and respiratory adenovirus varied during the pandemic.[14]

The common seasonal coronavirus (the strains 229E, NL63, OC43, and HKU1) had a persistent role during the SARS-CoV-2 pandemic and was often found in cocirculation with SARS-CoV-2.[14] The data on the diagnosis of seasonal coronavirus may have been limited because it is often not part of the diagnostic panels. Seasonal coronavirus follows a trend of peaking during winter months, which may suggest that factors including low temperature and low sunlight favor survival, and remains more common in the pediatric and adolescent populations.[27,28]

Rhinovirus is another commonly observed virus that is also noted to have persistence during the COVID-19 pandemic in various regions including the United Kingdom and Singapore.[29,30] Rhinovirus reductions were only seen after lockdown, and levels rebounded earlier than other respiratory viruses, which suggests that social distancing practices were more effective at suppressing other respiratory viruses.[30] The hypothesis surrounding the early reemergence of rhinovirus infections included its viral structure as a small, hydrophilic, nonenveloped virus with propensity for contact and droplet transmission.[29]

These various viruses have demonstrated some regional differences during the COVID-19 pandemic, but overall many regions exhibited similar trends of decreased annual seasonal respiratory viruses in 2020 to 2021 with reemergence in the 2021 to 2022 season.[31,32]

IMPACT OF SOCIAL DISTANCING AND VACCINATION ON THE SPREAD OF COMMON RESPIRATORY VIRAL INFECTIONS DURING THE CORONAVIRUS DISEASE 2019 PANDEMIC

Several interventions have influenced epidemiologic trends of respiratory infections since the pandemic began, including social distancing and implementation of nonpharmacologic measures such as wearing masks, eye protection, and strict hand hygiene practices.

Even before the COVID-19 pandemic, interventions to limit contact and droplet-related spread were studied. A systematic review of social distancing measures including crowd avoidance, workplace/school closures, lockdowns, isolation of infected persons, quarantining of exposed persons, and contract tracing had some benefit against influenza spread.[33–36] Transmission of

viruses was noted to be lower when physical distance was greater than 1 m, and protection was increased as distance increased.[37] Hand hygiene has long been a key infection prevention method and has been associated with reduction in respiratory viral illnesses.[38] Chan and colleagues[39] observed an 88.9% decrease in the prototypical community-acquired pneumonia (CAP) syndrome with pneumococcal pneumonia from pandemic years 2020 to 2021 when compared with the 5 years before the pandemic, hypothesizing that public health policies (eg, universal masking and social distancing) may have been the primary drivers of such a decrease. A reduction in bronchiectasis exacerbations was noted during the first 12 months of the COVID-19 pandemic upon implementation of social distancing measures.[40]

In addition, the implementation of mask wearing resulted in a large reduction in risk of COVID-19 infection. The use of respirator masks (like N95 masks) was associated with stronger protection when compared with the use of disposable surgical masks.[37] An N95 respirator mask has efficient airborne filtration with a tight-fitting design allowing for a seal around the nose and mouth. In contrast, surgical masks are loose fitting and less efficiently filter airborne particles.

Apart from masks, eye protection provided an added layer for infection prevention. In a study of frontline emergency room workers, mandatory eye protection in conjunction with universal masking was effective at reducing COVID-19; additional reviews have suggested that use of eye protection may help prevent eye inoculation, which could lead to respiratory infections.[41,42]

SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 AND VIRAL COINFECTIONS

Severe Acute Respiratory Syndrome Coronavirus 2 and Influenza

It can be expected that SARS-CoV-2 will become endemic and cocirculate with influenza, and therefore their similarities and differences should be reviewed. Before SARS-CoV-2, influenza was one of the largest public health challenges, resulting in approximately half a million deaths annually.[43] Several studies have compared both viruses given their similarity of symptoms and propensity to each cause severe illness (**table 1**).

Clinical presentation may be similar for both influenza and SARS-CoV-2; however, symptoms that tend to be more unique to SARS-CoV-2 include loss of taste and smell as a symptom. Additional variants of SARS-CoV-2, including the omicron variant, have been associated with less severe symptoms when compared with alpha and delta variants, and many individuals are asymptomatic and may be unaware of their infection. A large study demonstrated that patients with SARS-CoV-2 more frequently had conditions including obesity, diabetes, hypertension, and dyslipidemia when compared with patients with influenza, indicating the importance of metabolic syndrome as a risk factor for SARS-CoV-2 infection. Those with influenza more frequently had heart failure, chronic respiratory disease, and cirrhosis. This comparative study also demonstrated that patients hospitalized with SARS-CoV-2 infection more frequently developed acute respiratory failure, pulmonary embolism, septic shock, or hemorrhagic stroke than patients with influenza, although they were noted to have a lower incidence of myocardial infarction or atrial fibrillation. In-hospital mortality was higher in patients with SARS-CoV-2 than in patients with influenza,[62] and patients with SARS-CoV-2 more frequently have abnormal chest radiology and longer duration of stay during hospitalizations.[63]

Apart from the clinical presentations, the treatment and prevention for SARS-CoV-2 and influenza also differ. SARS-CoV-2 therapeutics include novel antiviral therapies such as remdesivir and vaccinations, which are currently the mainstay of outpatient therapy and prevention of SARS-CoV-2. For influenza, interferons and neuraminidase inhibitors play roles in the prophylaxis and treatment. Interferon types 1 and type 3 function to inhibit viral replication,[64] and neuraminidase inhibitors assist in preventing virions from being released from the surface of infected cells and are effective for both prophylaxis and treatment.[65] Antiviral medications for influenza are approved for use within the United States and have a mechanism of action based via neuraminidase inhibition and can lessen symptoms and shorten duration of illness. Annual influenza vaccination is recommended for everyone aged six months and older (**Table 2**), whereas CDC recommendations for SARS-CoV-2 vaccines include initial series and boosters. The efficacy for influenza vaccines varies by season and aids to reduce severity of illness.[66,67] There has been evidence that has also suggested that flu vaccination has the potential to reduce mortality of SARS-CoV-2 with lower risk of death at 60 days in patients who had received flu vaccinations.[68]

In cases of severe disease with refractory hypoxemia in both SARS-CoV-2 and influenza, extracorporeal membrane oxygenation can be considered as a salvage therapy.[72] When comparing symptoms after acute illness of SARS-CoV-2 and influenza infections, postacute sequalae of COVID ([PASC] or long COVID) has

Table 1
Comparison of characteristics of severe acute respiratory syndrome coronavirus 2, influenza, and respiratory syncytial virus

	SARS-CoV-2	Influenza	RSV
Viral structure	Single-stranded, positive-sense RNA	Negative-sense, single-stranded RNA with surface glycoproteins integral in determining influenza type	Filamentous enveloped, negative-sense, single-stranded RNA
Zoonotic infection	Bats	Avian and swine	Animal models of RSV infections in rodents and nonhumans primates
Virulence	Median r_0 2.79	Median r_0 1.28	Median r_0 1.2–.2.1
Population at risk	• Hypertension • Diabetes • Smoking history • Age: elderly • Male sex • Pregnancy • Obesity • History of heart disease • History of lung disease	• History of chronic disease • Neuromuscular disorders • Morbid obesity • Pregnancy • Age: elderly and young children	• Age: children and elderly • History of heart disease • History of lung disease
Time until postexposure presentation	3–7 d	2–5 d	4–6 d
Clinical symptoms	• Fever • Headache • Dyspnea • Cough • Myalgias • Fatigue • Anosmia and loss of taste May be asymptomatic	• Fever • Nasal congestion • Sore throat • Myalgias • Fatigue • Nausea?, vomiting • Abdominal pain • Diarrhea	• Fever • Poor appetite • Rhinorrhea • Cough • Dyspnea • Wheezing
Duration of symptoms	Depends on severity of illness	Typically resolves by day 8	Typically resolves by 3–7 d
Complications	Post-COVID syndrome and severe cases can lead to ARDS	Severe cases can lead to ARDS	Severe cases can lead to bronchiolitis and pneumonia (especially in pediatric cases)

Abbreviation: ARDS, acute respiratory distress syndrome.
Data regarding SARS-CoV-2 from Refs.[44–53]; data regarding influenza from Refs.[54–58]; data regarding RSV from Refs.[59–61]

been associated with symptoms of prolonged dyspnea, fatigue/malaise, chest/throat pain, headache, abdominal symptoms, myalgias, cognitive symptoms, and anxiety/depression.[73]

Systematic reviews report variable rates of coinfection, one stating rates of influenza infection were 0.8% in patients with confirmed SARS-CoV-2 with fever, cough, and shortness of breath being most common clinical manifestations.[74] Analyses also demonstrate higher coinfection rates in pediatrics compared with adults.[75] In one small pediatric study, nearly half of SARS-CoV-2 infected children had coinfection with other common respiratory pathogens.[76] Although there is no clear consensus on the implications of coinfection, one study suggests there is a potential for

Table 2
Influenza and severe acute respiratory syndrome coronavirus 2 vaccine comparison

	Influenza Vaccine	SARS-CoV-2 Vaccine		
Type	Inactivated, quadrivalent vaccine (live attenuated or recombinant vaccines also available)	mRNA vaccine		DNA viral vector
Mechanism	Surface glycoproteins hemagglutinin	RNA leads to generation of spike protein found on coronavirus and creation of antibodies against it		Modified virus is a vector carrying for COVID spike protein to trigger immune response
Brands	Not applicable	Pfizer-BioNTech	Moderna	Johnson & Johnson's Janssen (J&J)
Frequency of dosing	Annual	2 injections 21 d apart + booster	2 injections 28 d apart + booster	1 dose + booster
% Effectiveness	40–60	90	95	66
Population recommended for	6 mo and older	6 mo and older	6 mo and older	> 18 years old

Vaccine mechanisms reviewed from Refs.[69–71]

added harm with viral coinfection, because post-translational changes in angiotensin-converting enzyme-2 by influenza A may increase vulnerability to lung injury and acute respiratory distress syndrome (ARDS) during coinfections.[77] Although potential targets for therapy are under investigation,[78] no single medication is known to treat both SARS-CoV-2 and influenza simultaneously, although supportive care can be given for both. Similar to influenza infections, as many as one-fifth of patients with SARS-CoV-2 are found to have coinfection or superinfection with other pathogens, which increases mortality, and these coinfections and superinfections are discussed further in this article. Influenza is also associated with bacterial superinfection, specifically *Staphylococcus aureus* and *Streptococcus pneumoniae*.[79]

In the future, coinfection of SARS-CoV-2 and influenza virus will likely continue to occur because influenza epidemics may happen concurrently with the ongoing SARS-CoV-2 pandemic. WHO now recommends countries to prepare for the cocirculation of influenza and SARS-CoV-2 viruses with surveillance, monitoring, and vaccination programs for both SARS-CoV-2 and influenza.

Severe Acute Respiratory Syndrome Coronavirus 2 and Respiratory Syncytial Virus

Similar to influenza, we can expect that SARS-CoV-2 and RSV will start to cocirculate globally. Both RSV and SARS-CoV-2 can present with typical viral symptoms including fever, chills, myalgias, rhinorrhea, cough, and sore throat. Apart from cold-type symptoms (see **Table 2**) RSV can also lead to serious conditions such as bronchiolitis and predominantly affects pediatric and elderly patient populations.

Treatment of RSV is largely supportive and includes antipyretics and hydration. However, severe cases of bronchiolitis or pneumonia may require hospitalization and respiratory support. For prophylaxis against RSV, the medication palivizumab can be given to select pediatric patient populations who are at high risk of serious complications including lower respiratory tract infections from RSV and has been shown to reduce hospitalizations.[80] Ribavarin is approved for severe RSV disease, but its effectiveness is unclear and not well studied, including in patients who are immunocompromised. At this time, there are limited effective antiviral medications targeted to RSV infections; however, there are ongoing trials to evaluate new antivirals and vaccines for RSV, including during pregnancy.[81]

RSV is among the most common coinfections in patients with SARS-CoV-2 pneumonia.[82] Viral coinfection of RSV and SARS-CoV-2 may be associated with prolonged hospitalization, need for higher level of care, complicated lower respiratory infections,[83] and elevated procalcitonin levels[84];

however, its contribution to increased mortality remains unclear.[85–88]

Severe Acute Respiratory Syndrome Coronavirus 2 and Epstein-Barr Virus

SARS-CoV-2 has also demonstrated interaction with other viruses, although data for these viruses is based on smaller studies and case reports. Immune dysregulation from SARS-CoV-2 may potentiate other viral infections, particularly those with an asymptomatic course with potential to reactivate.

Epstein-Barr virus (EBV) can cause a wide range of diseases, from infectious mononucleosis in younger adults to various cancers or lymphoproliferative disorders, or it may be asymptomatic. Coinfection with both viruses demonstrated increased inflammation and consequently increased steroid use.[89] Indeed, both SARS-CoV-2 and EBV can infect epithelial cells of the respiratory tract or cause liver function abnormalities, thus elevated liver function tests in coinfection can be expected, especially in setting of EBV reactivation.[90] One study demonstrated up to 25% reactivation rate of EBV in patients with SARS-CoV-2, particularly in older and female persons, and suggested an associated increased mortality.[91] This enhanced inflammation from EBV viral reactivation is thought to play a significant role in the development of PASC symptoms,[92] possibly due to alternations in mitochondrial function and senescence.[93]

Severe Acute Respiratory Syndrome Coronavirus 2 and Cytomegalovirus

There are case reports of SARS-CoV-2 and cytomegalovirus (CMV), which have been associated with various clinical presentations including the development of CMV pneumonitis and presentations of gastrointestinal symptoms.[94] CMV seropositivity is associated with increased risk of hospitalization with SARS-CoV-2 infection[15] and increased severe bacterial infections.[95] Furthermore, there has been suggestion to consider secondary infection with CMV in the differential of transaminitis for those with SARS-CoV-2 and EBV infections, because reactivation of CMV has also been described,[96] although EBV is most consistently shown among opportunistic viruses.[97]

Additional considerations for viral reactivation include the alterations of the immune system associated with SARS-CoV-2 vaccination, which have been associated with sequelae of viral reactivation in CMV and varicella zoster virus.[98–102]

Severe Acute Respiratory Syndrome Coronavirus 2 and Other Respiratory Viruses

Although viral coinfections remains relatively rare, case reports have described coinfections of SARS-CoV-2 with human metapneumovirus,[103] human parainfluenza virus,[104] and adenovirus,[105] among others. Case reports of SARS-CoV-2 and coinfection with adenovirus have suggested a more severe hospital course than when with isolated infections.[106] It should be noted that studies reviewed here are not specific to patients who undergo transplant, although transplant recipients are already at increased risk of reactivation of certain viruses due to immunosuppression.

SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2, BACTERIAL COINFECTIONS, AND SUPERINFECTIONS

Bacterial coinfection and superinfection during severe viral illness has been a prominent issue documented as early as the 1918 influenza pandemic. Autopsies showed that virtually all influenza deaths were complicated, and perhaps caused by bacterial pneumonia coinfection; *Streptococcus pneumoniae* was a particularly significant pathogen with high mortality.[107]

The reasons for bacterial involvement in viral disease are unclear and can occur through several mechanisms (**Fig. 2**). Dysbiosis of the pulmonary microbiome during invasive mechanical ventilation has been demonstrated and hypothesized to be due to a combination of antibiotic use, translocation of gastrointestinal flora, dysfunction of pulmonary mucosal immunity, and impaired microbial clearance.[108] Viruses also impair host defenses resulting in increased susceptibility to bacterial infection, namely, by compromising the integrity of the respiratory epithelium, which allows for better adherence and invasion of bacteria.[109] In addition, there is preliminary evidence in extrapulmonary infection models that viruses alter host cytokine expression potentially "distracting" the immune system away from a bacterial pathogen leading to worsening of bacterial infection.[110] Because it pertains to SARS-CoV-2 specifically, some evidence also points toward an early immunoparalysis driven by virally infected monocytes and macrophages.[111]

The diagnosis of contemporaneous and secondary bacterial infections during SARS-CoV-2 infections has implications for patient outcomes, antibiotic stewardship, and health care costs.

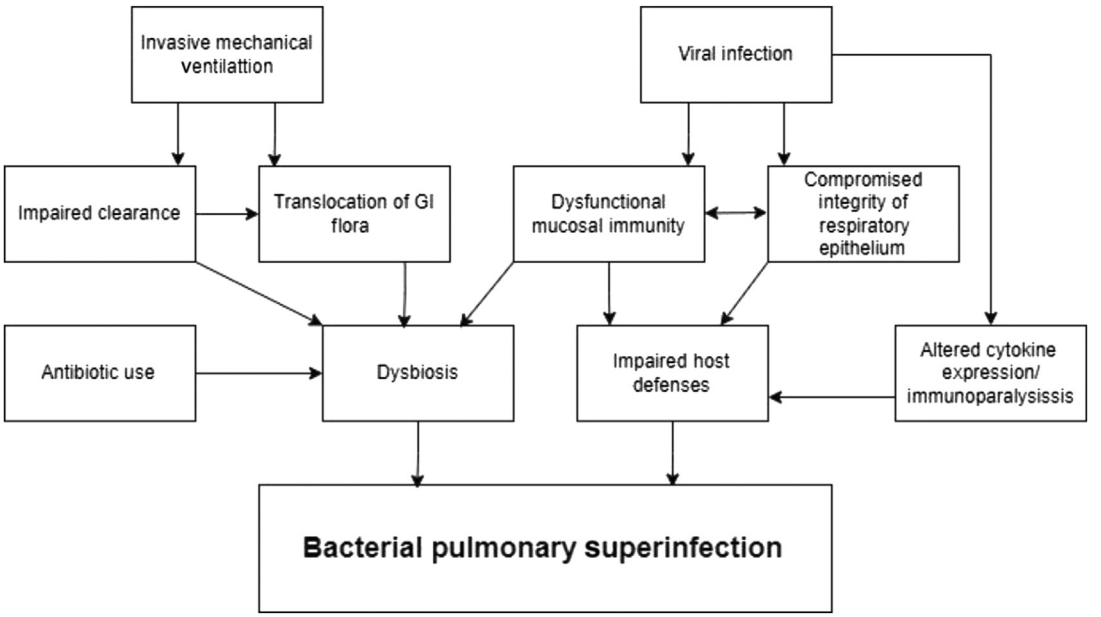

Fig. 2. The complex interplay of factors predisposing to bacterial pulmonary superinfection. GI, gastrointestinal.

SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 AND COMMUNITY-ACQUIRED PNEUMONIA

Definition

CAP is defined in clinical terms as the presence of symptoms attributable to pneumonia (eg, dyspnea, cough) plus radiographic confirmation.[112]

Epidemiology

A multicenter study done by the CDC in 2015 showed that among approximately 2300 patients presenting with CAP, a bacterial cause was only identified 17% of the time.[113] Patients presenting with SARS-CoV-2 have bacterial coinfection even less frequently. Lehmann and colleagues[114] found bacterial coinfection to occur in 7 of 321 SARS-CoV-2 presentations, with 4 cases of *S pneumoniae*, 2 cases of *S aureus*, and 1 case of *Proteus mirabilis*. This finding was further confirmed when an additional study showed that community-acquired bacterial coinfection occurred in only 59 of 1705 SARS-CoV-2 admissions.

The contrast between higher rates of coinfection during the influenza pandemic and the lower rate of bacterial CAP as a coinfection in SARS-CoV-2 is potentially explained by differing public health landscapes. Amin-Choudhury and colleagues[115] confirmed that public health policies, such as social distancing practices, can lead to of decreased rates of pneumococcal CAP in the setting of coinfection; however, they noted that when coinfection happened it was associated with a 7-fold increase in 28-day mortality.[39]

Diagnosis

Discerning a patient presenting from the community with solitary COVID-19 pneumonia versus one with a bacterial coinfection remains difficult. Unfortunately, procalcitonin level drawn at admission is neither sensitive nor specific for this purpose.[116] Radiographically, there are some findings that are more "typical" for COVID-19 than for bacterial pneumonia. In COVID-19, computed tomography (CT) of the chest shows bilateral, multilobar ground-glass opacities (GGOS) in a peripheral and subpleural distribution and focal areas of consolidation may be found within areas of GGOS.[117] In the second week of illness the GGOS may continue to expand and evolve to contain areas of irregular linear opacities signaling the transformation into an organizing pneumonia.[117]

In contrast, bacterial pneumonia may more frequently have centrilobular nodules and bronchial wall thickening with mucoid impactions, as well as the characteristic lobar consolidation.[116]

Treatment

Treatment of suspected bacterial CAP coinfection should be according to published Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) CAP guidelines.[112] Targeted diagnostics should include sputum culture and

blood culture for severe disease or if treatment is targeting *Pseudomonas aeruginosa* or methicillin-resistant *S aureus*. Although guidelines only recommend pneumococcal urinary antigen testing for severe cases, it should likely be done whenever coinfection with SARS-CoV-2 is being considered given the higher odds of severe disease developing. Current IDSA guidelines for management of COVID-19 do not recommend for or against antibiotics for CAP, but do describe mostly negative effects of indiscriminate antibiotic use at the time of admission such as resistant superinfection.[118]

CORONAVIRUS DISEASE 2019 AND VENTILATOR-ASSOCIATED PNEUMONIA

Definition

Hospital-acquired pneumonia (HAP) is specified as a pneumonia not incubating at the time of hospital admission and occurring 48 hours or more after admission. Ventilator-associated pneumonia (VAP) is defined as a pneumonia developing greater than 48 hours after endotracheal intubation.[119] Diagnosis of HAP or VAP is based on finding a new lung infiltrate plus clinical evidence that the infiltrate is of an infectious origin (new fever, purulent sputum, leukocytosis, and decline in oxygenation).

Epidemiology

There are considerably more data regarding VAP infections in the setting of COVID-19 when compared with CAP. Mechanically ventilated patients with COVID-19 are at higher risk for VAP than mechanically ventilated patients without COVID-19, with a virtually universal agreement among large studies using strict definitions and microbiological confirmation.[120] Furthermore, autopsy studies of patients who died of severe COVID-19 show that at least 32% had a bacterial superinfection.[121]

VAP was found to be the cause of more than 50% of hospital-acquired infections with *P aeruginosa* and *Klebsiella pneumoniae* being the most common isolated organisms.[122] In a retrospective study observing 192 patients intubated for COVID-19 with early bronchoalveolar lavage (BAL) occurring before intubation in most cases, 11.6% had a superinfection meeting diagnostic criteria for HAP before intubation, with at least one episode of VAP occurring in 44.4% of patients. The average time to diagnosis was 10.8 days postintubation.[123] In a study of more than 70,000 patients in the medical intensive care unit (ICU) divided into groups of prepandemic, pandemic without COVID-19 infection, and pandemic with COVID-19 infection, incidence of VAP was found to be higher in COVID-19-infected patients and had a higher attributable mortality. Attributable mortality for COVID-19 with VAP was 9.17%, whereas attributable mortality for prepandemic and pandemic COVID-19-negative patients was 3.15% and 2.91%, respectively.[124]

The explanation for such a high incidence of VAP in COVID-19 is likely multifactorial. Patients with COVID-19 who are intubated commonly have one or more of the traditional risk factors for VAP such as high lengths of stay, prolonged duration of mechanical ventilation, the presence of ARDS, sedation, neuromuscular blocking agents, and not least the high utilization of prone positioning.[125] Stress on both human and material resources during peak surges has also been argued to have a detrimental impact on the rate of secondary infection.[126]

Diagnosis

HAP/VAP in COVID-19 should be diagnosed in accordance with IDSA/ATS guidelines.[119,120] Although a spot test of procalcitonin on admission to the hospital was not found to be helpful for the diagnosis of bacterial CAP coinfection,[116] a procalcitonin trend for patients in the ICU may be more useful. Richards and colleagues[127] found that a 50% increase in procalcitonin levels from its previous value was independently associated with the presence of a secondary bacterial infection (VAP, ventilator-associated tracheobronchitis, or bacteremia) compared with increases in either white blood cell count or C-reactive peptide.

Treatment

Treatment of suspected bacterial HAP/VAP coinfections should be according to published IDSA/ATS guidelines.[120]

CORONAVIRUS DISEASE 2019 AND OTHER NOSOCOMIAL INFECTIONS

Bloodstream Infections

In a study comparing nosocomial bloodstream infections (BSIs) in non-COVID-19 and COVID-19 patients,[128] *Candida* species accounted for nearly 50% of infections with next commonest being *Enterococcus* (**Table 3**). A comparison between the COVID-19 and non-COVID-19 groups showed that patients with COVID-19 were more than 2 times as likely to have candidemia than non-COVID-19 patients. *Enterococcus* rates were similar; however, the investigators note that the typical risk factors for candidemia and enterococcal BSIs such as gastrointestinal surgeries, malignancies, and chemotherapy were present in the non-COVID-19 patients but tended to be

Table 3
Most common etiologic organisms in coronavirus disease 2019-associated bloodstream infections

Early	Late
S aureus	*Enterococcus*
Gram-negatives	*Candida*

absent in the patients with COVID-19, suggesting that these were distinct complications of COVID-19. The investigators also noted that these BSI organisms occurred later in hospitalization, proposing that perhaps antimicrobials, steroids, and the interleukin (IL)-6 inhibitor tocilizumab may have promoted translocations of these organisms over time (see **Table 3**).

In a study of 212 patients with severe COVID-19 in Brazil, Silva and colleagues[129] found bacteremia to carry an odds ratio for mortality of 21. Gago and colleagues[128] went further to specify that although there was not an observed statistically significant difference in mortality among patients with BSI due to *Candida* or *Enterococcus*, there was an increase in mortality clustered around cases of BSI that occurred earlier in hospitalization with the less common *S aureus* and gram-negative organisms.

Bhatt and colleagues[130] published a multicenter case-control study that highlighted some of the risk factors for secondary BSIs in a sample composed of all hospitalized patients: higher need of supplemental oxygen on admission, higher admission serum creatinine levels, and presentation with encephalopathy. Other potential risk factors include the use of antimicrobials, systemic corticosteroids, and IL-6 blockade. The study did, however, have a high proportion of coagulase-negative staphylococci, raising the concern of inappropriately screened contaminants.[130]

CORONAVIRUS DISEASE 2019 AND INVASIVE FUNGAL INFECTIONS

Aspergillosis and mucormycosis are diseases caused by fungal organisms that infect humans as molds. Although they are both recognized entities occurring in patients with COVID-19, considerable debate exists regarding the rate of occurrence, as it concerns COVID-19-associated pulmonary aspergillosis (CAPA).

Coronavirus Disease 2019-Associated Pulmonary Aspergillosis

One autopsy review series reports a CAPA rate of occurrence of approximately 2% in both mechanically ventilated and nonmechanically ventilated COVID-19 decedents.[131] Published incidences of CAPA ranges from 0% to 30% in studies without standardized definitions, and 2% to 11% in studies with standardized definitions.[132]

A definition of "probable CAPA" has been devised to include more than one of the following: new cavitary lung lesions on chest CT without alternative explanation, positive serum galactomannan Enzyme Immunoassay (EIA) index greater than or equal to 0.5, positive BAL galactomannan EIA index greater than or equal to 1.0, or positive aspergillus cultures from BAL specimen.[133–135] In their retrospective analysis of mechanically ventilated patients with COVID-19 in 5 Johns Hopkins Medicine health system hospitals, Permpalung and colleagues[136] added a diagnosis of "possible" CAPA for patients who had more than 1 of the following: positive BAL galactomannan index greater than or equal to 0.5 (lower threshold), positive serum (1, 3)-β-D-glucan (BDG) level greater than or equal to 80 pg/mL without alternate explanation, and/or non-BAL sample culture with growth of *Aspergillus*. The expanded definition was intended for centers that do not use bronchoscopy for BAL liberally and that use BDG as a fungal marker in addition to galactomannan. **Table 4** shows a comparison of diagnostics in probable versus possible CAPA.

In the study by Permpalung and colleagues,[136] rates of CAPA ranged from 5% to 10% and patients with CAPA had higher severity of illness, need for more ventilatory and hemodynamic support, and longer duration of hospitalization, although mortality was no different from non-CAPA patients. It is worth noting, however, that only 48.7% of patients with CAPA received antifungal therapy, likely representing the challenge of diagnosis.

Treatment of CAPA may be extrapolated from IDSA guidelines for invasive aspergillosis: triazoles (voriconazole, posaconazole, isavuconazole, itraconazole) are recommended as first-line agents, amphotericin B and derivatives can be used for salvage therapy and when voriconazole cannot be used, whereas echinocandins (eg, micafungin, anidulafungin) are not recommended to be used as initial monotherapy but may be effective as salvage therapy either alone or in combination with others.[137]

Coronavirus Disease 2019-Associated Mucormycosis

Mucormycosis is caused by several molds, but species *Rhizopus*, *Lichtheimia*, and *Mucor* account for 75% of infections.[138] Cases of COVID-19-associated mucormycosis are more commonly

Table 4
Diagnostics in "probable" compared with "possible" coronavirus disease 2019-associated pulmonary aspergillosis

	Probable CAPA	Possible CAPA
Imaging	New cavitary lung lesions on chest CT without alternative explanation	Not required
Serum markers	Serum galactomannan EIA index ≥ 0.5	Serum (1, 3)-β-D-glucan ≥ 80 pg/mL without alternate explanation
BAL markers	BAL galactomannan EIA index ≥ 1.0	BAL galactomannan EIA index ≥ 0.5
Lung specimen cultures	Positive *Aspergillus* cultures from BAL	Non-BAL sample culture with growth of *Aspergillus*

sinonasal and rhino-orbito-cerebral than pulmonary or disseminated.[139] Patients in the developing world have accounted for most cases reported thus far.

Mucormycosis is more diagnostically challenging than aspergillosis, in part because there are no approved biomarkers to aid in diagnosis. The etiologic agents of mucormycosis neither produce galactomannan nor do they have BDG in their cell walls. Diagnosis must be undertaken first with clinical suspicion of site of infection (eg, rhino-orbital) followed by surgical sampling and histopathology of the involved site.[140]

Treatment of mucormycosis also differs slightly from aspergillosis, and is likewise more limiting. In contrast to aspergillosis, amphotericin B and derivatives are considered first line for mucormycosis with triazoles being suitable for salvage therapy. Also unlike aspergillosis, echinocandins demonstrate breakthrough infection and may not be appropriate monotherapy for salvage or otherwise. Importantly, voriconazole and itraconazole do not have activity against mucormycosis organisms, therefore a clinician hoping to select coverage for both mucormycosis and aspergillosis without needing to concern themselves with the potential of toxicity from amphotericin B would have only isavuconazole and posaconazole as options.[140] At that point of consideration, consultation with an infectious disease specialist would be recommended.

SUMMARY

The COVID-19 pandemic had a significant impact on the epidemiology of other respiratory infections. The implementation of social distancing and wearing masks and eye protection was associated with a decline in rates of influenza and RSV during 2020 to 2021; now there is a reemergence of these and other community-acquired respiratory viruses. Although coinfections of COVID-19 with other respiratory viruses remain relatively rare, there have been some evidence that coinfection is associated with increased severity of illness. Treatment of coinfections includes a specific antiviral agents if available for the virus and supportive care.

Regarding bacterial pneumonia and COVID-19, CAP and nonintubated HAP are infrequent coinfections; an exception is perhaps merited for CAP caused by *S pneumoniae*. Once patients are endotracheally intubated, however, they become highly susceptible to VAP development in a manner out of proportion to similar patients with non-COVID-19 indications for intubation. About 60% to 70% of COVID-19-related VAPs involve gram-negative organisms[126]; treatment should be according to local antibiograms and resistance patterns in combination with published guidelines.[120] A procalcitonin trend may be a useful adjunct in diagnosis.

Last, nosocomial infections including BSI and opportunistic invasive fungal infections can occur in patients with COVID-19 especially in patients with higher severity of illness.

CLINICS CARE POINTS

- Changes in population behaviour early in the COVID-19 pandemic including; social distancing and masking; were associated with reduced transmission of SARS-CoV-2, influenza, respiratory syncytial virus, along with other seasonal coronavirus and rhinovirus infections.
- Symptoms of many respiratory viral illnesses are similar to SARS-CoV-2 infection. Symptoms that are more unique to SARS-CoV-2 infection than other respiratory viral illness include loss of taste and smell.

- Vaccination and treatment options are available for prevention and management of SARS-CoV-2 and influenza infections.
- Bacterial coinfection and superinfection during SARS-CoV-2 infections have implications for patient outcomes, antibiotic stewardship and health care costs. Bacterial infections include community-acquired pneumonias, hospital-acquired pneumonia, ventilator-associated pneumonias and blood stream infections.
- Fungal infections including COVID-19-associated pulmonary aspergillosis (CAPA) and mucormycosis were identified amongst patients infected with SARS-CoV-2.

DISCLOSURE

Authors involved in this chapter have nothing to disclose.

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