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

Understanding the role of bacterial and fungal infection in COVID-19

Timothy M. Rawson [1, 2, *], Richard C. Wilson [1, 2], Alison Holmes [1, 2]

[1)] National Institute for Health Research, Health Protection Research Unit in Healthcare Associated Infections and Antimicrobial Resistance, Imperial College London, Hammersmith Campus, Du Cane Road, London, W12 0NN, United Kingdom
[2)] Centre for Antimicrobial Optimization (CAMO), Imperial College London, Hammersmith Campus, Du Cane Road, London, W12 0NN, United Kingdom

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The novel coronavirus disease (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has placed an unprecedented strain on healthcare systems. An emerging concern is the potential impact of the novel coronavirus SARS-CoV-2 pandemic on antimicrobial resistance (AMR) [1,2].

Early literature reported low rates of bacterial and fungal infection in hospitalized COVID-19 patients but high use of empirical broad-spectrum antimicrobials [3–5]. In hospitals, the difficulty in clinically differentiating COVID-19 and its progression from bacterial and fungal infection provides a significant challenge to clinicians and antimicrobial stewardship [6]. High-quality evidence to support decision-making on bacterial and fungal infection in COVID-19 is limited. Clinical uncertainty is likely to drive unnecessary antimicrobial prescribing in COVID-19 patients both on and during admission, potentially increasing the selection of drug-resistant infections [7].

In this issue of *Clinical Microbiology and Infection*, Garcia-Vidal and colleagues report their experience of co-infection and superinfection in hospitalized patients with COVID-19 [8]. Of 989 patients with COVID-19 admitted to a hospital in Barcelona, Spain, 31/989 (3%) presented with community-acquired co-infections. The majority of these were respiratory bacterial infections with *Streptococcus pneumoniae* and *Staphylococcus aureus* pneumonia [8]. Hospital-acquired infection was diagnosed in 43/989 patients (4%), with 25/44 (57%) occurring in critical care. Ventilator-associated pneumonia, hospital-acquired pneumonia, and bacteraemia were common infections amongst that 4%, with usual nosocomial organisms predominating. These included *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella* spp., and *Staphylococcus aureus* [8]. Coagulase-negative staphylococci were the most common organisms causing documented bloodstream infection (7/16; 44%). Fungal co-infection was identified in 7/989 patients (0.7%). Three patients were diagnosed with *Aspergillus fumigatus* tracheobronchitis and four patients with *Candida albicans* bloodstream infection ($n = 2$), urinary tract infection ($n = 1$), and intra-abdominal infection ($n = 1$) [8].

Garcia-Vidal and colleagues conclude that bacterial and fungal co-infection and superinfection was low in their cohort of COVID-19 patients. This was despite many of their patients receiving immunosuppressive therapy. Critical care admission was associated with more than half the diagnosed hospital-acquired infections [8].

Low observed rates of bacterial and fungal infection in COVID-19 patients have also been reported from other countries, including the UK. Hughes and colleagues identified bacterial infection in 51/836 COVID-19 patients (6%) admitted to two London hospitals [9]. Secondary bacterial infection was uncommon in this cohort. Of 60 positive blood cultures, 39/60 (65%) were deemed to be contaminants, the majority of these being coagulase-negative staphylococci [9].

Whilst both studies report similar rates of bacterial and fungal infection in COVID-19 patients, their limitations must be considered. Variable and at times low rates of microbiological sampling were reported. For example, Garcia-Vidal and colleagues report a limited microbiological sampling being performed after the diagnosis of COVID-19. Hughes and colleagues report a significantly greater proportion of patients for whom blood culture was performed (77% versus 27%). A limited number of patients in both studies (13% and

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* Corresponding author: Timothy Miles Rawson, Health Protection Research Unit in Healthcare Associated Infections & Antimicrobial Resistance, Hammersmith Hospital, Du Cane Road, London W12 0NN, United Kingdom.
E-mail address: timothy.rawson07@imperial.ac.uk (T.M. Rawson).

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25%) underwent respiratory sampling. Furthermore, a high proportion of patients received empirical antimicrobial therapy. These factors could significantly impact the detection rate of infections in hospitalized patients with COVID-19, leading to underreporting. Generally, the retrospective design of current literature within this field must also acknowledge the inherent biases of these types of study, which may over- or under-estimate true infection rates. Many studies investigating infection fail to define the severity of the disease in the COVID-19 patients included. Furthermore, they often fail to differentiate those who develop infection in critical versus non-critical care [3]. This makes stratification of risk factors difficult to evaluate.

Based on prior respiratory viral pandemics with influenza, concerns were initially raised regarding the potential for high rates of bacterial and fungal co-infection, often associated with high mortality [10–12]. To date, in COVID-19 no evidence has emerged to support concerns regarding increased rates of co-infection with SARS-CoV-2. Whilst documented hospital-acquired infection in COVID-19 cases has been higher, these appear to be largely associated with critical care and to be common nosocomial infections rather than directly attributable to COVID-19. Similarly, in previous coronavirus pandemics and epidemics—such as SARS-1 and Middle-Eastern respiratory syndrome (MERS)—little evidence of bacterial and fungal infection has been reported [3].

A significant gap in our knowledge is whether bacterial and fungal infections in COVID-19 are directly attributable to SARS-CoV-2 or a consequence of factors such as managing high numbers of critically unwell patients, overstretched healthcare systems, and prolonged duration of mechanical ventilation/critical care admission. For example, lower respiratory tract infection with influenza is believed to be associated with a number of virulence factors that predispose the host to secondary infection with bacteria such as *Streptococcus pneumonia* [10,11]. However, in COVID-19 the relatively low rates of co-infection identified and their similar nature to community-acquired organisms suggests that these observations are more coincidental occurrences than attributable directly to SARS-CoV-2.

Similarly, for hospital-acquired infections in COVID-19 patients, a recurring observation is the predominance of bacterial and fungal infections occurring in critical care [13]. Ventilator-associated pneumonia appears to be a predominant hospital-acquired infection reported in the literature [4,13]. Invasive fungal infection has also been highlighted as a concern in critically unwell patients with COVID-19 [14]. Additionally, increased rates of contaminants in blood and line culture are commonly reported [9].

When considering ventilator-associated pneumonia and invasive fungal infections, few data are available to compare expected rates of infection in local departments to expected rates in non-COVID cohorts. Similarly, for reported contaminants in blood and line culture, there are no data describing whether these represent an expected increase in the number of contaminants per line days based on the expanded critical care capacity and sickness of patient cohorts being managed during this period. Any links between the presence of increased contaminants and true infections—such as candidaemia or true coagulase-negative staphylococcal bloodstream infection—have yet to be explored in depth.

The WHO currently recommends against the prescribing of antimicrobials in mild to moderate COVID-19 cases without clear indication of bacterial infection [15]. A broader evidence base to support these recommendations could support significant reductions in overall antimicrobial exposure given that the majority of COVID-19 cases fall into the mild to moderate category.

Future prospective cohort studies with defined and longitudinal microbiological sampling must be designed with these factors in mind. In particular, they must control for patient factors such as length of mechanical ventilation, use of immunosuppression, and line days. They must consider institutional factors such as the number of COVID-19 cases, staffing during the pandemic, and potential compromise in routine infection prevention measures. Controlling for these factors prospectively may provide greater insight into secondary infection in COVID-19 and may facilitate assessment of whether observed rates of infection differ from normal patterns of nosocomial infection. Greater understanding of the relationship between bacterial/fungal infection and COVID-19 will support the development of targeted antimicrobial stewardship interventions and a better understanding of the potential long-term impact on AMR. In COVID-19 patients meeting the WHO guidelines for avoidance of antimicrobial prescribing [15], randomized control trials exploring early empirical antimicrobial therapy versus no prescribing would provide robust data to demonstrate any impact on mortality and disease progression.

Whilst we await prospective data to support clinicians with decision-making, antimicrobial stewardship programmes should focus on utilization of available data and diagnostics to support optimal antimicrobial treatment decisions. An enhanced focus on infection prevention and control measures should be capitalized upon. The importance of good hand hygiene, aseptic techniques, surveillance of multidrug-resistant organisms, and isolation must be promoted as key interventions in reducing nosocomial infection.

The impact of COVID-19 on AMR must be carefully considered. Concerns regarding increased antimicrobial use in hospitals, overcrowding of hospitals, and reduction in opportunities to isolate patients with multidrug-resistant organisms may have a negative impact on AMR. However, this must be balanced against increased social distancing, a renewed focus on hand hygiene, and apparent reductions in community antimicrobial use that may have a positive impact on AMR [1]. Providing access to appropriate antimicrobial therapy for individuals who develop symptoms of bacterial infection that may be potentially misdiagnosed as COVID-19 leading to self-isolation must be a core focus for interventions.

Although determining the true impact of COVID-19 on AMR is challenging at present, it does provide an important opportunity to promote the consequences of infectious diseases on human health. There is currently an increased public focus on communicable disease, the importance of infection prevention including hand hygiene, and the inability of antibiotics to treat viral infections. This creates an opportunity to engage healthcare professionals and the public on the rising problem of AMR.

In conclusion, evidence so far suggests that detection of bacterial and fungal infection in COVID-19 is relatively low. Risk factors for nosocomial infection appear to be associated with critical care, especially mechanical ventilation and line use. Current data contrast with those of other respiratory viral pandemics, such as influenza, suggesting that SARS-CoV-2 may not have a significant impact on bacterial or fungal virulence. Reports of high rates of antimicrobial prescribing in secondary care mean that antimicrobial stewardship interventions must focus on improving the diagnosis of bacterial and fungal infections, reducing unnecessary use of antimicrobials in low-risk areas, and supporting access to therapy when required. Prospective studies are urgently required to provide greater insight into the risk factors and potential outcome of bacterial and fungal infection in COVID-19 and to support evidence-based recommendations. Although the true impact of COVID-19 on AMR is difficult to predict, the enhanced

focus on the consequences of infectious disease on human health should be capitalized upon to support the long-term AMR agenda.

Author contributions

TMR drafted the initial manuscript. RW and AH contributed significantly to revision of the manuscript and its finalization for submission.

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