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SYNOPSIS

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Bacterial Infections in Hospitalized COVID-19 Patients – What We Know So Far

Introduction

PHO is actively monitoring, reviewing and assessing relevant information related to Coronavirus Disease 2019 (COVID-19). "What We Know So Far" documents are intended to provide a rapid review of the evidence related to a specific aspect or emerging issue related to COVID-19.

The development of these documents includes a systematic search of the published literature as well as scientific grey literature (e.g., ProMED, CIDRAP, Johns Hopkins Situation Reports) and media reports, where appropriate. Relevant results are reviewed and data extracted for synthesis. All "What We Know So Far" documents are reviewed by PHO subject-matter experts before posting.

As the COVID-19 outbreak continues to evolve and the scientific evidence rapidly expands, the information provided in these documents is only current as of the date of posting.

Key Points

- A meta-analysis of 24 cohort studies of 3338 hospitalized patients with COVID-19 found that bacterial co-infection (estimated on presentation) was identified in 3.5% of patients (95% Confidence Interval (CI)0.4 to 6.7%) and secondary bacterial infection (after presentation) was identified in 14.3% of patients (95%CI 9.6 to 18.9%). The overall proportion of COVID-19 patients with bacterial infection was 6.9% (95%CI 4.3 to 9.5%).
- Bacterial infection was more common in critically-ill patients (8.1%, 95%CI 2.3 to 13.8%).
- The majority of patients with COVID-19 received antibiotics (71.9%, 95%CI 56.1 to 87.7%) which tend to be broad-spectrum agents. However, as bacterial co-infection is relatively infrequent in hospitalized patients with COVID-19, the majority of these patients may not require empiric antibiotics, particularly those without critical illness.

Background

Bacterial co-infection in patients with acute viral respiratory infections such as influenza has been associated with more severe illness, greater use of healthcare resources and increased risk of death.[1] The rate of co-infection in severe influenza has been reported to be up to 20-30%.[2-3] The proportion and characteristics of individuals infected with SARS-CoV-2 and bacterial co-infection are not currently well understood and this knowledge gap has important implications. While antibiotics are not effective for treatment of COVID-19, current guidelines recommend the use of empiric antibiotics for patients with severe COVID-19 disease based on data extrapolated from influenza pandemics.[4-5] Understanding the proportion of COVID-19 patients with bacterial infections, and the causative pathogens, is essential to

help mitigate antibiotic overuse and minimize unintended consequences such as bacterial resistance.[6] A rapid systematic review was performed to determine the prevalence of bacterial infection in patients with COVID-19 and to identify the most common co-infecting respiratory organisms in these individuals.[7]

Methods

A systematic search of MEDLINE, OVID Epub and EMBASE databases for English language literature from Jan 1 2019 to April 16 2020. See Langford et al. for a detailed description of methodology.[7]

- Studies were screened in duplicate and included if they evaluated patients with confirmed COVID-19 and reported the prevalence of acute bacterial infection in these patients. Editorials, letters, and case series of <10 patients were excluded. Studies that did not report data on bacterial infection or exclusively reported data on chronic co-infection or non-bacterial pathogens were also excluded.
- Patient characteristics, bacterial infection and antibiotic prescribing data were extracted.
- The main outcome was the overall proportion of COVID-19 patients with bacterial infection, defined as an acute infection including either co-infection on presentation or secondary infection emerging during the course of illness or hospital stay.
- In secondary analyses this was further stratified by co-infection and secondary infection. Studies were categorized as reporting co-infection unless they explicitly stated that they were capturing secondary infection data. Bacterial infection rates were also stratified by patient population as an estimate of severity of COVID-19 illness (all hospitalized patients, critically-ill patients admitted to intensive care unit).
- Data were pooled using random-effects meta-analysis. Sensitivity analyses were performed based on whether bacterial diagnostic method was reported; whether bacterial infection was explicitly subcategorized (i.e. co-infection vs. secondary infection), and with removal of studies with potentially overlapping patient cohorts.

Results

Of 1308 publications that were screened, 24 studies (3506 patients) were included in the final analysis.

- All were retrospective cohort studies (n=24) and most took place in Asia (n=21). Studies were carried out between December 25, 2019 and March 31, 2020.
- Most studies included only adult patients (18/24, 75%). The median proportion of female patients was 45.8% (IQR 37.6 to 50.0%). Among studies reporting specific patient characteristics, a median of 6.4% (IQR 3.9 to 9.7%, n=11 studies) were smokers, 3.2% (IQR 0.4 to 5.5%, n=18 studies) had chronic obstructive pulmonary disease, 9.7% (IQR 4.9 to 19.2%, n=18 studies) had cardiovascular disease, and 11.5% (IQR 7.7% to 18.3%, n=20 studies) had diabetes.
- Nineteen studies reported on hospitalized patients in general and 5 reported on critically-ill patients only.
- Seven studies exclusively reported secondary infections, the other 17 studies were categorized as reporting co-infections.
- Bacteriological testing method was reported as respiratory with or without blood culture in 10 studies, respiratory nucleic acid amplification in 2 studies, and not specified in 12 studies.

Bacterial Infection in Patients Hospitalized with COVID-19

Of 3506 patients, 3338 were evaluated for bacterial infection of which 281 had a reported bacterial infection.

- In the meta-analysis:
  - Bacterial co-infection was identified in 3.5% of patients (95%CI 0.4 to 6.7%) and secondary infection was identified in 14.3% of patients (95%CI 9.6 to 18.9%).
  - When pooling all included studies, the proportion of COVID-19 patients with bacterial infection was 6.9% (95%CI 4.3 to 9.5%)
  - In a sensitivity analysis that stratified studies explicitly and not explicitly differentiating between co-infection and secondary infection, the estimates of overall bacterial infection, co-infection or secondary infection did not significantly differ with original estimates.
- Specific species of bacterial co-pathogens were reported in 11/24 (45.8%) studies, representing < 14% of all patients with reported bacterial infections. The most commonly reported organisms were *Mycoplasma* species (n=11 patients, n=3 reported as *M. pneumoniae*), *Haemophilus influenzae* (n=5 patients) and *Pseudomonas aeruginosa* (n=5 patients).

Bacterial Infection Stratified by Patient Population

- Bacterial infection was 5.9% in all hospitalized patients (95%CI 3.8 to 8.0%) and 8.1% in critically-ill patients (95%CI 2.3 to 13.8).

Use of Antibiotics and Antimicrobial Stewardship Implications

- The majority of patients with COVID-19 received antibiotics (71.9%, 95%CI 56.1 to 87.7%) which tended to be broad-spectrum agents. Fluoroquinolones and 3rd generation cephalosporins together accounted for 74% of antibiotics prescribed.
- However, as the overall proportion of reported bacterial infections was 6.9% in patients hospitalized with COVID-19, the majority of this patient population may not require empiric antibiotics.
- Given that antibiotics are associated with significant unintended consequences including adverse events, toxicity, resistance, and *Clostridioides difficile* infections, antimicrobial stewardship strategies to limit unnecessary antibiotic use continue to be relevant for patients with COVID-19 and have been highlighted in the literature:[6]
  - Consider empiric antibiotic therapy only in patients who are critically-ill or in those with suspected or documented bacterial infection.
  - Obtain respiratory cultures before initiation of antibiotic therapy and select empiric therapy based on local epidemiology.
  - Re-assess the need for continuing antibiotics on the basis of imaging, laboratory, biomarkers, and culture results and consider early discontinuation if no evidence of bacterial infection.
  - Where continuation of antibiotic treatment is deemed necessary, evaluate the appropriateness of therapy including route (i.e. intravenous to oral stepdown) and duration of therapy.

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