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Multidrug Resistant Bacterial Co-Infections in Critically Ill Patients with COVID-19: A Review after Three Years of Pandemic

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Abstract

Secondary bacterial infections and co-infections frequently affect COVID-19 patients. However, bacterial co-infection rates increase in patients admitted in the Intensive Care Units (ICUs), and those diseases can be due to superinfections by Multidrug-Resistant (MDR) bacteria. Most of these infections are related to high-risk carbapenemase-producing clones and occasionally with resistance to new β-lactam-β-lactamase inhibitor combinations. This highlights the urgency to revise frequent and empiric prescription of broad-spectrum antibiotics in COVID-19 patients, with more attention to evidence-based studies and the need to maintain antimicrobial stewardship and infection control programs in pandemic crises. Additionally, the SARS-CoV-2 pandemic highlighted the challenge that an emerging pathogen provides in adapting prevention measures regarding both the risk of exposure to caregivers and the need to maintain quality of care.

Keywords: Secondary bacterial infections; COVID-19; Pandemic outbreak; Health Care; Bacteria

Abbreviations SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; COVID-19: Coronavirus Disease 2019; MDR: Multidrug-Resistant; MDRO: Multi-Drug Resistant Organism; HAI: Healthcare–Associated Infection; EU: European Union; EEA: European Economic Area; EARS-Net: European Antimicrobial Resistance Surveillance Network; ICU: Intensive Care Unit; ARDS: Acute Respiratory Distress Syndrome; MV: Mechanical Ventilation; CRBSI: Catheter-Related Bloodstream Infection; BSI: Bloodstream Infection; PPE: Personal Protective Equipment; DALY: Disability-Adjusted Life Year; DDD: Defined Daily Dose; VAP: Ventilator-Associated Pneumonia; ESCMID: European Society Clinical Microbiology and Infectious Diseases

Introduction

Healthcare–Associated Infections (HAIs) are a major public health burden [1]. HAIs are associated with more than 140,000 deaths worldwide each year [2]. From EARS-Net data collected between Jan 1, 2015, and Dec 31, 2015, Cassini, et al. [3,4] estimated that 671,689 cases of infections with selected antibiotic-resistant bacteria occurred in 2015 in the European Union (EU) and European Economic Area (EEA). These infections accounted for 33,110 attributable deaths and 874,541 DALYs. These estimates corresponded to an incidence of 131 infections per 100,000 populations and an attributable mortality of 6.44 deaths per 100,000 populations, causing 170 DALYs per 100,000 populations [3]. Prevalence surveys in the United States (US) suggest that 30% of HAIs occur in Intensive Care Units (ICUs) [5]. Moreover, HAIs prolong ICU and hospital stays, increase antibiotic consumption and inflate the costs of care. The occurrence of HAIs result from a complex interplay of pathogen factors, host factors, treatment factors, healthcare processes [6-8].

Literature Review

SARS-CoV-2 pandemic outbreak had an enormous impact on worldwide health, causing over 533 million confirmed cases and over 6.3 million deaths worldwide by 12 June 2022 (according to the WHO Coronavirus disease situation report), with up to 25% admitted to ICU and 80% of those requiring invasive Mechanical Ventilation (MV) [9,10].

Coronavirus Disease 2019 (COVID-19) considerably increased the incidence of VAP with a pooled estimated incidence of 45.4% [11]. COVID-19 related Acute Respiratory Distress Syndrome (ARDS) is associated with more profound hypoxia than ARDS from other origins resulting in longer duration of mechanical ventilation and more application of prone positioning, factors affecting the risk of HAIs and CRBSI [12-15]. COVID-19 amplifies the risk of HAI due to multiple factors: less rigorous use of standard prevention strategies, disease and therapy-associated immune impairment, prolonged duration of mechanical ventilation and sedation, more frequent prone ventilation and higher risk for pulmonary infarction with associated superinfection. ICU overcrowding the use of suboptimal trained healthcare personnel may have reduced compliance with HAI prevention programs [16-19].

Health crisis due to COVID-19 required healthcare facilities reorganization with the increase of ICUs beds together human and material resources. COVID-ICUs were characterized by the extensive use of Personal Protective Equipment (PPE), by an increased workload and by the presence of healthcare professionals deployed

from other areas [20]. All these reasons may have reduced the overall compliance with HAIs prevention programs, independently from COVID-19 infection [21].

Critically ill patients with COVID-19 are more susceptible to develop secondary infections, compared to non-COVID-19 patients admitted in the same period [22], with an infection rate that varies among studies, from 13% [23] to 46% [10]. Despite this, the effect of the pandemic on non-COVID-19 patients, and specifically on the onset of HAIs in this category of patients, is still poorly explored [24,25]. Patients admitted to Intensive Care Units (ICUs) are exposed to a greater risk of secondary infectious complications due to multi-drug-resistant microorganisms [26] that require the use of next-generation antimicrobials with a serious impact on antimicrobial stewardship programs and on the appropriateness of the use of antibiotics. Difficulty in ruling out secondary bacterial infection remains a dangerous and common complication in hospitalized patients, particularly with COVID-19 disease. A study aimed to evaluate the frequency of microorganisms isolated in different samples obtained from hospitalized ICU patients with or without COVID-19 positive patients in the pre-pandemic period and during the initial period of the pandemic showed that microorganisms more frequently isolates in the ICU-COVID ward were *Acinetobacter baumannii, Enterococcus faecium, E. faecalis, S. epidermidis, Stenotrophomonas maltophilia, Candida albicans and C. tropicalis* [26]. MDR-*A. baumannii* BSI remain an important ICU-acquired infection [27].

Furthermore, it was highlighted that an increase in the number of positive microbial analyzes and cultures was accompanied by an increase in the consumption of antimicrobial drugs, calculated as expenditure per drug and as DDD/100 days of bed [26].

Discussion

Inappropriate use of broad spectrum antibiotics in hospitalized patients is a major cause of antibiotic resistance [28]. ICUs are the setting in which MDRO isolation is most often seen due to the high consumption of antibiotics. Antibiotic resistance was even more emerging in COVID-19 patients admitted to ICUs often treated empirically without a certain confirmation from microbiological analyses.

Therefore, based on existing microbiological data, antibiotics in COVID-19 patients with secondary bacterial infections should be used appropriately by adjusting the initial empirical therapy as soon as the confirmed result of the microbiological analyzes is available. There are few data on the etiology or spectrum of secondary infections in COVID-19 patients.

A multicenter observational study reports that over a third of patients admitted to ICU for COVID-19 pneumonia developed at least one episode of severe bacterial infection. Interestingly, the study showed that the peak incidence of the infection was recorded between 8 and 14 days after admission to the ICU. The most frequent infections reported were VAP, bacteremia, and urinary tract infection. Unlike VAP alone, bacteremia was associated with worse outcome. There was a tendency towards a shift from Gram-positive to Gram-negative species as the length of ICU stay increased [29].

The possibility of diagnosing with certainty a secondary infection in COVID-19 positive patients with the isolation of the etiological agents could lead to proper treatment with the appropriate use of antibiotics, reducing the adverse effects due to the excessive and inappropriate use of antibiotics.

It has been shown that serum lactate levels >2 mmol/l at time of infection, *Acinetobacter baumannii* colonization, development of a BSI, and steroid therapy were the most important factors associated with MDR-AB infection in COVID-19 patients and resulted as important determinants of 30-day mortality also in all study population. Moreover, COVID-19 etiology, white blood cells count>11,000 mm^3, serum lactate levels >2 mmol/l, infection at time of ICU admission, *Acinetobacter baumannii* colonization, and steroid therapy during hospitalization were associated with higher risk of BSI development [27].

Abu-Rub and coworkers published recently a systematic review to evaluate the prevalence of antibiotic prescribing for patients admitted to ICU settings with confirmed SARS-CoV-2 infection, involving 16 different countries, including China, USA, Italy, and France, where the pandemic was more evident. The review demonstrated the significant global healthcare hospital prescribing of antimicrobials, as a temporary pattern associated with the serious pandemic. Since the first wave of this pandemic, multiple regional protocols included empirical antimicrobials such as ceftriaxone and azithromycin, leading to a substantial increase in antimicrobial consumption at various healthcare settings. This review described that most of the studies (69.2%) demonstrated the spectrum of prescribing antibiotics for patients admitted to ICUs with COVID-19 lacking any clear evidence of bacterial co-infection [30]. Recent ESCMID COVID-19 guidelines on drug treatment and clinical management showed that the use of azithromycin had no effect on 28-day mortality, risk of disease progression or need for supplemented oxygen with strong recommendation against use of azithromycin for COVID-19. Similarly, it showed insufficient evidence to make an appropriate recommendation on empiric antibiotic treatment and antifungal prophylaxis for the prevention of pulmonary aspergillosis [31,32].

Conclusion

In conclusion, based on the literature review, we identified an urgent need of high quality, controlled, perspective studies addressing the issue of antibiotic resistance in COVID-19 settings, with special focus on COVID-19 ICUs that may be new drivers of AMR selection. Novel approaches to stewardship must adapt to COVID-19 settings and local epidemiology and, most importantly, a new focus on adherence to infection prevention and control measures is urgently needed. Antimicrobial resistance will continue to pose a substantial threat to healthcare systems for the years to come.

It would be important to perform multicenter studies in which antibiotic therapy can be based on the evidence of microbiological analyses. Knowledge of local epidmiology in one's hospital or better in each department is always of great importance to set up an initial empirical antimicrobial therapy which must be adapted as soon as possible on the basis of the results of microbiological analyses.

Author Contributions

For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used “Conceptualization, R.C.; methodology, R.C., B.Q, C.A.V and D.S..; investigation, S.S., D.C. and R.P.; data curation, D.S.; writing—original draft preparation, R.C.;

writing—review and editing, R.C. All authors have read and agreed to the published version of the manuscript".

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Conflicts of Interest

The authors declare no conflict of interest

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