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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Narrative review

The interface between COVID-19 and bacterial healthcare-associated infections

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ABSTRACT

Background: A wide range of bacterial infections occur in coronavirus disease 2019 (COVID-19) patients, particularly in those with severe coronaviral disease. Some of these are community-acquired co-infections.
Objective: To review recent data that indicate the occurrence of hospital-onset bacterial infections, including with antibiotic-resistant isolates, in COVID-19 patients.
Sources: Using PubMed, the literature was searched using terms including: 'COVID-19'; 'SARS-CoV-2'; 'bacterial infection'; 'healthcare-associated infection'; 'antibiotic resistance'; 'antimicrobial resistance'; 'multi-drug resistance'; '*Streptococcus*'; '*Staphylococcus*'; '*Pseudomonas*'; '*Escherichia*'; '*Klebsiella*'; '*Enterococcus*'; '*Acinetobacter*'; '*Haemophilus*'; 'MRSA'; 'VRE'; 'ESBL'; 'NDM-CRE'; 'CR-Ab'; 'VRSA'; 'MDR'.
Content: There is a growing number of reports of bacterial infections acquired by patients with severe COVID-19 after hospital admission. Antibiotic-resistant pathogens found to cause healthcare-associated infections (HAIs) in COVID-19 patients include methicillin-resistant *Staphylococcus aureus*, New Delhi metallo-β-lactamase-producing carbapenem-resistant Enterobacterales, carbapenem-resistant *Acinetobacter baumannii*, extended-spectrum β-lactamase *Klebsiella pneumoniae* and vancomycin-resistant enterococci. COVID-19 has impacted bacterial HAIs in a number of ways with an increase in the incidence of New Delhi metallo-β-lactamase-producing carbapenem-resistant Enterobacterales and carbapenem-resistant *A. baumannii* reported at some hospital sites compared with before the pandemic. Recommended guidelines for antimicrobial stewardship in COVID-19 patient treatment are discussed regarding minimization of empiric broad-spectrum antibiotic use. Other studies have reported a decrease in methicillin-resistant *S. aureus* and vancomycin-resistant enterococci cases, which has been attributed to enhanced infection prevention and control practices introduced to minimize intra-hospital spread of COVID-19.
Implications: Poorer outcomes have been observed in hospitalized COVID-19 patients with an antibiotic-resistant infection. Although heightened IPC measures have been accompanied by a reduction in some HAIs at specific sites, in other situations, COVID-19 has been associated with an increase in bacterial HAI incidence. Further research is needed to define the cost–benefit relationship of maintaining COVID-19-related infection prevention and control protocols beyond the pandemic to reduce the burden of HAIs. In addition, the longer-term impact of high usage of certain broad-spectrum antibiotics during the COVID-19 pandemic requires evaluation. **Ronan F. O'Toole, Clin Microbiol Infect 2021;27:1772**

Introduction

On 31 December 2019, the WHO Western Pacific Regional Office was notified of reports of cases of 'pneumonia of unknown cause' from Wuhan, China [1]. The disease, identified as being caused by a novel strain of coronavirus designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was named coronavirus

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disease 2019 (COVID-19). The relatively rapid international spread and rise in COVID-19 cases prompted WHO to declare the disease a pandemic on 11 March 2020 [1]. There have been more than 166 million cases recorded and over 3.4 million estimated deaths across 186 countries attributed to COVID-19 by WHO as of 23 May 2021 [2]. Hence, COVID-19 is the largest WHO-recognized pandemic since the influenza A viral subtype H1N1 'Spanish Flu' in 1918–1920, which was estimated to have killed 20–50 million people worldwide [3].

Emergence of reports of bacterial infections related to COVID-19

In the early stages of the COVID-19 outbreak and before the declaration of the pandemic, data on bacterial infections in COVID-19 patients were limited. Guan and colleagues assessed medical records of 1099 adult patients across China with laboratory-confirmed COVID-19 reported between 11 December 2019 and 29 January 2020 [4]. They identified common symptoms of the disease as being fever and cough [4]. Unfortunately, they noted that 'many patients did not undergo sputum bacteriologic or fungal assessment on admission because, in some hospitals, medical resources were overwhelmed.' There may also be difficulty in collecting sputum samples from COVID-19 patients because they are not always attainable from patients who do not have a productive cough and furthermore, induction of cough may promote viral spread [5]. Zhou et al., in an analysis of 191 hospitalized adult COVID-19 patients in Wuhan, found that sepsis was the most frequently observed complication in both non-survivors and survivors of the disease [6]. The authors noted that sepsis could have resulted from viral infection in these patients and hence, specific data confirming bacterial involvement in COVID-19 were still needed.

With more studies, a relationship between COVID-19 and bacterial infection began to appear in severe cases of COVID-19. Among 221 adult COVID-19 patients admitted to the Zhongnan Hospital in Wuhan, severely affected patients, for example those who required intensive care unit (ICU) admission and mechanical ventilation therapy, exhibited a significantly higher rate of bacterial co-infection compared with patients with non-severe COVID-19 disease (25.5% versus 1.8%; $p < 0.001$) [7]. This indicated that bacterial infection may play a lesser role in early non-severe stages of COVID-19. Indeed, a UK study of 836 patients with SARS-CoV-2 infection reported a low frequency of bacterial co-infection during early COVID-19 hospitalization (3.2% at 0–5 days post admission) [8].

Findings have begun to reveal specific bacterial pathogens that cause infections in COVID-19 patients. In a study of 989 adult patients admitted to hospital with COVID-19 for >48 hours in Barcelona, Spain, 74 bacterial infections were recorded in 72 of the patients [9]. Bacterial species identified included *Streptococcus pneumoniae* (16.2%), *Staphylococcus aureus* (16.2%), *Pseudomonas aeruginosa* (13.5%), *Escherichia coli* (9.5%), *Klebsiella pneumoniae* (8.1%), *Enterococcus faecium* (5.4%) and *Haemophilus influenzae* (2.7%). While *Streptococcus pneumoniae* and *H. influenzae* were associated with community-acquired pneumonia alone, *S. aureus* was linked to both community-acquired co-infection (community-acquired pneumonia) and hospital-associated superinfections (ventilator-associated pneumonia and hospital-acquired pneumonia) [9]. Community- and hospital-acquired urinary tract infections were caused by *Escherichia coli*, *K. pneumoniae* and *E. faecium* [9]. The authors noted that systematic testing for co-infections was not performed in their study, such that bacterial infections may have been missed in some patients.

An analysis by Rawson et al. of investigations from China and the USA, reported that 8% of 806 COVID-19 patients had a bacterial or fungal co-infection [10]. In 712 hospitalized adult COVID-19 patients in Valladolid, Spain, 16% were reported as presenting with bacterial/fungal co-infections or superinfections [11]. Another study reported that co-infections and secondary infections varied from as low as 0.6% to as high as 45% of COVID-19 patients [12].

Given the wide range of positivity for co-infection or secondary infection across different studies, it is clear that larger studies are needed that are specifically designed to ascertain the levels of bacterial infection in COVID-19 patients, and that the data obtained should be stratified with respect to variables including infection site and bacterial species. A recent PCR-based analysis of 50 419 respiratory samples from nasopharyngeal, oro-pharyngeal and sputum swabs in the USA reported that *S. aureus* infected SARS-CoV-2-positive patients at a significantly higher rate than SARS-CoV-2-negative individuals (13.17% versus 11.64%, $p < 0.05$) [13].

Bacterial healthcare-associated infections in COVID-19 patients

The WHO defines a healthcare-associated infection (HAI) as 'an infection occurring in a patient during the process of care in a hospital or other healthcare facility, which was not present or incubating at the time of admission' [14]. One of the issues in relation to COVID-19 is obtaining data that differentiate between healthcare versus community sources of bacterial infection in patients.

The leading culprits in causing HAIs globally are the so-called ESKAPE pathogens—*E. faecium*, *S. aureus*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa* and *Enterobacter* species [15]. *Staphylococcus aureus* is the second most frequent cause of HAIs in the USA, causing up to 11.8% of all HAIs and 20.7% of surgical-site infections [16]. Of 92 adult patients admitted to a 40-bed ICU in Argenteuil, France, for acute respiratory failure due to SARS-CoV-2 pneumonia, 26 (28%) were regarded as being co-infected with a pathogenic bacterium [17]. Among these, methicillin-sensitive *S. aureus* made up 31% of bacteria detected [17]. Thirty patients had been hospitalized for >48 hours before ICU admission, indicating that *S. aureus* infection of a number of these patients occurred in the healthcare setting.

Of 2679 patients hospitalized for COVID-19 in New York, USA, 42 (1.57%) had *S. aureus* bacteraemia [18]. More specifically, 28 of these patients were categorized as having hospital-onset bacteraemia, defined as a positive blood *S. aureus* culture on or after the fourth day post hospital admission [18]. This provides direct evidence of the acquisition of healthcare-associated *S. aureus* infection by COVID-19 patients. It is of concern as 54.8% and 66.7% of these patients died by days 14 and 30, respectively, after their first positive blood culture [18].

Enterococcus faecalis and *E. faecium* have emerged as further common nosocomial pathogens in the USA, responsible for up to 7.4% and 3.7% of all HAIs, respectively [16]. The abundance of *Enterococcus* sp. was reported to increase significantly in the gut microbiome of adult COVID-19 patients with a poor prognosis [19]. In 78 critically ill COVID-19 patients who developed a bloodstream infection following ICU admission in Genoa, Italy, *Enterococcus faecalis* was identified as the cause of the bloodstream infection in 18% of patients [20]. Most ICU-related bloodstream infections in 60 hospitalized COVID-19 patients in Milan, Italy, were found to be caused by an *Enterococcus* species, in particular, *E. faecalis* or *E. faecium* [21].

COVID-19 and antibiotic-resistant HAIs

Data are emerging on antibiotic-resistant HAIs in COVID-19 patients. Among 4221 adult patients admitted with COVID-19 pneumonia in New York, USA, 472 patients (11.1%) produced a positive respiratory culture [22]. In these patients, the prevalence of

methicillin-resistant *S. aureus* (MRSA) in respiratory cultures rose from a low of 0.6% on day 3 to 5.7% at day 28 post admission. The authors deduced that the MRSA in severe COVID-19 cases was 'more likely to be a hospital-acquired or ventilator-associated complication than a community-acquired coinfection' [22]. *Staphylococcus aureus* has been reported as a frequently isolated organism from deep respiratory specimens taken from critically ill COVID-19 patients with ventilator-associated pneumonia [23].

With regard to New Delhi metallo-β-lactamase-producing carbapenem-resistant Enterobacterales (NDM-CRE), five cases in COVID-19 patients at the Albert Einstein College in Medicine, New York, USA were believed to have been hospital acquired [24]. Heightened prevalence of NDM-CRE colonization/infection was positively associated with length of hospital stay in a study of 331 COVID-19 patients in Pisa, Italy [25]. Only 3 COVID-19 patients were NDM-CRE-positive at admission; however, 40 COVID-19 patients acquired NDM-CRE during their hospitalization [25]. COVID-positive patients with NDM-CRE had a longer duration of hospital stay compared with NDM-CRE patients during the previous pre-COVID-19 year (40.2 versus 15.8 days, p 0.0001) [25]. Furthermore, the rate of NDM-CRE cases increased from 25.3 per 10 000 hospital days in the previous year to 75.9 during the COVID-19 study period in the same wards [25].

An outbreak of carbapenem-resistant *Acinetobacter baumannii* (CR-Ab) has also been reported in COVID-19 patients at a hospital in Israel [26]. Superinfections by CR-Ab of hospital ICU patients with COVID-19 have been reported in Spain, Mexico and Brazil [11,27,28]. Recent work at three hospitals in Bologna, Italy found that the overall incidence of CR-Ab infections increased from 5.1 per 10 000 ICU-patient-days in January–April 2019 to 26.4 per 10 000 ICU-patient-days in January–April 2020 [29]. This suggests that a worsening of CR-Ab incidence in ICU patients at these hospitals coincided with the advent of COVID-19. All of the CR-Ab isolates from one hospital clustered into a single monophyletic group based on whole-genome sequencing analysis, indicating transmission of CR-Ab to COVID-19 patients from a common source.

Whole-genome sequencing has also previously been used to decipher transmission networks of vancomycin-resistant enterococci (VRE) in hospitalized patients [30,31]. The spread of VRE to COVID-19 patients in a healthcare setting has been demonstrated through the application of whole-genome sequencing in work conducted at the University Hospital Münster in Germany [32]. The researchers detected clonally related isolates of VRE in both ICU patients and in environmental samples indicating a role for contaminated surfaces in VRE transmission to COVID-19 patients [32].

Multi-drug resistance and antimicrobial stewardship

Several bacterial HAI pathogens isolated from COVID-19 patients display resistance to multiple antibiotic classes. Of 32 critically ill COVID-19 patients admitted to an ICU in Naples, Italy, half of them developed a multi drug-resistant (MDR) infection during their ICU stay [33]. Ten patients were infected with a single MDR agent, but multiple MDR pathogens were identified in the remaining six patients. A shorter time to onset of MDR infection was associated with higher mortality in COVID-19 patients (p 0.042) [33].

Of 1617 hospital discharges in Rome, Italy over a 4-month period in each of the years 2017 to 2020, a reduction in total MDR bacterial infections was observed during the pandemic compared with the pre-pandemic years ($p < 0.05$) [34]. However, COVID-19 departments had a higher incidence of MDR infection than non-COVID-19 departments over the same period (29.2% versus 19.2%, $p < 0.05$). In particular, the incidence of extended-spectrum β-lactamase *K. pneumoniae* was significantly higher in COVID-19 departments ($p < 0.05$) [34]. The authors speculated that a number of factors may have contributed to this finding, including COVID-19 departments are commonly managed by infectious disease specialists who are more likely to request microbiological testing; intrinsic characteristics of COVID-19 patients including co-morbidities, impaired immunity and repeat hospitalization; and widespread use of broad-spectrum antibiotics in COVID-19 patients [34].

The latter potential contributory factor is currently a major focus of attention. A study of 36 COVID-19 ICUs across Lombardy, Italy, reported that 359 of 774 adult COVID-19 pneumonia patients had microbiologically confirmed HAIs during their ICU stay including ventilator-associated pneumonia (51%) and bloodstream infection (34%) [35]. The authors also observed that a high proportion of their patients (68%; 524/774), were already receiving a broad-spectrum antibiotic before ICU admission [35].

High empiric use of broad-spectrum antibiotics observed for COVID-19 patients is heightening concern that antibiotic overuse during the COVID-19 pandemic will exacerbate the problem of antimicrobial resistance in microorganisms of clinical significance in the future [36–38]. The review by Rawson et al. found that 72% of COVID-19 patients had received antibacterial therapy and that recorded agents tended to be broad-spectrum antibiotics prescribed empirically in both critical and non-critical settings [10]. A meta-analysis by Langford et al. of 3338 hospitalized and critical COVID-19 patients across 24 studies reported that a majority of COVID-19 patients received antibiotics (71.9%, 95% CI 56.1%–87.7%) [39]. This high level of antibiotic usage occurred despite the fact that the bacterial co-infection and secondary infection rates in these COVID-19 patients were much lower—3.5% (95% CI 0.4%–6.7%) and 14.3% (95% CI 9.6%–18.9%) of patients, respectively. They concluded that 'there is currently insufficient evidence to support widespread empirical use of antibiotics in most hospitalized patients'. The overall rate of bacterial infection was higher in critically ill COVID-19 patients (8.1%, 95% CI 2.3%–13.8%) than in hospitalized COVID-19 patients (5.9%, 95% CI 3.8%–8.0%). A disparity in bacterial infection levels has also been reported in another meta-analysis study whereby the overall proportion of COVID-19 patients in ICU who had laboratory-confirmed bacterial co-infection was 14% (95% CI 5%–26%, $n = 204$) compared with 4% of COVID-19 patients from mixed hospitalizations (95% CI 1%–9%, $n = 1979$) [40].

For patients with suspected bacterial infections, Langford et al. have recommended that antibiotic selection be based on local epidemiology and patient factors, with early discontinuation when there is no evidence of bacterial infection [39]. Elements of this antimicrobial stewardship approach are exhibited in current WHO guidelines for the clinical management of COVID-19, which advise against the use of antibiotic therapy or prophylaxis in patients with suspected or confirmed mild COVID-19, or in patients with suspected or confirmed moderate COVID-19 unless there is clinical suspicion of a bacterial infection [41]. Furthermore, WHO recommends that 'Antimicrobial therapy should be assessed daily for de-escalation' [41]. Similarly, the COVID-19 Rapid Guideline for managing COVID-19 from the National Institute for Health and Care Excellence in the UK, recommends against the use of antibiotics 'for preventing or treating COVID-19' and that antibiotics should only be used 'if there is strong clinical suspicion of additional bacterial infection' [42].

COVID-19 and infection prevention and control

In terms of infection prevention and control (IPC), a variety of measures were introduced during the pandemic to hinder nosocomial spread of COVID-19 between patients and healthcare workers (HCWs). This was necessitated by reports such as that

from University College London Hospitals NHS Trust that 66 of its 435 (15%) COVID-19 inpatient cases between 2 March and 12 April 2020 were definitely or probably hospital-acquired [43]. Rickman et al. identified patient-to-patient transmission as being involved in 55% of hospital-acquired COVID-19 cases, and shared-use facilities and equipment, or staff movement as potentially contributing to another 14% of cases [43]. Measures used to minimize nosocomial outbreaks of COVID-19 include expansion of testing to asymptomatic patients, residents and HCWs; physical distancing; and visitor restrictions [44]. In addition, there is increased use of personal protective equipment, for example surgical masks, gloves, face shields, fluid-resistant aprons and isolation gowns, as part of contact and droplet precautions by HCWs caring for patients with suspected or confirmed COVID-19 as currently recommended by national governments and WHO [45–48]. New research is also emerging on the type of gowns that best promote hand washing among HCWs [49].

As well as reducing COVID-19 spread in healthcare settings, there is interest in whether augmentation of hospital IPC measures during the COVID-19 pandemic has affected the prevalence of bacterial HAIs. A study from Los Angeles, USA, reported a decline in the MDR organism rate per 1000 patients between Q1 and Q2 2020 of 41% for MRSA, 80% for VRE and 20% for extended-spectrum β-lactamase [50]. The authors attributed the decrease in MDR organisms over this period to IPC measures adopted in response to COVID-19, in particular, increased usage of alcohol sanitizer and hand soap among HCWs [50].

Another study examined the incidence of HAIs and MDR organisms at a 1700-bed medical centre in Taiwan between January and May 2020, encompassing the COVID-19 outbreak period, and compared with the same time-frames from 2018 and 2019 [50]. Measurable increases in 75% alcohol and surgical mask use during the COVID-19 pandemic coincided with a significantly lower level of VRE incidence at the centre in 2020 relative to 2018 and 2019 [50]. The authors concluded that there was 'a collateral benefit of the COVID-19 prevention measures on the incidence density of MDRO' at their hospital [50].

The Singapore General Hospital campus introduced a comprehensive multimodal IPC bundle that included: improved segregation of patients with respiratory symptoms into respiratory surveillance wards; upgrading of mandatory personal protective equipment for HCWs in respiratory surveillance wards from surgical masks to N95 respirators, face-shields, gowns and gloves; housing of confirmed COVID-19 cases in dedicated airborne-infection-isolation-rooms; cleaning with 1:1000 hypochlorite-based disinfectant three times per day; and post-discharge UV-C disinfection of areas that housed COVID-19 patients [51]. As well as coinciding with a reduction in healthcare-associated respiratory viral infections at the hospital in August 2020 compared with January 2018, the IPC measures were accompanied by a decrease in healthcare facility onset MRSA infection [51].

It should be noted that increasing the number and stringency of IPC measures is not possible in all situations. In settings where hospitals have reached inpatient capacity, segregation of all patients with signs of COVID-19 disease into specialized wards may not be possible. There is also burnout risk among HCWs associated with a patient-to-nurse ratio above 2:1, higher workloads, deaths of COVID-19 patients and a shortage of personal protective equipment [52]. Such effects of intense COVID-19 caseloads on hospitals could potentially impact IPC practices. Supply shortages of personal protective equipment have been previously reported during the pandemic as well as the role they could play in nosocomial infection [53–55]. Therefore, while heightened IPC protocols may assist in further control of HAIs, an ongoing challenge will be balancing these measures with other immediate clinical demands.

Conclusions and future directions

It is becoming apparent from early studies that COVID-19 patients are at a low but significant risk of acquiring an HAI following admission. This risk increases markedly with severity of COVID-19 disease and duration of hospitalization. Many of the bacterial HAIs detected in COVID-19 patients exhibit antibiotic non-susceptibility including multidrug resistance. Studies comparing pre- and mid-pandemic periods have reported a higher incidence of some HAIs at specific hospitals since the advent of COVID-19. It has been proposed that underlying factors may include the high empiric use of broad-spectrum antibiotics documented in COVID-19 patients. Conversely, an intensification of IPC measures to prevent nosocomial transmission of COVID-19 has been linked to reduced incidence of some bacterial HAIs at certain sites. Further research is required to validate these findings and provide a cost–benefit evidence base for maintenance of intensified IPC measures beyond the COVID-19 pandemic for augmented control of HAIs. Although beyond the scope of this review, there is also evidence for the occurrence of viral and fungal co-infections in COVID-19 patients [56–60]. Ultimately, it is hoped that valuable lessons can be drawn from the COVID-19 pandemic in terms of improving infection control and antimicrobial stewardship practices in health care to lower the burden of HAIs and antibiotic resistance in the future.

Transparency declaration

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