Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Commentary

When two for the price of one isn't a bargain: estimating prevalence and microbiology of bacterial co-infections in patients with COVID-19

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In people with viral respiratory tract infections, the presence of a concomitant bacterial infection has been associated with poor clinical outcomes. For example, in patients with influenza, superimposed bacterial infection is present in 20–30% of patients [1,2] and has been associated with increased rates of shock, mechanical ventilation and mortality [1,2]. Similarly, in children with severe respiratory syncytial virus infection, multiple studies have demonstrated rates of superimposed bacterial pneumonia in excess of 30%, and this has been associated with a longer duration of mechanical ventilation [3]. Studying the rates and microbiology of bacterial co-infection in patients with viral respiratory infections can aid in how we determine empiric antibiotic therapy, understand prognosis and discern pathogenesis in viral-bacterial co-infections.

The prevalence and microbiology of concomitant bacterial infections in patients with SARS-CoV-2 infection are not yet well understood. Therefore, we read with interest the study by Langford and colleagues in which they performed a rapid systematic review of studies that examined rates of bacterial pneumonia or bloodstream infection in patients with COVID-19 [4]. In this meta-analysis they identified a large cohort of 3448 patients from 28 studies that primarily consisted of hospitalized adults in Asia. There was heterogeneity in the outcomes of the studies that were included in the meta-analysis, as some reported whether bacterial infection was noted on presentation to the hospital ($n = 20$ studies; termed *bacterial co-infection*), while the remaining studies reported whether a concomitant bacterial infection developed during the course of the patient's hospitalization ($n = 8$ studies; termed *secondary bacterial infection*). In a random effects meta-analysis, bacterial co-infection was identified in 3.5% of COVID-19 patients, and secondary bacterial infection was identified in 15.5% of COVID-19 patients. No data on prevalence of bacteraemia versus bacterial pneumonia were presented. Interestingly, stratification of patients by illness severity showed that bacterial infections were more prevalent in fatal (11.6%) and ICU (8.1%) cases relative to non-ICU hospitalized patients (5.8%). It is not yet clear if the concomitant bacterial infections are driving poor clinical outcomes or if they are simply more common in sicker patients that are receiving a higher level of care (e.g. ventilator-associated pneumonia in intubated patients). The overall low prevalence of bacterial infection in patients with COVID-19 was similar as that noted in another recent meta-analysis (7%) [5] and rapid review (8%) [6] of the literature, though there is significant overlap in the studies included in these reviews. Taken together, the overall rate of bacterial respiratory or bloodstream infection in patients with COVID-19 is lower than what has been described in pandemic influenza.

Data from Langford et al. also suggest that patients with COVID-19 may differ from influenza patients with respect to the microbiology of concomitant bacterial infections. While only a minority of patients with bacterial infection reported bacterial species data (<14%), the most commonly identified organisms were *Mycoplasma* species, *Haemophilus influenzae* and *Pseudomonas aeruginosa* [4]. *Staphylococcus aureus* was identified in only 5% of cases of bacterial infection, and *Streptococcus pneumoniae* was not identified at all. This is in contrast with influenza, where *S. aureus* and *S. pneumoniae* are the most commonly identified causes of concomitant bacterial infection [1,2]. While the microbiological findings in Langford et al. require validation with additional datasets, this study lends support to the idea that host response to COVID-19 versus influenza may differ in fundamental ways. For

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example, in patients with influenza, the increased susceptibility to *S. aureus* has been demonstrated to be dependent upon factors such as disruption of the Nox2 inflammatory pathway [7] and increased TLR9 expression [8]. Whether SARS-CoV-2 similarly disrupts such pathways is as yet unknown.

Despite the lower prevalence of bacterial co-infection in patients with SARS-CoV-2 infection relative to other viral respiratory pathogens, many patients with COVID-19 (71%) were treated with antibiotics. Most commonly, these were broad-spectrum agents such as fluoroquinolones or carbapenems. While detailed information on antibiotic use patterns such as timing and duration of antibiotic therapy is not provided, the data from Langford et al. suggest common use of broad-spectrum antibiotics in the face of relatively low rates of bacterial infection. While concomitant bacterial infection is higher among critically ill patients, the available data do not support the widespread use of empiric antibiotic therapy in all hospitalized patients with COVID-19. Measures to limit unnecessary antibiotic use are needed as the COVID-19 pandemic threatens to increase antimicrobial resistance through expanded empirical antimicrobial therapy. One potential tool in limiting empiric antibiotic use is procalcitonin, though its role in identifying concomitant bacterial infections in patients with COVID-19 is not yet known. Preliminary reports suggest that procalcitonin levels in patients with COVID-19 are low [9]. However, procalcitonin levels rise with disease severity [10], and it is unclear if this rise is due to concomitant bacterial infection or general systemic inflammation related to immune dysregulation or acute respiratory distress syndrome.

Studies to date that have investigated concomitant bacterial infections in patients with COVID-19 have several important limitations. First, current data on bacterial co-infection rates in patients with COVID-19 are limited both geographically and temporally, as data from recent reviews [4–6] involved studies primarily from China and early in the COVID-19 pandemic. Data on bacterial co-infection rates from varied geographic sites are needed as there could be variability in the proportion of patients tested for bacterial infection, the microbiology of bacterial infections or in antimicrobial stewardship policies. To this end, Langford et al. have proposed a living review, hosted by the Toronto Antimicrobial Resistance Research Network (TARRN) website (https://www.tarrn.org/covid), in which an updated analysis of bacterial co-infection rates will be performed every 3 months throughout the course of the pandemic. This will be particularly beneficial in the coming months as the use of immunomodulatory therapies may independently affect infection risk [11]. Second, there is poor reporting of testing methods for detection of bacteria and no standardization in these testing procedures. For example, in Langford et al. testing methods for bacterial infections were only reported in half of the included studies. Future work should clearly identify the techniques used to identify bacterial infections so that we can better understand how differences in methodology influence co-infection rates. Third, there is little reporting of infection versus colonization or contamination. While it is often challenging for clinicians to distinguish colonization of the respiratory tract or contamination from true infection, future studies should clearly differentiate and report these aetiologies when possible. Fourth, little is known about the temporal relationship between SARS-CoV-2 infection and concomitant bacterial infection. Langford et al. distinguished bacterial co-infection (present at hospital admission) from secondary infection (develops over course of hospitalization); however, this definition of co-infection is problematic as it is not clear if COVID-19 and the bacterial infection truly began around the same time. More detailed analysis and reporting of the onset of bacterial infections relative to the course of COVID-19 are needed to understand the pathogenesis of these viral–bacterial co-infections. Fifth, we do not have a good understanding of the clinical risk factors for concomitant bacterial infection in patients with COVID-19, and so additional data on how demographics and medical comorbidities influence bacterial infection risk are needed. Finally, concomitant infections with fungal [6] or mycobacterial [12] pathogens have been described in patients with COVID-19, though such data are sparse.

At present we do not have enough data to make firm conclusions on the rates and microbiology of bacterial infections in patients with COVID-19. Yet while the available data are limited, the emerging picture is one of lower bacterial co-infection rates in patients with COVID-19 relative to pandemic influenza. Despite this, the reported use of broad-spectrum antibiotic therapy in patients with COVID-19 is high. At present there is not good evidence to support the broad use of empiric antibiotics in patients with COVID-19, particularly in those without critical illness. Antibiotic therapy should be limited to those with suspected or proven bacterial co-infection, with frequent re-evaluation based on the clinical course, laboratory findings, and imaging findings.

Transparency declaration

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