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Review

Bacterial Co-Infection In Covid-19 Patient: A Systematic Review

Dini Agustina[1*], Bagus Hermansyah[2], Yehuda Tri Nugroho Supranoto[3]

[1] Department of Microbiology, Faculty of Medicine, Universitas Jember, Indonesia
[2] Department of Parasitology, Faculty of Medicine, Universitas Jember, Indonesia
[3] Faculty of Medicine, Universitas Jember, Indonesia

* Corresponding author: dini_agustina@unej.ac.id

Abstract: Coronavirus disease 2019 (COVID-19) is an infection caused by SARS-CoV-2. The course of the disease often has more severe clinical symptoms if accompanied by a bacterial infection, known as co-infection or secondary bacterial infection. Apart from having a clinical impact, it also causes the use of more antibiotics, increasing antibiotic resistance. To overcome this, we need data showing the most frequent etiologic agents of bacterial coinfection in patients with COVID-19. This systematic review aims to determine the etiologic agent of the most common secondary bacterial infection in COVID-19. This systematic review is presented based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) criteria. The electronic databases used for the literature search are; PubMed, ScienceDirect, CochraneLibrary, and Google Scholar. Keywords used in the electronic database are described using Boolean operators as follows: (("SARS-CoV-2 Infection" OR "Coronavirus Disease 19" OR "COVID-19") AND ("Secondary Bacterial Infection" OR "Bacterial Co-infection")). All literature was selected taking into account the eligibility criteria and reference standards. The protocol of this review has been registered in International Prospective Register of Systematic Reviews (PROSPERO) with the registration number is CRD42022331998. Eleven studies were included in the qualitative synthesis. The results of the study showed that Gram-negative bacteria were the most common etiologic agents. These bacteria include Escherichia coli, Klebsiella pneumonia, and Pseudomonas aeruginosa. This systematic review provides valuable evidence of the most frequent etiologic agents of secondary bacterial infection in COVID-19 patients.

Keywords: COVID-19; SARS-CoV-2; Secondary Bacterial Infection; Bacterial Co-Infection; Systematic Review

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1. Introduction

The coronavirus disease 2019 (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that was first identified in December 2019 in Wuhan, China, and is currently circulating throughout the world [1], [2]. Viral infections predispose patients to secondary bacterial infections, which often have a more severe clinical course. Some reports showed that adult COVID-19 patients with increased inflammatory markers, worse lymphopenia and cardiovascular comorbidities are more frequently to have clinically diagnosed with bacterial co-infection [3], [4]. These patients tend to have severe clinical manifestations and have high probability to develop multiple organ failure [5], [6]. Bacterial co-pathogens are commonly identified in viral respiratory tract infections including COVID-19 and are an important cause of morbidity and mortality, necessitating timely diagnosis and antibacterial therapy [7]. The prevalence of secondary infections could be as high as 50% among non-survivors [8]. The mechanisms underlying post-viral bacterial infections are complex and include multifactorial processes mediated by interactions between viruses, bacteria, and the host immune system [9], [10], [11]. Actually COVID-19 is quite rare complicated by bacterial co-infection in the time when patients are admitted to the hospital, but commonly, bacterial co-infection occurs in the time patients stay in the hospital [12]. The median of COVID-19 patients

hospital length of stay is 7-14 days and the risk of a hospital-associated pneumonia increases significantly the longer of the hospital length of stay. Bacterial co-infection with COVID-19 is relatively common as a complication that is found in 10% hospitalized adult patients [13], [14]. More than 90% of hospital-associated pneumonia are induced by mechanical ventilator which is one of the most intervention used in the treatment of severe COVID-19 [15], [16], [17]. Not only bacterial, but also fungal ventilator-associated pneumonia in critically ill COVID-19 patients is commonly occurs and a serious problem in the current pandemic that requires certain strategic treatment to keep it under control [18], [19], [20].

Given a rise in morbidity and mortality in patients with bacterial co-infetion with COVID-19, it is crucial to treat COVID-19 patients responsibly in terms of using antibiotics in order to minimize the negative impact of overuse [21], [22]. Using more antibiotics to save COVID-19 patients from bacterial co-infections needs consideration because this could affect the prevalence of antibiotic-resistant bacteria globally. The presence of antibiotic-resistant bacteria could potentially explain the high rates of bacterial co-infections in critically ill patients despite extensive antibiotic treatments [23]. To tackle this serious issue, research in secondary bacterial or bacterial co-infections is urgently needed to investigate the mechanism of this occurrence and to find new antimicrobial compounds to eradicate multidrug-resistant bacteria in patients with COVID-19. This systematic review aimed to investigate the most frequent etiologic agent of secondary bacterial infection in COVID-19.

2. Materials and Methods

2.1 Research design

This review followed the guidelines provided by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The protocol of this review has been registered in International Prospective Register of Systematic Reviews (PROSPERO) with the registration number is CRD42022331998.

2.2 Search methods

A literature search process was carried out with multiple electronic databases, such as PubMed, ScienceDirect, CochraneLibrary, and Google Scholar. Time restrictions applied for this study. Only studies published between 2019 and 2020 were included. The keywords used in electronic databases were described using Boolean operator as follows: ((“SARS-CoV-2 Infection” OR “Coronavirus Disease 19” OR “COVID-19”) AND (“Secondary Bacterial Infection” OR “Bacterial Co-Infection”)). All the studies from these databases were exported and stored in the authors’ library in Rayyan QCRI and Ms. Excel 2016 (Microsoft, USA).

2.3 Inclusion and exclusion criteria

Type of Studies

This systematic review included a case report, case series, and research article only. Review and conference abstracts were excluded. Articles with full-text unavailability, non-English, and irrelevant topics were also excluded.

Samples

All of the secondary bacterial infection or bacterial co-infection samples in patients with COVID-19 were included in this review.

Reference Standard

The reference standard was a laboratory observational research or reports performed by qualified professionals by evaluating the causative agents of a secondary bacterial infection or bacterial co-infection in patients with COVID-19.

2.4 Screening of articles

After duplicates removal, retrieved articles were screened based on their titles and abstracts by three independent reviewers (DA, BH, and YTNS)

2.5 Data extraction

The following data were extracted from the included studies: first author, year, region, study design, setting, sample size, subject characteristics, clinical manifestation, types of specimen, specimen inspection method, infection type, species, and gram staining result.

2.6 Quality appraisal

Potentially eligible full-text articles were thoroughly assessed using the eligibility criteria described above. Any emerging discrepancies were resolved by consensus among the review team. The study selection process is illustrated in the PRISMA flow chart (Figure 1).

2.7 Data analysis

A preliminary search obtained 3031 journals. As many as 255 duplicate journals were removed. Then, the authors read the title and abstract of the remaining 2776 journals for preliminary screening. Authors include only clinical research articles and reported events of secondary or bacterial co-infection studies of humans with laboratory-confirmed SARS-CoV-2 infection (COVID-19). Literature did not report data on bacterial infection are excluded by the authors. Finally, full texts were retrieved for 39 papers, and 11 studies were included for qualitative analysis according to our eligibility criteria. Our study selection process was presented in the PRISMA flowchart (Figure 1).

3. Results

Characteristics of Included Studies

The specimen inspection in this study uses several methods including; culture, PCR, and Rapid antigen test (urine), and one article did not specify which method was used. Same as with the examination method, the specimens used also more than one, namely, throat swabs, endotracheal aspiration, CSF, urine, blood, bronchoalveolar lavage fluid, nasopharyngeal and oral swabs. Bacterial infection in patients with COVID-19 is predominantly co-infection rather than secondary infection or superinfection. This is in most settings is of hospitals.

Bacterial Pathogens

There were 38 bacteria identified in these studies. As many as 27(71%) were Gram-negative, 10(26%) Gram-positive and acid-fast bacilli were 1(3%). The most reported were Klebsiella pneumonia (K. pneumoniae), Pseudomonas aeruginosa (P. aeruginosa), and Staphylococcus aureus (S. aureus) in 7 patients each, 6 patients with Escherichia coli (E. coli), and Streptococcus pneumonia (S. pneumoniae) in 5 patients. Some species can cause extrapulmonary manifestation, like bacteremia secondary to a urinary tract infection by E. coli6 and Neisseria meningitides (N. meningitides) causes meningococcal meningitis [24]. Besides gram-negative and positive bacteria found one acid-fast bacillus in these studies was called Mycobacterium tuberculosis (M. tuberculosis).

Of 11 studies included, one of them found co-infection bacterial which is included in bacterial zoonosis. A rare zoonotic infection in an immunocompromised patient called Bordetella bronchiseptica. These bacteria are usually obtained from the respiratory tract of animals such as dogs, cats, rabbits, and various rodents. Isolation is frequent in immunocompromised patients with pneumonia and/or bacteremia [25].

Type of Respiratory Infection

Respiratory tract infections in these studies were confirmed as bacterial, viral, and fungal infections, but the highest number were bacterial infections, with characteristics such as co-infection, superinfection, and secondary infection. Meanwhile, based on clinical and epidemiology, bacterial infection was reported as a community, ventilator, and hospital-acquired infection.

The most common respiratory pathogen isolated in community-acquired coinfection were K. pneumoniae, S. pneumoniae, S. aureus, Haemophilus influenza (H. influenza), and Moraxella catarrhalis (M. catarrhalis). Ventilator-associated pneumonia was related

to Enterobacter cloacae (E. cloacae), S. aureus, P. aeruginosa, Stenotrophomonas maltophilia (S. maltophilia), K. pneumoniae, dan Serratia marcescens (S. marcescens). The last, reported bacteria of hospital-acquired pneumonia (HAP) were Acinetobacter baumannii (A. baumannii), K. pneumoniae, Escherichia coli (E. coli), Burkholderia cepacia, P. aeruginosa, S. aureus and S. maltophilia [26], [27], [28].

Usage of antibiotics

As in all bacterial infections, antibiotics will be considered, including co-infection with COVID-19. So, some studies in these papers used antibiotics for a patient with COVID-19. The initial administration of broad-spectrum antibiotics was empirically based, both as prophylaxis or therapy. One of the studies on the hospital setting reported that the C-reactive protein level, oxygen requirement, and positive cultures were associated with prolonged duration of therapy. The median duration of antimicrobial therapy was seven days [29].

The antimicrobial resistance rates of the major isolated bacteria are generally high. Some multidrug-resistant nosocomial pathogens were Methicillin-Resistance Staphylococcus aureus (MRSA), Methicilin-Resistance Coagulase-negative staphylococci, carbapenem-resistant A. baumannii (CRAB) and carbapenem-resistant K. pneumoniae (CRKP), an extended-spectrum beta-lactamase (ESBL)-producing E. coli [30].

4. Discussion

The sources of organisms that caused a secondary bacterial infection in COVID-19 may be microbiota of the respiratory tract carried by the patients before they developed COVID-19, especially for those with underlying diseases such as chronic kidney disease or solid organ transplant recipients [27], [31]. Based on the extracted data, the mortality of secondary bacterial infection not only causes respiratory failure but also extrapulmonary manifestation [32]. At least there were 4 cases of extrapulmonary secondary bacterial infection in COVID-19 which are, urinary tract infections caused by Escherichia coli [26], meningococcal meningitis caused by Neisseria meningitides [24], rare zoonotic septicemia caused by Bordetella bronchiseptica [25], and Extrapulmonary tuberculosis caused by Mycobacterium tuberculosis [33]. The role of bacterial co-infection with SARS-CoV-2 remains speculative and poorly characterized although presumptive treatment of suspected bacterial infection is commonplace and antibiotic use is widespread [24], [34]. The use of antibiotics is a widespread way can increase the potencies of multidrug resistant-bacteria infection in a patient with COVID-19 [35], [36], [37], [38].

In our findings, the majority of bacteria that caused a secondary bacterial infection in patients with COVID-19 are Gram-negative strains. It correlates with the research findings from [39], [40], [41], [42] that all bacteria growth from sputum samples from patients with COVID-19 were Gram-negative bacilli. Gram-negative bacilli are more typically associated with oropharyngeal colonization than community-acquired pneumonia. Other research results also said that the proportion of pathogens detected increased with the duration of ICU stay, consisting largely of Gram-negative bacteria, particularly Klebsiella pneumonia and Escherichia coli, a high rate of Gram-negative infection acquired during ICU stay. This results showed that Gram-negative bacteria dominating the nosocomial infection including secondary bacterial infection in COVID-19.

5. Implication and limitations

Due to the lack of controlled clinical trials on the use of empiric antibacterial agents in COVID-19 patients, the current recommendations are based upon the extrapolation of data from other viral pneumonia. Empiric use of third-generation cephalosporin combined enzyme inhibitors for secondary bacterial infections has been recommended in severe patients. But the broader application of antibacterial agents may further lead to changes in etiology and antimicrobial resistance. The secondary bacterial infections in patients hospitalized with COVID-19 should be treated according to further

microbiological data. Currently, there is no report nor research data on the pathogenic spectrum of secondary bacterial infections in COVID-19. Since this systematic review explain the most frequent etiological agent are Gram-negative bacteria as the main cause of secondary bacterial infection, this review can be baseline research guidance to make a proper combination in antibiotic treatments.

6. Conclusion

In conclusion, a secondary bacterial infection is one of the main complications in patients hospitalized with COVID-1t leads to high mortality rates. This systematic review's main finding was Gram-negative bacteria are the main etiologic agent of this infection. These key findings act as a baseline for future research to uncover the most empirical antimicrobial agents since the antimicrobial resistance rates of the major isolated bacteria in COVID-19 are generally high.

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Author contribution : DA drafts the concept; YTNS prepares the research design; DA, BH, and YTNS conducted data collection, data analysis, and data interpretation; DA is in charge of data collection in the field; DA, BH, and TYNS prepare papers; and DA and BH revised the final paper for publication

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