



Methicillin-resistant *Staphylococcus aureus* lung infection in coronavirus disease 2019: how common?

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Purpose of review

Some patients with coronavirus disease 2019 (COVID-19) may develop pulmonary bacterial coinfection or superinfection, that could unfavorably impact their prognosis.

Recent findings

The exact burden of methicillin-resistant *Staphylococcus aureus* (MRSA) lung infection in peculiar populations such as patients with COVID-19 remains somewhat elusive, possibly because of wide heterogeneity in methods and endpoints across studies.

Summary

There was important heterogeneity in the retrieved literature on the epidemiology of MRSA lung infection in patients with COVID-19, both when considering all other bacteria as the denominator (relative prevalence ranging from 2% to 29%) and when considering only *S. aureus* as the denominator (relative prevalence ranging from 11% to 65%). Overall, MRSA is among the most frequent causative agents of pulmonary infection in patients with COVID-19. Improving our ability to rapidly reach etiological diagnosis of bacterial lung infection in COVID-19 patients remains fundamental if we are to improve the rates of appropriate antibiotic therapy in patients with COVID-19 and concomitant/superimposed MRSA infection, at the same time avoiding antibiotic overuse in line with antimicrobial stewardship principles.

Keywords

coronavirus disease 2019, lung, methicillin-resistant *Staphylococcus aureus*, SARS-CoV-2, *Staphylococcus aureus*

INTRODUCTION

Some patients with coronavirus disease 2019 (COVID-19) may develop pulmonary bacterial coinfection or superinfection, that could unfavorably impact their prognosis [1,2,3^{*}]. Overall, the prevalence of bacterial pneumonia in hospitalized patients with COVID-19 has been reported to reach 7%, with the risk of community-acquired bacterial pneumonia (CABP) being lower than that of developing hospital-acquired bacterial pneumonia (HABP), especially ventilator-associated bacterial pneumonia (VABP) [4–6].

Although not the most frequent, *Staphylococcus aureus* is a well recognized cause of bacterial pneumonia in general [7–10]. In particular, a non-negligible risk of developing *S. aureus* pulmonary infection has been reported in patients with severe influenza, with also a high crude mortality of >50% [11]. Another factor associated with increased mortality in patients with *S. aureus* pneumonia in previous studies was the presence of methicillin resistance [7,9,12–14]. Overall, methicillin-resistant

S. aureus (MRSA) has been reported to cause up to 9% and 23% of CABP and HABP, respectively. However, the exact burden of MRSA lung infection in peculiar populations such as patients with COVID-19 remains somewhat elusive, possibly because of wide heterogeneity in methods and endpoints across studies (with many of them focused on other aspects and reporting only marginally on the epidemiology of causative agents of bacterial co-infection or superinfection), as well as in the approach to etiological diagnosis (e.g., different frequencies of collection of deep respiratory specimens for culture

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KEY POINTS

- Some patients with coronavirus disease 2019 (COVID-19) may develop pulmonary methicillin-resistant *Staphylococcus aureus* (MRSA) coinfection or superinfection, that could unfavorably impact their prognosis.
- There is important heterogeneity in the literature on the epidemiology of MRSA lung infection in patients with COVID-19, both when considering all other bacteria as the denominator (relative prevalence ranging from 2% to 29%) and when considering only *S. aureus* as the denominator (relative prevalence ranging from 11% to 65%).
- Overall, MRSA remains among the most frequent causative agents of pulmonary infection in patients with COVID-19.
- Improving our ability to rapidly reach etiological diagnosis of MRSA lung infection in COVID-19 patients remains fundamental to optimize its therapy in line with antimicrobial stewardship principles.

or molecular testing in COVID-19 patients with VABP) [1,2,4,15–22].

In this narrative review, we discuss existing observational studies reporting either selectively or marginally on the epidemiology of *S. aureus* and MRSA pulmonary co-infection or superinfection in patients with COVID-19, in the attempt to provide a global overview of its prevalence in this population.

METHODS

In September 2021, we performed a literature search through the PubMed online database, using various combinations of the keywords ‘COVID-19’, ‘aureus’, and ‘MRSA’. Then, title and abstract screening were performed in order to check consistency with the selected topic, followed by full text review of selected papers and pertinent references. Eventually, observational studies reporting on the epidemiology of *S. aureus* and/or MRSA pneumonia in patients with COVID-19 were included in the present review and narratively discussed.

HETEROGENEITY OF CURRENT LITERATURE AND MORTALITY OF MRSA LUNG INFECTION

The characteristics of available studies reporting on the epidemiology of *S. aureus* and MRSA lung infection in patients with COVID-19 are summarized in Table 1. As shown in the table, there is certainly heterogeneity in the study populations

(hospitalized patients with COVID-19 vs. only critically ill patients with COVID-19), but the two most important factors hampering a clear delineation of the prevalence of MRSA pneumonia in COVID-19 patients are the different denominators exploited for assessing absolute/relative prevalence of lung infection (e.g., whole study population, patients who underwent microbiological investigation, patients with positive cultures, presence/lack of clear definition for lung infection) and the level of details of information (e.g., antimicrobial susceptibility of *S. aureus* isolates). Keeping in mind these crucial limitations, the results of available studies providing information on MRSA lung infection epidemiology are discussed in the following paragraphs. With regard to mortality of *S. aureus* and MRSA lung infections in patients with COVID-19 (also reported in the last column of Table 1, whenever the information was available with sufficient detail), it should be acknowledged that we focused on studies from which we could extrapolate prevalence data, and thus this narrative review was not primarily aimed to delineate mortality of MRSA lung infection. A recent scoping review was conversely aimed to synthesize available evidence on clinical outcomes in patients with COVID-19 and *S. aureus* coinfection, reporting a crude mortality of 65% in 115 coinfecting patients (mostly bacteremia, followed by pneumonia) from 28 studies, also including case reports [23]. Mortality was not stratified in detail for methicillin susceptibility [23].

STUDIES REPORTING ON THE EPIDEMIOLOGY OF *Staphylococcus aureus* AND/OR METHICILLIN-RESISTANT *Staphylococcus aureus* LUNG INFECTION IN PATIENTS WITH CORONAVIRUS DISEASE 2019

As anticipated in the previous paragraph, a general stratification can be made based on the study population: hospitalized patients with COVID-19; only critically ill patients with COVID-19. In addition, another important division in the retrieved literature, which we considered for the organization of the following paragraphs, was: studies reporting on the epidemiology of *S. aureus* lung infection (without providing information on *S. aureus* antimicrobial susceptibility); studies reporting information on the epidemiology of MRSA lung infection.

Epidemiology of *S. aureus* lung infection in patients with coronavirus disease 2019

With regard to studies reporting on the epidemiology of *S. aureus* lung infection in general, Silva and

Table 1. Epidemiology of *S. aureus* and MRSA pneumonia in hospitalized patients with COVID-19 in observational studies

First author, year [ref] type of study	Type of population	Definitions and samples collected	Epidemiology of <i>S. aureus</i> /MRSA pneumonia	Comments on <i>S. aureus</i> impact on mortality
Baskaran, 2021 [40] • Retrospective • Multicenter	<ul style="list-style-type: none"> Critically ill COVID-19 patients in ICU 	<ul style="list-style-type: none"> No formal definition for bacterial pneumonia Microbiological tests were performed as per standard testing protocols within NHS laboratories at local participating center Tracheal aspirate, sputum culture and BALF culture performed 	<ul style="list-style-type: none"> 254 critically ill patients with COVID-19; • Patients with co-colonization/co-infection at ICU admission or within 48 h after ICU admission (11/254, 4.3%) Patients with <i>S. aureus</i> cocolonization/co-infection at ICU admission or within 48 h after ICU admission (4/254, 1.5%) Patients with MRSA cocolonization/co-infection at ICU admission or within 48 h after ICU admission (1/254, 0.4%) Patients with cocolonization/co-infection beyond 48 h after ICU admission (77/254, 30.3%) <i>S. aureus</i> cocolonization/co-infection reported as proportion on the total number of bacteria detected (between 5% and 10% both 3–7 days and >7 days after ICU admission) 	<ul style="list-style-type: none"> No specific details reported on mortality of <i>S. aureus</i> pneumonia
Grasselli, 2021 [2] • Retrospective • Multicenter	<ul style="list-style-type: none"> Critically ill COVID-19 patients in ICU 	<ul style="list-style-type: none"> VABP was defined according to international guidelines [51] Local microbiological cultures and molecular tests performed as per local standard procedures 	<ul style="list-style-type: none"> 759 critically ill patients with COVID-19 The incidence rate of VABP was of 26 episodes per 1 000 ICU days, for a total of 389 VABP episodes <i>S. aureus</i> caused 28% of VAP (110/389) 55% of <i>S. aureus</i> isolates from VAP episodes were MRSA (61/110) 	<ul style="list-style-type: none"> No specific details reported on mortality of <i>S. aureus</i> pneumonia
Silva, 2021 [24] • Retrospective • Single center	<ul style="list-style-type: none"> Hospitalized patients with severe COVID-19 	<ul style="list-style-type: none"> CDC/NHSN definition for hospital-acquired infections [52] Sputum, tracheal aspirate, BALF culture 	<ul style="list-style-type: none"> 212 hospitalized patients with severe COVID-19 Patients with positive tracheal aspirate bacterial culture (53/212, 25%) 15% of positive tracheal aspirate culture yielded <i>S. aureus</i> (8/53), but no information on <i>S. aureus</i> antimicrobial susceptibility 	<ul style="list-style-type: none"> Patients with any type of <i>S. aureus</i> infection had an odds ratio for mortality of 10.72 [95% CI from 1.35 to 85.32]
Yang, 2021 [29] • Retrospective • Single center	<ul style="list-style-type: none"> Critically ill COVID-19 patients in ICU 	<ul style="list-style-type: none"> No formal definition for bacterial pneumonia Sputum and BAL culture; sputum and nasopharyngeal PCR 	<ul style="list-style-type: none"> 20 critically ill patients with COVID-19 58% positive respiratory samples (56/96) <i>S. aureus</i>-positive respiratory samples were 7% with conventional culture and 31% with PCR No information on <i>S. aureus</i> antimicrobial susceptibility 	<ul style="list-style-type: none"> No specific details reported on mortality of <i>S. aureus</i> pneumonia
Giacobbe, 2021 [16] • Retrospective • Multicenter	<ul style="list-style-type: none"> Critically ill COVID-19 patients in ICU 	<ul style="list-style-type: none"> VABP was defined as new or changing chest X-ray infiltrate/s occurring more than 48 h after initiation of invasive mechanical ventilation, plus both of the following: (i) new onset of fever (≥ 38 °C)/hypothermia (≤ 35 °C) and/or leukocytosis (≥ 10 000 cells/μl)/leukopenia (≤ 4500 cells/μl) > 15% immature neutrophils; (ii) new onset of suctioned respiratory secretions and/or need for acute ventilator support system changes to enhance oxygenation 	<ul style="list-style-type: none"> 586 critically ill patients with COVID-19 29% developed VABP (171/586) 77 cases of VABP had positive BALF culture Patients with <i>S. aureus</i> VABP were 18/77 (23%) Patients with MRSA VABP were 8/77 (10%) 	<ul style="list-style-type: none"> No specific details reported on mortality of <i>S. aureus</i> pneumonia
Elabbadi, 2021 [41] • Retrospective • Single center	<ul style="list-style-type: none"> Critically ill COVID-19 patients in ICU 	<ul style="list-style-type: none"> Respiratory specimens obtained within 48h from ICU admission. Quantitative cultures were performed on usual media for sputum, tracheal aspirate, plugged telescoping catheter, or BALF, considering the respective positivity thresholds: 10^6 CFU/ml, 10^5 CFU/ml, 10^3 CFU/ml, and 10^4 CFU/ml 	<ul style="list-style-type: none"> 101 critically ill patients with COVID-19 20/101 patients had positive respiratory culture (20%) 11/20 of them yielded <i>S. aureus</i> (55%) 2/11 of them yielded MRSA (18%) 	<ul style="list-style-type: none"> No specific details reported on mortality of <i>S. aureus</i> pneumonia
Cusumano, 2020 [31] • Retrospective • Multicenter	<ul style="list-style-type: none"> Hospitalized patients with COVID-19 who developed <i>S. aureus</i> bacteremia 	<ul style="list-style-type: none"> COVID-19 patients with <i>S. aureus</i> bacteremia within 24h from SARS-CoV-2 detection Pneumonia defined as possible source of <i>S. aureus</i> bacteremia according to infectious disease provider and verified by two independent physicians 	<ul style="list-style-type: none"> 42 hospitalized patients with COVID-19 and <i>S. aureus</i> bacteremia 8/42 patients (19%) had pneumonia as identified source of <i>S. aureus</i> bacteremia, of which only 2 cases were community-acquired 19/42 bacteremia were caused by MRSA (45%), no information of how many cases of pneumonia were caused by MRSA 	<ul style="list-style-type: none"> No specific details reported on mortality of <i>S. aureus</i> pneumonia

Table 1 (Continued)

First author, year [ref] type of study	Type of population	Definitions and samples collected	Epidemiology of <i>S. aureus</i> /MRSA pneumonia	Comments on <i>S. aureus</i> impact on mortality
Hoshiyama, 2020 [53] • Retrospective • Single center	• Hospitalized patients with mild/asymptomatic COVID-19	• No formal definition for bacterial pneumonia • Sputum and throat swab cultures	• 7 hospitalized patients with COVID-19 • 4/7 patients had positive bacterial cultures (57%) • 2/4 of them had cultures positive for <i>S. aureus</i> (50%) • No information on <i>S. aureus</i> antimicrobial susceptibility	• All patients discharged (mild/symptomatic infections)
Sharov, 2020 [25] • Not specified if retrospective or prospective • Multicenter	• Both outpatients and inpatients with COVID-19	• Pneumonia diagnosed by medical personnel based on radiology • Respiratory swabs, sputum, and BALF cultures	• 1204 patients with COVID-19 • 433/1204 patients reported to have bacterial pneumonia (36%) • 24/433 had <i>S. aureus</i> CAPB (6%), with no information on antimicrobial susceptibility • 63/433 had <i>S. aureus</i> HABP (15%), with no information on antimicrobial susceptibility	• No specific details reported on mortality of <i>S. aureus</i> pneumonia
García-Vidal, 2021 [1] • Retrospective • Single center	• Hospitalized patients with COVID-19	• Bacterial respiratory infection diagnosed in case of one or more positive cultures of respiratory pathogens obtained from blood, pleural fluids, good-quality sputum (>25 polymorphonuclear leukocytes and <25 epithelial cells), and/or BALF	• 989 hospitalized patients with COVID-19 • <i>S. aureus</i> lung coinfection at COVID-19 diagnosis observed in 6/21 early coinfections (29%), with no information on <i>S. aureus</i> antimicrobial susceptibility • <i>S. aureus</i> isolated in 1/4 HABP (25%), no information on <i>S. aureus</i> antimicrobial susceptibility • <i>S. aureus</i> isolated in 4/11 VABP (36%), no information on <i>S. aureus</i> antimicrobial susceptibility	• No specific details reported on mortality of <i>S. aureus</i> pneumonia
Raychaudhuri, 2021 [54] • Prospective • Single center	• Hospitalized pediatric patients with moderate to severe COVID-19	• No formal definition for bacterial pneumonia • Respiratory tract cultures and PCR from nasopharyngeal swab or respiratory tract specimens were performed within the first 48 h of hospital admission	• 286 pediatric patients with COVID-19 • Bacterial coinfection was diagnosed in 43/286 patients (15%) • 4/43 had MRSA infection (9%), of which three bacteremia and one pneumonia	• No specific details reported on mortality of <i>S. aureus</i> pneumonia
Bhargava, 2021 [55] • Retrospective • Single center	• Hospitalized patients with COVID-19	• No formal definition for bacterial pneumonia	• 290 hospitalized patients with COVID-19 • 11/290 patients had MRSA bacteremia (4%) of which seven cases were community-acquired and four nosocomial • Overall, pneumonia was identified as source of bacteremia in 35% of community acquired BSI and in 69% of nosocomial BSI	• No specific details reported on mortality of <i>S. aureus</i> pneumonia
Senack, 2021 [26] • Retrospective • Multicenter	• Hospitalized patients with COVID-19	• No formal definition for bacterial pneumonia • Standard culture and molecular tests on respiratory specimens • Endotracheal aspirates, sputum, and BALF samples	• 29 802 hospitalized patients with COVID-19 • Coinfections diagnosed in 392/29802 patients (1%) • 8/392 had <i>S. aureus</i> isolated from lower respiratory tract specimens (2%) • No information on <i>S. aureus</i> susceptibility	• No specific details reported on mortality of <i>S. aureus</i> pneumonia
Son, 2021 [32] • Retrospective • Multicenter	• Hospitalized patients with COVID-19	• No formal definition for bacterial pneumonia • Local standard identification methods, not further specified	• 152 hospitalized patients with COVID-19 • 47/152 patients with cultures available (31%) • 3/47 of them had positive MRSA respiratory culture (6%)	• In-hospital mortality was 75% in patients with sputum culture positive for MRSA (3/4)
De Pascale, 2021 [56] • Prospective • Single center	• Critically ill COVID-19 patients with VABP in ICU	• VABP defined according to international guidelines [56]	• 92 critically ill patients with COVID-19 and VABP • 40/92 had <i>S. aureus</i> VABP (43%) • 65% of <i>S. aureus</i> isolates were MRSA	• In-hospital mortality in critically ill COVID-19 patients with <i>S. aureus</i> VABP was 35% (14/40)
Mahmoudi, 2020 [33] • Cross-sectional • Single center	• Hospitalized patients with COVID-19 and positive bacterial cultures	• No formal definition for bacterial pneumonia • Blood cultures and endotracheal aspirates performed	• 43 hospitalized patients with COVID-19 and positive bacterial cultures • 14% had MRSA positive cultures (6/43, of which 2 were cultures of respiratory specimens)	• No specific details reported on mortality of <i>S. aureus</i> pneumonia

Table 1 (Continued)

First author, year [ref] type of study	Type of population	Definitions and samples collected	Epidemiology of <i>S. aureus</i> /MRSA pneumonia	Comments on <i>S. aureus</i> impact on mortality
Ramadan, 2020 [57] • Prospective • Multicenter	• Hospitalized patients with COVID-19	• No formal definition for bacterial pneumonia • Presence of $\geq 10^5$ CFU/ml in sputum or endotracheal aspirates indicated bacterial co-infection • Resistance detected with molecular methods	• 260 hospitalized patients with COVID-19 • 28/260 were diagnosed with bacterial/fungal coinfection (11%) • 5/28 had MRSA coinfection (18%) • Site of infection not reported	• No specific details reported on mortality of <i>S. aureus</i> pneumonia
Li, 2020 [34] • Retrospective • Single center	• Hospitalized patients with COVID-19	• Pneumonia diagnosed clinically plus identification of bacteria from sputum, endotracheal aspirate, BALF, or blood	• 1495 hospitalized patients with COVID-19 • 102/1495 were diagnosed with secondary bacterial infection (7%) • 3% had MRSA isolates (3/102, of which 2 MRSA from respiratory specimens)	• No specific details reported on mortality of <i>S. aureus</i> pneumonia
Sharifpour, 2020 [42] • Not specified if retrospective or prospective • Single center	• Critically ill COVID-19 patients in ICU	• VABP was identified based on the following criteria: a new and persistent (>48 h) or progressive infiltrate on the chest radiograph plus 2 of the following minor criteria: fever >38°C or hypothermia <36°C, blood leukocyte count of > 10,000 cells/ml or <5000 cells/ml, purulent tracheal secretions, or decrease in the PaO ₂ /FiO ₂ • In cases with clinically suspected pneumonia, VAP diagnosis was established with a positive quantitative culture (cutoff point $\geq 10^6$ CFU/ml)	• 19 critically ill patients with COVID-19, all diagnosed with secondary bacterial infection • 2/19 patients had <i>S. aureus</i> VABP (11%) • 1/19 patients had MRSA VABP (5%)	• Death was reported in the patient with MRSA VABP, while the patient with MRSA VABP survived
Punjabi, 2020 [35] • Retrospective • Single center	• Hospitalized patients with COVID-19	• MRSA infection prevalence primary endpoint of the study • No formal definition for bacterial pneumonia • Included patients with respiratory cultures obtained within 3, 7, 14, or 28 days of admission	• 4221 hospitalized patients with COVID-19 • 472/4221 had respiratory cultures available (11%) • The prevalence of MRSA in respiratory cultures ranged from a 0.6% on day 3, to 5.7% on day 28, cumulatively	• No specific details reported on mortality of <i>S. aureus</i> pneumonia
Gerver, 2021 [27] • Retrospective • Multicenter	• Hospitalized patients with COVID-19	• Co-infection and secondary infection defined as a laboratory-confirmed blood or respiratory culture of a clinically relevant bacterial/fungal organisms • Lower respiratory samples defined as bronchial, lung, alveolar lavage, pleura, bronchoalveolar lavage, sputum, endotracheal aspirate, and pleural fluid	• 223 413 hospitalized patients with COVID-19 • 2279/223 413 were diagnosed with bacterial infection (1%) • 209/2279 had <i>S. aureus</i> co-infection (9%) • 301/2279 had <i>S. aureus</i> secondary infection (13%) • Of 510 patients with <i>S. aureus</i> infection, 262 had respiratory infections (51%) • No information on <i>S. aureus</i> susceptibility	• No specific details reported on mortality of <i>S. aureus</i> pneumonia
Risa, 2021 [19] • Retrospective • Multicenter	• Critically ill COVID-19 patients in ICU	• VABP defined in presence of lower respiratory cultures growing bacteria and treatment for VABP • Sputum, tracheal aspirate, BALF	• 126 critically ill patients with COVID-19 • 77/126 had positive bacterial cultures (61%) • 12% had MRSA infection (9/77, of which 6 were respiratory infections)	• No specific details reported on mortality of <i>S. aureus</i> pneumonia
Saeed, 2021 [58] • Retrospective • Multicenter	• Hospitalized patients with COVID-19	• No formal definition for bacterial pneumonia	• 1380 hospitalized patients with COVID-19 • 15/1380 had <i>S. aureus</i> infection (1%) • 8/1380 had MRSA infection (1%) • No information about the site of infection	• No specific details reported on mortality of <i>S. aureus</i> pneumonia
Ruiz-Basim, 2021 [36] • Retrospective • Single center	• Hospitalized patients with COVID-19	• Pulmonary bacterial infection defined as presence of significant semi-quantitative bacterial culture in respiratory samples • Culture and PCR of bronchial aspirate and BALF	• 1195 hospitalized patients with COVID-19 • 66/1195 had bacterial pathogens detected on respiratory specimens (6%) • 18/66 had <i>S. aureus</i> isolates (27%) • 44% of isolates were MRSA (8/18)	• No specific details reported on mortality of <i>S. aureus</i> pneumonia
Soto, 2021 [21] • Prospective • Single center	• Hospitalized patients with COVID-19	• No formal definition for bacterial pneumonia • Molecular detection on sputum samples	• 93 patients with clinical diagnosis of COVID-19 • 69 patients with a confirmed diagnosis of COVID-19 • 11/93 patients had <i>S. aureus</i> sputum isolates (12%) • No information on <i>S. aureus</i> antimicrobial susceptibility	• Unfavorable outcome reported in 2/11 patients with <i>S. aureus</i> isolates (18%)

Table 1 (Continued)

First author, year [ref] type of study	Type of population	Definitions and samples collected	Epidemiology of <i>S. aureus</i> /MRSA pneumonia	Comments on <i>S. aureus</i> impact on mortality
Sreenath, 2021 [59] • Retrospective • Single center	• Hospitalized patients with COVID-19	• No formal definition for bacterial pneumonia • Molecular detection on nasopharyngeal/oropharyngeal samples	• 191 hospitalized patients with COVID-19 • 38/191 had <i>S. aureus</i> detection (20%) • No information on <i>S. aureus</i> antimicrobial susceptibility	• No specific details reported on mortality of <i>S. aureus</i> pneumonia
Catano-Correa, 2021 [28] • Cross-sectional • Multicenter	• Hospitalized patients with COVID-19	• Combination of clinical, laboratory, and radiological criteria • Tracheal aspirate culture with at least 10 ⁶ CFU/ml	• 399 hospitalized patients with COVID-19 • 18/399 patients had respiratory <i>S. aureus</i> infection (5%) • No information on <i>S. aureus</i> antimicrobial susceptibility	• No specific details reported on mortality of <i>S. aureus</i> pneumonia
Russel, 2021 [20*] • Retrospective • Multicenter	• Hospitalized patients with COVID-19	• No formal definition for bacterial pneumonia • Sputum, tracheal aspirate, BALF, and pleural fluid	• 48902 hospitalized patients with COVID-19 • 8649/48902 underwent relevant microbiological investigations (18%) • 21/118 patients had <i>S. aureus</i> isolated from sputum collected within 48 h of admission (18%) • 14/45 patients had <i>S. aureus</i> isolates in lower respiratory specimens collected within 48 h of admission (31%) • 81/642 patients had <i>S. aureus</i> isolates in lower respiratory specimens collected beyond 48 h of admission (13%)	• No specific details reported on mortality of <i>S. aureus</i> pneumonia
Foschi, 2021 [43] • Retrospective • Multicenter	• Critically ill COVID-19 patients in ICU who underwent a lower respiratory tract sampling for culture and PCR	• No formal definition for bacterial pneumonia • Tracheal aspirate, BALF culture and PCR	• 178 critically ill patients with COVID-19 for a total of 230 lower respiratory tract specimens • 15/230 lower respiratory tract cultures positive for <i>S. aureus</i> (7%), with 6/15 being MRSA (40%) • 25/230 had lower respiratory tract PCR positive for <i>S. aureus</i> (11%), with 8/25 being <i>mecA</i> positive (32%)	• No specific details reported on mortality of <i>S. aureus</i> pneumonia
Maes, 2021 [60] • Retrospective • Single center	• Critically ill COVID-19 patients in ICU	• VABP defined according to ECDC surveillance definitions [61]	• 81 critically ill patients with COVID-19 • 64/81 developed suspected VABP (79%) • 39/81 developed microbiologically confirmed VABP (48%) • Some cases were caused by <i>S. aureus</i> (exact number not available in COVID-19 patients), and no information on <i>S. aureus</i> antimicrobial susceptibility	• No specific details reported on mortality of <i>S. aureus</i> pneumonia
Camelena, 2021 [44] • Prospective • Single center	• Critically ill COVID-19 patients in ICU who underwent bronchoscopy	• No formal definition for bacterial pneumonia • BALF culture and PCR	• 43 critically ill patients with COVID-19 for a total of 96 BALF samples • 5/43 patients with first BALF drawn positive for <i>S. aureus</i> (18%) • 6/43 patients with subsequent BALF samples positive for <i>S. aureus</i> (6/43, 14%) • Overall, <i>mecA</i> gene was detected in 2 cases	• No specific details reported on mortality of <i>S. aureus</i> pneumonia
Thomsen, 2021 [62] • Retrospective • Multicenter	• Critically ill COVID-19 patients in ICU	• No formal definition for bacterial pneumonia • Tracheal aspirate culture and PCR	• 34 critically ill patients with COVID-19 • 2/34 patients with <i>S. aureus</i> isolates (6%) • No information on <i>S. aureus</i> antimicrobial susceptibility	• No specific details reported on mortality of <i>S. aureus</i> pneumonia
Tang, 2021 [22] • Retrospective • Single center	• Hospitalized patients with COVID-19	• Pneumonia defined according to international guidelines [51]	• 142 hospitalized patients with COVID-19 • 32/142 patients had positive sputum culture (23%) • 6/32 patients had <i>S. aureus</i> positive culture (19%) • No information on <i>S. aureus</i> antimicrobial susceptibility	• No specific details reported on mortality of <i>S. aureus</i> pneumonia
Temperoni, 2021 [63] • Retrospective • Single center	• Critically ill COVID-19 patients in ICU	• VABP defined as a pneumonia that arose more than 48 h after endotracheal intubation • No information on the type of collected samples	• 89 critically ill patients with COVID-19 • 1/48 VABP episodes was caused by MRSA (2%)	• No specific details reported on mortality of <i>S. aureus</i> pneumonia

Table 1 (Continued)

First author, year [ref] type of study	Type of population	Definitions and samples collected	Epidemiology of <i>S. aureus</i> /MRSA pneumonia	Comments on <i>S. aureus</i> impact on mortality
Contou, 2020 [64] • Retrospective • Single center	<ul style="list-style-type: none"> Critically ill COVID-19 patients in ICU 	<ul style="list-style-type: none"> No formal definition for bacterial pneumonia Culture of the respiratory tract secretions, multiplex respiratory PCR performed on nasopharyngeal swabs or on respiratory tract secretions collected within 48h from ICU admission 	<ul style="list-style-type: none"> 92 critically ill patients with COVID-19 26/92 patients had bacterial co-infection upon ICU admission (28%) MSSA was isolated in 10/26 patients <i>S. aureus</i> was the leading pathogen, identified both by conventional culture (n=9) and PCR (n=5) 	<ul style="list-style-type: none"> No specific details reported on mortality of <i>S. aureus</i> pneumonia
Fontana, 2021 [38] • Retrospective • Single center	<ul style="list-style-type: none"> Hospitalized patient with COVID-19 	<ul style="list-style-type: none"> No formal definition for bacterial pneumonia BALF and sputum samples collected for conventional culture and multiple PCR testing 	<ul style="list-style-type: none"> 21/66 BALF samples positive for <i>S. aureus</i> (32%); 16/21 <i>mecA</i> positive (76%) 27/86 sputum samples positive for <i>S. aureus</i> (31%); 14/27 <i>mecA</i> positive (52%) 	<ul style="list-style-type: none"> No specific details reported on mortality of <i>S. aureus</i> pneumonia
Hughes, 2020 [37] • Retrospective • Multicenter	<ul style="list-style-type: none"> Hospitalized patients with COVID-19 	<ul style="list-style-type: none"> No formal definition for bacterial pneumonia BAL and sputum samples sent for conventional culture 	<ul style="list-style-type: none"> 836 hospitalized COVID-19 patients 4/14 respiratory samples positive for bacteria from community-acquired infections grew <i>S. aureus</i> (29%) 2/19 respiratory samples positive for bacteria from healthcare-associated infections grew <i>S. aureus</i> (11%) No information on <i>S. aureus</i> antimicrobial susceptibility 	<ul style="list-style-type: none"> No specific details reported on mortality of <i>S. aureus</i> pneumonia
Hughes, 2020 [37] • Retrospective • Multicenter	<ul style="list-style-type: none"> Clinical specimens received at a single laboratory in the US 	<ul style="list-style-type: none"> No formal definition for bacterial pneumonia Nasal and oropharyngeal swabs, sputum 	<ul style="list-style-type: none"> 4259 SAKS-CoV-2-positive specimens 13% of specimens yielded <i>S. aureus</i> No information on <i>S. aureus</i> antimicrobial susceptibility 	<ul style="list-style-type: none"> No specific details reported on mortality of <i>S. aureus</i> pneumonia
DeVoe, 2021 [39] • Retrospective • Single center	<ul style="list-style-type: none"> Hospitalized patients with COVID-19 	<ul style="list-style-type: none"> CDC/NHSN definition for hospital-acquired infections [52] 	<ul style="list-style-type: none"> 314 hospitalized COVID-19 patients 5/314 (2%) VABP episodes, among which 2 were caused by MSSA and 1 by MRSA 	<ul style="list-style-type: none"> No specific details reported on mortality of <i>S. aureus</i> pneumonia
Meawad, 2021 [45] • Retrospective • Single center	<ul style="list-style-type: none"> Critically ill COVID-19 patients in ICU 	<ul style="list-style-type: none"> VABP was diagnosed by new or changing chest X-ray infiltrates appearing more than 48 h after the start of invasive mechanical ventilation plus new onset of fever ($\geq 38.0^{\circ}\text{C}$) or hypothermia ($\leq 35.0^{\circ}\text{C}$), leukocytosis ($\geq 10\,000$ cells/μl) or leukopenia (< 4000 cells/μl), new onset of suctioned respiratory secretions and/or the need to ventilator support system to improve oxygenation Sputum and endotracheal aspirate 	<ul style="list-style-type: none"> 197 critically ill patients with COVID-19 18/197 patients had MRSA VABP (9%) 	<ul style="list-style-type: none"> No specific details reported on mortality of <i>S. aureus</i> pneumonia
Pickens, 2021 [46] • Retrospective • Single center	<ul style="list-style-type: none"> Critically ill COVID-19 patients in ICU 	<ul style="list-style-type: none"> VABP was defined as a bacterial pneumonia newly suspected and diagnosed after 48h of endotracheal intubation Bacterial HAP was defined as a bacterial pneumonia newly suspected and diagnosed after 48 h of hospitalization BALF samples 	<ul style="list-style-type: none"> 196 critically ill patients with COVID-19 28 patients had BALF culture performed within 48 h from intubation MSSA and MRSA were isolated in 11/28 (39%) and 2/28 (7%) of cases, respectively 120 positive samples were drawn beyond 48 h of intubation (n=120); 15 and 10 of them yielded MSSA and MRSA, respectively 	<ul style="list-style-type: none"> No specific details reported on mortality of <i>S. aureus</i> pneumonia
Suarez-de-la-Rica, 2021 [30] • Retrospective • Single center	<ul style="list-style-type: none"> Critically ill COVID-19 patients in ICU 	<ul style="list-style-type: none"> CDC/NHSN definition for hospital-acquired infections [52] Endotracheal aspirate 	<ul style="list-style-type: none"> 107 critically ill patients with COVID-19 35/107 had VABP (33%) 8/35 of VABP were caused by <i>S. aureus</i> (23%) No information on <i>S. aureus</i> antimicrobial susceptibility 	<ul style="list-style-type: none"> No specific details reported on mortality of <i>S. aureus</i> pneumonia

Table 1 (Continued)

First author, year [ref] type of study	Type of population	Definitions and samples collected	Epidemiology of <i>S. aureus</i> /MRSA pneumonia	Comments on <i>S. aureus</i> impact on mortality
Blonz, 2021 [47] • Retrospective • Multicenter	• Critically ill COVID-19 patients in ICU	• VABP diagnosed according to ECDC criteria [65]	<ul style="list-style-type: none"> • 188 critically ill patients with COVID-19 • 141 VABP episodes • <i>S. aureus</i> accounted for 14% of VABP episodes (28/205 bacterial isolates) • 24/28 <i>S. aureus</i> were isolated from late VABP (≥ 5 days) • 3/28 <i>S. aureus</i> isolates were MRSA (11%) 	<ul style="list-style-type: none"> • No specific details reported on mortality of <i>S. aureus</i> pneumonia
Moretti, 2020 [66] • Retrospective • Single center	• Critically ill COVID-19 patients in ICU	• CDC/NHSN definition for hospital-acquired infections [52]	<ul style="list-style-type: none"> • 39 critically ill patients with COVID-19 • 21/39 had probable VABP (54%) • 7% of VABP episodes were due to <i>S. aureus</i> • No information on <i>S. aureus</i> antimicrobial susceptibility 	<ul style="list-style-type: none"> • No specific details reported on mortality of <i>S. aureus</i> pneumonia
Luyf, 2020 [48] • Retrospective • Single center	• Critically ill COVID-19 patients requiring ECMO support	<ul style="list-style-type: none"> • VAP was diagnosed in patients having received mechanical ventilation for at least 48 h plus: (1) clinically suspected VABP, defined as a new and persistent pulmonary infiltrate on chest radiograph associated with at least two of the following: temperature $\geq 38^\circ\text{C}$, white blood cell count ≥ 10 Giga/l, purulent tracheal secretions, increased minute ventilation, arterial oxygenation decline requiring modifications of the ventilator settings, and/or need for increased vasopressor infusion. For patients with ARDS, for whom demonstration of radiologic deterioration is difficult, at least two of the preceding criteria sufficed; and (2) significant quantitative growth (≥ 104 colony-forming units/ml) of distal BALF samples 	<ul style="list-style-type: none"> • 50 critically ill COVID-19 patients requiring ECMO • 43/50 developed at least one VABP episode (86%) • <i>S. aureus</i> was isolated in 3 episodes (7%), of which 1 caused by MRSA and 2 caused by MSSA 	<ul style="list-style-type: none"> • No specific details reported on mortality of <i>S. aureus</i> pneumonia
Bardi, 2020 [49] • Retrospective • Single center	• Critically ill COVID-19 patients in ICU	<ul style="list-style-type: none"> • No formal definition for bacterial pneumonia • Tracheal aspirate 	<ul style="list-style-type: none"> • 140 critically ill COVID-19 patients • 21/140 developed VABP (15%), of which 5 were due to MRSA (24%) • 9/140 developed HAP/tracheobronchitis (6%), of which two were due to MRSA (22) 	<ul style="list-style-type: none"> • No specific details reported on mortality of <i>S. aureus</i> pneumonia
Sogaard, 2021 [67] • Retrospective • Single center	• Hospitalized patients with COVID-19	<ul style="list-style-type: none"> • CABP was defined as a microbiology-confirmed pneumonia diagnosed concurrent with SARS-CoV-2 infection or within less than 48 h of hospital admission • HAPB was defined as pneumonia occurring 48 h or more after hospitalization • Possible VABP was diagnosed after 48 h from intubation, together with FiO_2 value increase by ≥ 0.20 or PEEP value increase by ≥ 3 cm H₂O over 48 h and purulent respiratory secretions and/or a positive culture for a respiratory pathogen • Nasopharyngeal swabs, sputum, tracheal secrete, and BALF 	<ul style="list-style-type: none"> • 162 hospitalized COVID-19 patients • 5/162 developed VABP (3%) • 13/162 (8%) developed hospital-acquired tracheobronchitis, in 2 cases due to <i>S. aureus</i> • 1/162 developed HAPB (1%) • 1/162 developed CABP (1%) • No information on <i>S. aureus</i> antimicrobial susceptibility 	<ul style="list-style-type: none"> • No specific details reported on mortality of <i>S. aureus</i> pneumonia
Rouzé, 2021 [50*] • Retrospective • Multicenter	• Critically ill COVID-19 patients in ICU	<ul style="list-style-type: none"> • VABP was defined by the presence of at least two of the following criteria: body temperature of more than 38.5°C or less than 36.5°C; leucocyte count greater than 12000 cells per μl or less than 4000 cells/μl, and purulent tracheal secretions. In addition, all episodes of infection needed microbiological confirmation, and new or progressive infiltrates on chest X-ray needed to be present 	<ul style="list-style-type: none"> • 586 critically ill COVID-19 patients • 287 developed ventilator-associated lower respiratory tract infections (VABP or tracheobronchitis) • 27 episodes were caused by MSSA (10%) • 8 episodes were caused by MRSA (3%) 	<ul style="list-style-type: none"> • No specific details reported on mortality of <i>S. aureus</i> pneumonia

Table 1 (Continued)

First author, year [ref] type of study	Type of population	Definitions and samples collected	Epidemiology of <i>S. aureus</i> /MRSA pneumonia	Comments on <i>S. aureus</i> impact on mortality
Razazi, 2020 [68] • Retrospective • Single center	• Critically ill COVID-19 patients in ICU	• VABP was clinically suspected if any of the following happened 48 h or more after mechanical ventilation initiation: new or worsening infiltrates on chest X-ray, systemic signs of infection [new-onset fever, leukocytosis or leucopenia, increased need for vasopressors], purulent secretions, and impaired oxygenation. Suspected VABP were confirmed from quantitative cultures of lower respiratory tract secretions sampled before administering new antibiotics	<ul style="list-style-type: none"> • 82 critically ill COVID-19 patients • 58 developed VABP • 2 episodes were caused by MSSA • No episodes were due to MRSA 	<ul style="list-style-type: none"> • No specific details reported on mortality of <i>S. aureus</i> pneumonia

BALF, bronchoalveolar lavage fluid; CABP, community-acquired bacterial pneumonia; COVID-19, coronavirus disease 2019; ECMO, extra-corporeal membrane oxygenation; HABP, hospital-acquired bacterial pneumonia; ICU, intensive care unit admission; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; PCR, polymerase chain reaction; VABP, ventilator-associated bacterial pneumonia.

colleagues conducted a retrospective, single center study in Brazil [24]. Among 212 hospitalized patients with severe COVID-19, 53/212 patients had positive tracheal aspirate bacterial culture (25%), with 8/53 positive cultures yielding *S. aureus* (15%) [24]. A multicenter study in Russia involved both outpatients and inpatients with COVID-19 [25]. Among 1204 patients diagnosed with SARS-CoV-2 infection, 433 were also diagnosed by their treating physicians to have secondary bacterial pneumonia (36%), of which 24/433 were *S. aureus* CABP (6%) and 63/433 were *S. aureus* HABP (15%) [25]. *S. aureus* was the third most frequent causative agent of CABP following *Streptococcus pneumoniae* and *Haemophilus influenzae*, and the second most frequent causative agent of HABP following *S. pneumoniae* [25]. In a retrospective single center study among 989 hospitalized patients with COVID-19 in Spain, Garcia-Vidal *et al.* [1] observed *S. aureus* lung coinfection at COVID-19 diagnosis in 6/21 cases of coinfections (29%), with *S. aureus* being the most frequently isolated pathogen after *S. pneumoniae*. With regard to secondary infections in hospitalized patients, *S. aureus* was the most frequent causative agent of VABP (4/11, 36%) [1]. In a multicenter retrospective study conducted in the United Arab Emirates, Senok *et al.* [26] registered 392 co-infections among 29 802 hospitalized patients with COVID-19, with *S. aureus* being isolated from lower respiratory tract specimens in 8/392 cases of coinfections (2%). Several other organisms (e.g., *Pseudomonas aeruginosa*, *Enterobacterales*) were more frequently isolated than *S. aureus*, but it should be noted that this count also included infections other than pneumonia [26]. In a large retrospective, multicenter study in England, including 223 413 hospitalized patients with COVID-19, bacterial infections were diagnosed in 2279/223 413 cases (1%) [27]. Of 2279 bacterial infections, 209 were early *S. aureus* infections (defined as co-infections), and 301 late *S. aureus* infections during hospitalization (defined as secondary infections). Of the cumulative 510 patients with *S. aureus* infections, 262 had respiratory infections (51%). Overall, *S. aureus* was the most frequent causative agent of respiratory infections in this large cohort (with early and late infections being considered together for this calculation) [27]. In a prospective, single center study conducted in Peru, among 93 hospitalized patients with COVID-19, 11 patients had sputum culture yielding *S. aureus* (12%), which was the most frequently isolated pathogen from sputum [21]. In a cross-sectional, multicenter study of 399 hospitalized patients with COVID-19 in Colombia, 18 of them had respiratory *S. aureus* infection (5%). In terms of frequency as causative agent of respiratory

infections, *S. aureus* was second only to *K. pneumoniae* (32%) [28]. In a large retrospective, multicenter study in the UK, among 48 902 hospitalized patients with COVID-19, 21 had *S. aureus* isolated from sputum collected from patients with bacterial coinfection (21/118 [18%] positive specimens, with *S. aureus* representing the most frequently isolated pathogen), 14 had *S. aureus* isolated from lower respiratory specimens collected from patients with bacterial co-infection (14/45 positive specimens, 31%, again with *S. aureus* representing the most frequently isolated pathogen), 81 had *S. aureus* isolated from sputum collected from patients with secondary bacterial infection (81/642 specimens, 13%, with *S. aureus* second only to *Escherichia coli* in terms of relative frequency), and 29 had *S. aureus* isolated from lower respiratory specimens collected from patients with secondary bacterial infection (29/277 specimens, 10%, with *S. aureus* representing the third most frequently isolated pathogen after *E. coli* and *K. pneumoniae*) [20]. In a retrospective, single center study conducted by Tang *et al.* [22] in 142 hospitalized patients with COVID-19 in China, 32/142 patients had positive sputum cultures (23%), of which 6/32 were positive for *S. aureus* (19%). Together with *P. aeruginosa*, *S. aureus* was the second most frequently isolated bacterial pathogen from sputum after *K. pneumoniae* [22]. In a retrospective, single center study by Yang *et al.*, among 20 critically ill patients with COVID-19 for a total of 96 respiratory samples, bacteria were identified in 56/96 cases (58%) [29]. *S. aureus* was identified from 7% and 31% of specimens by conventional culture and by polymerase chain reaction (PCR), respectively [29]. In a retrospective, single center study of 107 critically ill patients with COVID-19, 35 had VABP (33%), and 8/35 episodes were caused by *S. aureus* (23%) [30]. In this latter study, *P. aeruginosa* and *Klebsiella* spp. were isolated from respiratory specimens slightly more often than *S. aureus* [30].

Epidemiology of methicillin-resistant *Staphylococcus aureus* lung infection in patients with coronavirus disease 2019

With regard to studies providing information on the epidemiology of MRSA lung infection, in a retrospective study of hospitalized patients with COVID-19 who developed *S. aureus* bacteremia, Cusumano *et al.* [31] identified pneumonia as the source of bacteremia in 19% of cases (8/42), mostly hospital-acquired (only two cases were CABP). Overall, 19/42 blood isolates were MRSA (45%), but no details were provided on how many were isolated from the eight patients who also had pneumonia

[31]. In a multicenter, retrospective study conducted by Son *et al.* in South Korea, 47 patients had available culture results among 152 hospitalized patients with COVID-19 (31%) [32]. Of them, 3/47 had respiratory cultures positive for MRSA (6%) [32]. In a single center, cross-sectional study of 43 hospitalized patients in Iran with COVID-19 and positive bacterial cultures, 6/43 patients had cultures positive for MRSA (14%), with two being cultures of respiratory specimens [33]. In another single-center, retrospective study, conducted among 1495 hospitalized patients with COVID-19 in Wuhan, China, 102/1495 were reported to have secondary bacterial infection (7%), and 3/102 had positive MRSA cultures (2/3 were from respiratory specimens) [34]. In this study from Wuhan, Gram-negative bacteria were more frequently isolated than MRSA from respiratory specimens (43% and 31% for *Acinetobacter baumannii* and *Klebsiella pneumoniae*, respectively, vs. 2% for MRSA) [34]. In a retrospective, single center study conducted in the United States, among 4221 hospitalized patients with COVID-19 there were 472/4221 with available respiratory culture results (11%) [35]. The prevalence of MRSA in respiratory cultures ranged from a 0.6% on day 3, to 5.7% on day 28, cumulatively [35]. In a retrospective, single center, Spanish study involving 1195 hospitalized patients with COVID-19, bacteria were detected from cultures of respiratory specimens in 66/1195 patients (6%), with *S. aureus* being identified in 18/66 cases (and 8/18 were MRSA, 44%) [36]. *S. aureus* was the most frequently isolated pathogen from respiratory specimens, followed by *P. aeruginosa* (17/66) [36]. In a multicenter, retrospective study in 836 hospitalized patients with COVID-19 in the UK, *S. aureus* was the most frequent pathogen isolated from respiratory samples (sputum or bronchoalveolar lavage fluid [BALF]) collected within 5 days of admission (4/14, 29%), whereas *S. aureus* was less frequently isolated than *P. aeruginosa* and *Enterobacteriales* from positive respiratory samples collected beyond 5 days of admission (2/19, 11%) [37]. In a retrospective, single center study in Italy, Fontana *et al.* [38] evaluated 152 respiratory samples from consecutive COVID-19 patients by multiplex polymerase chain reaction. Overall, 21/66 positive BALF samples yielded *S. aureus* (32%), of which 16/21 were *mecA* positive (76%), and 27/86 positive sputum samples yielded *S. aureus* (31%), of which 14/27 were *mecA* positive (52%). In this latter study by Fontana *et al.* [38], *S. aureus* was the most frequently detected pathogen from respiratory samples. In a single center, retrospective study in 314 hospitalized patients with COVID-19, a diagnosis of probable VABP due to methicillin-susceptible *S. aureus* (MSSA) and MRSA was posed in two and

one patients, respectively [39]. Baskaran *et al.* [40] conducted a retrospective study among 254 critically ill patients with COVID-19, of whom 4/254 had *S. aureus* colonization/infection at ICU admission or within 48 h after admission, with 1/4 being MRSA. In the same study, the relative prevalence of late *S. aureus* co-colonization/co-infection was also collected, being between 5% and 10% both 3–7 days and >7 days after ICU admission. Overall, *S. aureus* was the most frequently isolated pathogen within 48 h of ICU admission, whereas Gram-negative bacteria predominated subsequently [40]. Grasselli *et al.* [2] conducted a multicenter, retrospective study in 759 critically ill patients with COVID-19, calculating an incidence rate of VABP of 26 episodes per 1000 ICU days, for a total of 389 VABP episodes. Overall, 110/389 VABP were caused by *S. aureus*, with 61/110 being caused by MRSA (55%). Overall, *S. aureus* was the most frequently isolated pathogen from patients with VABP, although most VABP episodes were caused by Gram-negative bacteria (64%). Giacobbe *et al.* [16] registered an incidence rate of 18 VABP events per 1000 ventilator days among 586 critically ill patients with COVID-19 in a multicenter study in Italy. Overall, 171/586 of patients developed VABP (29%), and 77/171 patients with VABP had positive BALF cultures. *S. aureus* VABP and MRSA VABP were diagnosed in 18/77 cases (23%) and 8/77 cases (10%), respectively. *S. aureus* was the second most frequently isolated pathogen after *P. aeruginosa* [16]. In a retrospective, single center study of 101 critically ill patients with COVID-19, of whom 20/101 had positive respiratory cultures (20%), Elabbadi *et al.* [41] reported a relative prevalence of *S. aureus* of causative agent of pulmonary infection of 55% (11/20), with 2/11 isolates being MRSA (18%). *S. aureus* was the most frequent pathogen isolated in this cohort [41]. In a prospective, single center study of 40 critically ill patients with COVID-19 and *S. aureus* VABP in Italy, MRSA was responsible for 65% of cases [15]. Sharifipour *et al.* [42] reported on 19 critically ill patients with COVID-19, all diagnosed with secondary bacterial infections, and of whom 2/19 patients had *S. aureus* VABP (11%), one of the two caused by MRSA. Most cases of VABP in their study were caused by *A. baumannii* [42]. In a retrospective, multicenter study of 126 critically ill patients with COVID-19, of whom 77/126 had positive respiratory cultures (61%), Risa *et al.* [19] observed 6/77 cases of *S. aureus* respiratory infection, of which 6 were caused MRSA. In a retrospective study of 178 critically ill patients with COVID-19 for a total of 230 lower respiratory tract specimens, there were 15/230 lower respiratory tract cultures positive for *S. aureus* (7%), and 6/15 were MRSA (40%). In addition, in 25/230 specimens

PCR results were positive for *S. aureus* (11%), with 8/25 being also *mecA* positive (32%) [43]. In this cohort, *S. aureus* was preceded by *P. aeruginosa* and *K. pneumoniae* in terms of relative frequency of detection [43]. Among 43 critically ill patients with COVID-19 who underwent bronchoscopy, a total of 96 BALF samples were collected [44]. Overall, there were 5/43 patients with first BALF drawn positive for *S. aureus* (12%) and 6/43 patients with subsequent BALF specimens positive for *S. aureus* (6/43, 14%). The *mecA* gene was detected in two cases. The only pathogen isolated more frequently than *S. aureus* was *P. aeruginosa* [44]. In a retrospective, single center study of 197 critically ill patients with COVID-19 in Egypt, 18/197 were diagnosed with VABP due to MRSA (9%), which overall was less frequent than VABP due to Gram-negative bacteria [45]. In a retrospective, single center study of 196 critically ill patients with COVID-19, 28 had BALF culture performed within 48 h from intubation, with MSSA and MRSA being isolated in 11/28 (39%) and 2/28 (7%) cases, respectively [46]. With regard to positive samples drawn beyond 48 h of intubation ($n=120$), 15 and 10 of them yielded MSSA and MRSA, respectively, with *S. aureus* being the most frequently isolated pathogen [46]. In a retrospective, multicenter study conducted in 188 critically ill patients with COVID-19 there were 141 VABP, with *S. aureus* accounting for 14% of episodes [47]. *S. aureus* was the most frequently isolated pathogen from respiratory specimens, and most of *S. aureus* isolates (24/28) were from late VABP. Overall, 3/28 *S. aureus* isolates were MRSA (11%) [47]. In a retrospective, single center study of 50 critically ill patients with COVID-19 requiring extracorporeal membrane oxygenation (ECMO), 43/50 developed at least one VABP episode (86%). [48]. *S. aureus* was isolated in three episodes (7%), of which one was caused by MRSA and two by MSSA. *Enterobacteriales* and nonfermenting Gram-negative bacteria were isolated more frequently than *S. aureus* [48]. In a single center retrospective study conducted in 140 critically ill patients with COVID-19, development of VABP was registered in 21/140 patients (15%), and in five cases was caused by MRSA (24%) [49]. In this latter study, MRSA was the second most frequently isolated pathogen from respiratory specimens following *P. aeruginosa* [49]. Finally, in a multicenter, retrospective study, of 586 critically ill COVID-19 patients, 287 of them developed ventilator-associated lower respiratory tract infections (VABP or tracheobronchitis) [50*]. Overall, 27 episodes were caused by MSSA (10%) and 8 by MRSA (3%). Most ventilator-associated lower respiratory tract infections were caused by Gram-negative bacteria (84%) [50*].

Some brief considerations on the relative risk of methicillin-resistant *Staphylococcus aureus* vs. methicillin-susceptible *Staphylococcus aureus* lung infection in coronavirus disease 2019 patients

While a specific, formal statistical analysis of any possible independent association of potential predisposing factors with the development of MRSA lung infection in COVID-19 is not available, it is of note that the available relative frequency of MRSA vs. MSSA as causative agent of lung infection in COVID-19 suggest a relative prevalence of MRSA >30% in COVID-19 patients with VABP, whereas a study reported a relative frequency of MRSA <30% as a causative agent of CABP [2,16,39,40,42,47,48,50^{*}]. While this may suggest late infection during hospitalization as a reasonable potential risk factor for MRSA, such crude relative prevalences should still be interpreted with caution pending further investigation, especially considering the limited information on the relative prevalence of MRSA as causative agent of CABP in this patient population. Furthermore, many studies reported the relative prevalence of MRSA lung infection in COVID-19 patients at ICU admission, which, without providing additional details, does not allow to clearly understand whether the patients had CABP, HABP, or ventilated HABP.

Another factor certainly deserving further investigation as a potential risk factor for MRSA infection in COVID-19 patients is previous antibiotic therapy. Of note, this applies both to CABP (empirical antibiotic therapy at home) and to HABP/VABP (previous therapy either at home or in the hospital). Unfortunately, most initial experiences registered a large, likely excessive, use of antibiotics in COVID-19 patients, a fact that significantly hampered any possible reliable assessment of the role of previous therapy in independently influencing the risk of MRSA infections [4–6].

CONCLUSION

In the previous paragraphs, we narratively summarized the results of studies reporting on the epidemiology of *S. aureus* and MRSA lung infection in patients with COVID-19. Of note, our summary was qualitative and not quantitative, thereby not allowing to provide proper quantitative measures, but at the same time relaxing inclusion criteria and allowing a wider qualitative interpretation. Overall, keeping into account the wide heterogeneity in study designs, populations, and denominators, as well as the wide range of the relative prevalences of *S. aureus* lung infection registered in the different studies (2–

36%), the following general trajectories seem to stem from the currently available literature on the epidemiology of *S. aureus* lung infection in COVID-19 patients: *S. aureus* is among the most frequently isolated bacteria from the respiratory tract of patients with COVID-19 during the first days of hospitalization; conversely, although *S. aureus* remains one of the most frequently isolated pathogen also in late secondary respiratory infections (that overall are far more frequent than early infections), Gram-negative bacteria frequently predominate in late scenarios. Nonetheless, *S. aureus* predominated as cause of HABP/VABP in some local scenarios. In this regard, the hypothesis-generating findings of De Pascale *et al.* [15], who reported a lower species diversity and enrichment in *S. aureus* in the lung microbiota of critically ill COVID-19 patients with *S. aureus* VABP in comparison with non-COVID-19 critically ill patients with *S. aureus* VABP, is intriguing and deserves further investigation.

Regarding MRSA lung infection in patients with COVID-19, there was important heterogeneity in the retrieved literature on its epidemiology, both when considering all other bacteria as denominator (relative prevalence ranging from 2% to 29%) and when considering only *S. aureus* as denominator (relative prevalence ranging from 11% to 65%). All of this likely reflect the local microbiological epidemiology, although it should be noted that MRSA was not rare as causative agent of CABP in patients with COVID-19, therefore, in our opinion, it may be prudent to consider it in patients presenting with severe COVID-19 pneumonia and high suspicion of bacterial co-infection. Against this background, improving our ability to rapidly detect the causative agents of pneumonia and their crucial resistance determinants in COVID-19 patients (either through conventional or molecular methods) remains, in our opinion, fundamental if we are to improve our rates of appropriate empirical therapy in patients with COVID-19 and concomitant/superimposed MRSA infection, at the same time avoiding antibiotic overuse in line with antimicrobial stewardship principles.

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Conflicts of interest

Outside the submitted work, MB has participated in advisory boards and/or received speaker honoraria from Achaogen, Angelini, Astellas, Bayer, Basilea,

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