Secondary infections in critically ill patients with COVID-19: a retrospective single-center study

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Abstract

Background

Patients infected with COVID-19 admitted to the intensive care unit may have a higher incidence of developing secondary infections. These infections can further deteriorate the hospital course and increase mortality. Therefore, the objectives of this study were to investigate the incidence, associated risk factors, outcomes, and pathogens associated with secondary bacterial infections in critically ill patients with COVID-19.

Methods

All adult COVID-19 patients admitted to the Intensive Care Unit requiring mechanical ventilation from 1st October 2020 until 31st December 2021 were screened for inclusion in the study. A total of 86 patients were screened, and 65 who met the inclusion criteria were prospectively entered into a customized electronic database. The database was then retrospectively analyzed to investigate secondary bacterial infections. 41.54% acquired at least one of the studied secondary bacterial infections during their ICU stay.

Results

The most common secondary infection (59.26%) seen was hospital-acquired pneumonia followed by acquired bacteremia of unknown origin (25.92%), and catheter-related sepsis (14.81%). Diabetes mellitus (P = < 0.001), cumulative dose of corticosteroids (P = 0.001), and older age (P = < 0.001) were associated with an increased risk of secondary bacterial infection. The most commonly isolated pathogen in patients with secondary pneumonia was Acinetobacter baumannii. Staphylococcus aureus was the most common organism associated with a bloodstream infection or catheter-related sepsis.

Conclusion

Incidence of secondary bacterial/fungal infections was high in critically ill patients with COVID-19 and was associated with a longer duration of admission to the hospital and ICU and higher mortality. Age, a history of diabetes mellitus, and the administration of corticosteroids were associated with an increased risk of secondary bacterial infection.

Background

In the last two decades alone, humans have experienced six major pandemics caused by infectious agents - SARS-CoV-1 (2002–2004); Influenza A H1N1 (2009–2010); Middle East Respiratory Syndrome (MERS) CoV (2012–2020); Ebola virus (2013–2016); Zika virus (2015–2016); SARS-CoV-2 (2019-
present), four of which (SARS-CoV-1, Influenza A H1N1, MERS-CoV, SARS-CoV-2) directly affects the respiratory tract.\textsuperscript{[1]} As of 20th May 2022, the ongoing COVID-19 pandemic has affected more than 500 million patients worldwide. Clinical manifestation of SARS-CoV-2 varies in the general population: from asymptomatic carrier state to severe pneumonia and respiratory distress requiring intensive care.\textsuperscript{[2]}

It has been proposed that SARS-CoV-2 can directly damage the lung epithelium, which indirectly results in a ‘cytokine storm’, eventually leading to acute respiratory distress syndrome and multi-organ failure necessitating corticosteroid use.\textsuperscript{[3, 4]} Patients with COVID-19 admitted to the intensive care are at high risk of developing secondary bacterial infections during their ICU stay, which may be a result of immunosuppressive drugs, and comorbid conditions like diabetes or virus-mediated immunosuppression.\textsuperscript{[5, 6]} This may lead to a prolonged hospital stay and increased mortality\textsuperscript{[7]}.

The data on secondary infections in critically ill COVID-19 patients is surprisingly scarce. A report from the early phase of the pandemic indicated that the incidence of secondary infection is much lower than in previous pandemics.\textsuperscript{[8]} However, most reports subsequently have shown a high incidence (up to 51\%) of secondary bacterial infections with wide variations in reported incidences.\textsuperscript{[9]} The most common secondary bacterial infection in critically ill patients with COVID-19 was secondary pneumonia, including ventilator-assisted lower respiratory tract infection (VA-LRTI).\textsuperscript{[9]} A recent multicenter study from Europe described a cumulative incidence of VA-LRTI of 50.5\% in patients with COVID-19 admitted to the ICU\textsuperscript{[10]}. Bloodstream infections are the second major group of secondary infections reported in critically ill COVID-19 patients, with incidences as high as 50\% in some reports\textsuperscript{[11, 12]}.

It is crucial to identify the most common bacterial agents and possible risk factors associated with secondary bacterial infections leading to secondary infections in critically ill patients with COVID-19, which may help in recognizing the infection earlier and guide newer prevention strategies and empiric antibiotic therapy for secondary infections. Therefore, the objectives of this study were to investigate the incidence, associated risk factors, outcomes, and identify the most common groups of pathogens with secondary bacterial infections in critically ill patients with SARS-CoV-2.

**Methods**

Patients and study design

This single-center, investigator-initiated, longitudinal, retrospective observational cohort study was performed at the Intensive Care Unit of the Jawaharlal Nehru Medical College, Aligarh, after approval by the Institutional Ethical Committee. This study is reported according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement.\textsuperscript{[13]}

All adult patients, with RT-PCR-confirmed SARS-CoV-2 infection and requiring mechanical ventilation for acute respiratory distress syndrome admitted to the ICU of the Jawaharlal Nehru Medical College and Hospital, Aligarh from 1st October 2020 until 31st December 2021, were eligible for inclusion in the study.
All demographic, clinical, and biological follow-up data was anonymized and collected from electronic case report forms. Laboratory confirmation of COVID-19 infection was defined as positive polymerase chain reaction (PCR) assays of nasopharyngeal swab samples or bronchoalveolar lavage. This resulted in the screening of 86 COVID-19 patients admitted to the ICU. (Fig. 1)

All patients were treated according to the COVID protocol issued by the ICMR-COVID-19 National Task Force, Ministry of Health & Family Welfare, Government of India, based on the latest insights on COVID-19 at that time[14]. Data from all patients were anonymized and entered into a custom database that included medical history, clinical parameters, length of stay, treatment, and laboratory results. The following outcome measures were investigated: mortality in the ICU, and total length of stay (LOS) in the ICU and the hospital. Following completion of the database, the data were retrospectively reviewed.

Diagnosis of secondary bacterial infection

The diagnosis of a secondary bacterial infection was based on clinical symptoms combined with laboratory analyses. Secondary pneumonia was defined as positive cultures of a respiratory specimen obtained by bronchoscopy-guided bronchoalveolar lavage (BAL) or bronchial aspirate (BRASP). Bloodstream infections (BSIs) were defined as a single positive blood culture for a likely pathogen or two or more positive blood cultures for common skin colonizers (i.e., coagulase-negative staphylococci, diphtheroids, Bacillus spp., Propionibacterium spp., viridans group streptococci), without a concomitant microbiologically documented lower respiratory tract infection due to the same pathogen. Catheter-related bloodstream infection (CRBSI) was defined as having at least one positive blood culture obtained from a peripheral vein, with clinical manifestations of infection (i.e., fever, chills, and/or hypotension), no apparent source for the BSI, and the same organism (species and antibiogram) isolated from the catheter segment and peripheral blood culture. All positive cultures were further analyzed to identify the responsible pathogen.

Statistical analyses

Continuous data are shown as mean ± standard deviation (SD), and categorical data are presented as frequencies and percentages. For quantitative variables, the KS test was used, and if significant, a non-parametric Mann Whitney U test was applied otherwise, the comparisons were performed with the Student’s t-test. For categorical variables, the Chi-Square test was used with a Fisher’s exact test correction for expected values < 5. Statistical Package for Social Sciences (IBM® SPSS®) version 26 was used for analysis.

Univariable logistic regression was used to investigate the association of possible risk factors (age, gender, hypertension, smoking, obesity, diabetes mellitus, cardiac disease, pulmonary disease, cumulative dose of corticosteroids, and other immunosuppressives administered in the ICU) and the acquisition of a secondary bacterial infection. A P-value < 0.05 was considered statistically significant.
A STROBE flow chart depicting the exclusion and inclusion of patients is shown in Fig. 1. In total, 21 patients were excluded. This resulted in data of 65 patients for final analysis. The clinical characteristics are summarized in Table 1.

**Table 1**
Clinical characteristics of the patients with COVID-19 in the Intensive Care Unit:

<table>
<thead>
<tr>
<th></th>
<th>No secondary infection (N = 38)</th>
<th>≥ 1 Secondary infection (N = 27)</th>
<th>p-value</th>
<th>Statistical test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>38.13 ± 13.22</td>
<td>69.09 ± 8.45</td>
<td>&lt; 0.001</td>
<td>Mann Whitney U test</td>
</tr>
<tr>
<td>Gender (Males)</td>
<td>57.89% (22)</td>
<td>74.07% (20)</td>
<td>0.18</td>
<td>Chi-sqaure test</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>31.58% (12)</td>
<td>48.15% (13)</td>
<td>0.17</td>
<td>Chi-squaure test</td>
</tr>
<tr>
<td>Smoking</td>
<td>10.53% (4)</td>
<td>37.04% (7)</td>
<td>0.10</td>
<td>Chi-squaure test</td>
</tr>
<tr>
<td>Obesity</td>
<td>10.53% (4)</td>
<td>22.22% (6)</td>
<td>0.19</td>
<td>Chi-squaure test</td>
</tr>
<tr>
<td>DM</td>
<td>18.42% (7)</td>
<td>62.96% (17)</td>
<td>&lt; 0.001</td>
<td>Chi-squaure test</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>2.63% (1)</td>
<td>14.81% (4)</td>
<td>0.15</td>
<td>Fisher exact test</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>2.63% (1)</td>
<td>18.52% (5)</td>
<td>0.07</td>
<td>Fisher exact test</td>
</tr>
<tr>
<td>Rheumatological disease</td>
<td>2.63% (1)</td>
<td>7.41% (2)</td>
<td>0.57</td>
<td>Fisher exact test</td>
</tr>
<tr>
<td>Cumulative dose of corticosteroids* (mg)</td>
<td>349.23 ± 197.02</td>
<td>515.55 ± 160.70</td>
<td>0.001</td>
<td>Student's t-test</td>
</tr>
</tbody>
</table>

Length of stay and outcome

|                                   |                     |                                  |         |                  |
|                                   | LOS Hospital (days) | 5.82 ± 3.32                     | 8.50 ± 2.68 | 0.001 | Student's t-test |
|                                   | LOS ICU (days)     | 2.31 ± 1.42                     | 6.22 ± 1.99 | < 0.001 | Student's t-test |
|                                   | Mortality          | 10/38                           | 20/27   | < 0.001 | Student's t-test |

*Dose in milligram equivalent of prednisone
Antimicrobial Susceptibility

Susceptibility profiles against fifteen antimicrobials agents are listed in Table 2. The highest resistance was seen in K. pneumoniae isolates against nearly all antimicrobials agents. All A. baumannii isolates demonstrated resistance to most antimicrobials except Colistin, Polymyxin B, Tigecycline, and Minocycline. The S. aureus isolates were resistant to Azithromycin, Clindamycin, and Doxycycline and sensitive to Cefoxitin, Amoxicillin-Clavulanate, Levofloxacin, and Amikacin.

Table 2
Antimicrobial susceptibility of the common organisms isolated from the respiratory tract.

<table>
<thead>
<tr>
<th></th>
<th>Acinetobacter baumannii</th>
<th>Klebsisella</th>
<th>Pseudomonas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin/clavulanate</td>
<td>R</td>
<td>R</td>
<td>S/I</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>R</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>Amikacin</td>
<td>R</td>
<td>R</td>
<td>S/R</td>
</tr>
<tr>
<td>Ceftriazone</td>
<td>R</td>
<td>R</td>
<td>-</td>
</tr>
<tr>
<td>Cefoperazone/Sulbactam</td>
<td>R/I</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>R</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>Cefixime</td>
<td>R</td>
<td>R</td>
<td>-</td>
</tr>
<tr>
<td>Cefepime</td>
<td>-</td>
<td>-</td>
<td>S</td>
</tr>
<tr>
<td>Meropenem</td>
<td>R</td>
<td>R</td>
<td>-</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>R</td>
<td>R</td>
<td>-</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Piperacillin/Tazobactum</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Colistin</td>
<td>S</td>
<td>S/I</td>
<td>S</td>
</tr>
<tr>
<td>Polymyxin B</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>S/I</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Minocycline</td>
<td>S/I</td>
<td>R</td>
<td>R</td>
</tr>
</tbody>
</table>

Discussion

In this study, secondary infections were seen in 41.54% of critically ill patients infected with SARS-CoV-2 admitted to the intensive care. Secondary pneumonia (59.26%) was the most frequently diagnosed secondary infection, followed by bloodstream infection of unknown origin (25.92%) and catheter-related
sepsis (14.81%). The outcome analysis of this study suggests that patients with secondary infections are likely to be admitted to the ICU and hospital for a longer duration and have higher mortality.

The high incidence of secondary pneumonia observed in this study aligns with several studies done on patients with SARS-CoV-2. Most lower respiratory tract viral infections, such as influenza, Middle East Respiratory Syndrome coronavirus, and SARS-CoV-1 have also been associated with a high incidence of secondary bacterial pneumonia. The incidence of secondary pneumonia observed in critically ill patients with SARS-CoV-2 is more than double that seen in patients not infected with SARS-CoV-2 (13.5–23%). The most common pathogens identified in secondary pneumonia were the Gram-negative bacilli - Acinetobacter baumannii (N = 7), followed by Klebsiella pneumoniae (N = 4), Pseudomonas spp (N = 2), and Gram-positive cocci – Staphylococcus aureus (N = 2). This observation is consistent with other studies in the literature.

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The incidence of bloodstream infection and catheter-related sepsis observed in this study was comparable with other reported incidences of secondary infection in critically ill patients not infected with SARS-CoV-2. The most common pathogens identified from blood cultures or catheter cultures in this study were Staphylococcus aureus (N = 5), followed by the gram-negative organisms, E. coli (N = 3), and Klebsiella pneumoniae (N = 3). This is in line with the fact that Staphylococcus aureus is frequent a commensal on the skin and often responsible for bloodstream infections and catheter-related infections.

Two statistically significant risk factor – diabetes mellitus (p < 0.001) and cumulative dose of corticosteroids (p = 0.001) were identified contributing to secondary infections. Diabetes mellitus is known to alter immune response to infections and increase the susceptibility and severity of infectious diseases. Studies have also indicated that diabetic patients with COVID-19 admitted to an ICU also have higher reported mortality than non-diabetic patients. Cumulative dose of corticosteroids administered in the ICU was another risk factor identified, which is logical, as corticosteroids are a known suppressor of the immune system. However, because of the retrospective study design with limited information on timing, conclusions on the temporal association between corticosteroid therapy and
secondary infection is difficult to establish. It was observed that the median age of the patients secondary infections was higher than older than those without (mean 69 ± 8.45 years versus 38 ± 13.22 years). However, this could be the result of confounding as the younger patients had fewer comorbid conditions than the older patients.

Limitations

The retrospective single-center design and the small cohort size limit the generalizability of our findings. To confirm the described possible associations, further research is necessary.

Conclusion

This study confirms that the incidence of secondary bacterial infections in critically ill patients infected with SARS-CoV-2 is very high. More specifically, these patients are at the highest risk of developing secondary pneumonia, followed by bloodstream infection of unknown origin and catheter-related sepsis. A history of diabetes mellitus and higher dosing of corticosteroids were associated with an increased risk of secondary bacterial infection.

Declarations

Ethics approval and consent to participate:

The study was approved by the Jawaharlal Nehru Medical College Institutional Ethics Committee. It was performed per institutional ethics guidelines per the tenets of the Declaration of Helsinki.

Consent for publication:

Not Applicable.

Competing interests:

The authors declare that they have no competing interests.

Funding:

None

Authors’ contributions:

OLH contributed to proposal and implementation of the research, data collection, data analysis, draft preparation, editing, and submission of the manuscript. MS contributed towards the IRB approval process, editing of the manuscript; WH was involved in data collection, data analysis and editing of the manuscript.
Acknowledgments:

None

References


Figure 1

STROBE flow chart depicting the exclusion and inclusion of patients.