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MAJOR ARTICLE

Bacterial Superinfections Among Persons With Coronavirus Disease 2019: A Comprehensive Review of Data From Postmortem Studies

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Background. Limited clinical data suggest a ~16% prevalence of bacterial superinfections among critically ill patients with coronavirus disease 2019 (COVID-19).

Methods. We reviewed postmortem studies of patients with COVID-19 published in English through September 26, 2020, for histopathologic findings consistent with bacterial lung infections.

Results. Worldwide, 621 patients from 75 studies were included. The quality of data was uneven, likely because identifying superinfections was not a major objective in 96% (72/75) of studies. Histopathology consistent with a potential lung superinfection was reported in 32% (200/621) of patients (22–96 years old; 66% men). Types of infections were pneumonia (95%), abscesses or empyema (3.5%), and septic emboli (1.5%). Seventy-three percent of pneumonias were focal rather than diffuse. The predominant histopathologic findings were intra-alveolar neutrophilic infiltrations that were distinct from those typical of COVID-19-associated diffuse alveolar damage. In studies with available data, 79% of patients received antimicrobial treatment; the most common agents were beta-lactam/beta-lactamase inhibitors (48%), macrolides (16%), cephalosoprins (12%), and carbapenems (6%). Superinfections were proven by direct visualization or recovery of bacteria in 25.5% (51/200) of potential cases and 8% of all patients in postmortem studies. In rank order, pathogens included *Acinetobacter baumannii, Staphylococcus aureus, Pseudomonas aeruginosa,* and *Klebsiella pneumoniae*. Lung superinfections were the cause of death in 16% of potential cases and 3% of all patients with COVID-19.

Conclusions. Potential bacterial lung superinfections were evident at postmortem examination in 32% of persons who died with COVID-19 (proven, 8%; possible, 24%), but they were uncommonly the cause of death.

Keywords. bacteria; COVID-19; postmortem; SARS-CoV-2; superinfections.

The world is in the midst of a pandemic precipitated by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19). It is clear that bacterial superinfections, in particular pneumonias, can complicate COVID-19 [1]. However, data on the frequency of superinfections and their microbiology, treatment, and outcomes are incomplete. In a review of published COVID-19 studies, bacterial superinfections were reported in ~8% and ~16% of hospitalized and critically ill patients, respectively [2]. Lung infections, in particular health care– and ventilator-associated pneumonias, accounted for most cases, followed by other types of nosocomial infections; community-acquired infections were less common [1]. These data must be interpreted with caution because most COVID-19 studies have not included superinfections, or they have presented them as subsidiary rather than major end points. Clinical, microbiologic, and antimicrobial susceptibility data were usually limited and presented in passing; standardized diagnostic testing and rigorous case definitions of infections were rarely employed [1]. More comprehensive data on superinfections are crucial for understanding the spectrum of COVID-19 and its complications, and in optimizing patient care and antimicrobial stewardship.

Autopsies and other postmortem examinations are powerful but underutilized resources for understanding disease pathogenesis and manifestations [3, 4]. Histopathologic studies of archived tissue samples demonstrated that bacterial pneumonia, mostly commonly due to *Streptococcus pneumoniae*, was a leading cause of death among patients with influenza during the 1918–1919 pandemic [5]. Postmortem studies of patients dying with COVID-19 were initially limited by concerns over potential disease transmission [3]. Recently, however, autopsy studies have been published from throughout the world that have defined diffuse alveolar damage (DAD) as the histopathologic hallmark of

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severe SARS-CoV-2 infection [6]. The most common cause of death is acute respiratory distress syndrome (ARDS) stemming from DAD, often complicated by cardiopulmonary and other organ failure [6, 7]. To date, postmortem data on infections complicating COVID-19 have not been collated. We hypothesized that postmortem studies would give insight into the frequency, clinical and microbiologic features, and severity of bacterial superinfections. In this study, we reviewed published reports of persons who died with COVID-19 in whom postmortem histopathologic findings were consistent with bacterial lung infections.

METHODS

Review of Literature and Inclusion Criteria

We conducted a PubMed search of papers published in the peer-reviewed, English language literature through September 16, 2020, using the terms "coronavirus disease 2019," "COVID-19," "novel coronavirus," "severe acute respiratory syndrome virus coronavirus-2" or "SARS-CoV-2" *and* "autopsy," "postmortem," or "histopathology." Studies were considered for inclusion if they presented histopathologic data from postmortem samples of lungs from SARS-CoV-2-infected persons. Papers cited in eligible studies identified by PubMed searches were also reviewed. Cases were included if they described histopathologic findings in the lung that were consistent with bacterial superinfections (see definitions below). An author of this study (C.J.C. and/or I.S.S.) contacted the corresponding authors of eligible postmortem studies by e-mail with requests for clarification of published data, as well as queries about pathogen visualization and culture and polymerase chain reaction (PCR) results that may not have appeared in the respective publications.

Definitions

Proven superinfections were defined if bacteria were directly visualized in lung tissue or detected by culture or PCR in patients for whom histopathologic findings were consistent with superinfection. Culture results described as "mixed flora" or "consistent with postmortem contamination" were excluded. *Histopathology consistent with superinfection* was defined as (a) descriptions of intra-alveolar and/or peribronchial neutrophilic infiltrates that were distinct from diffuse interstitial and mild intra-alveolar neutrophil accumulations typically seen with DAD; (b) intra-alveolar and/or peribronchial neutrophilic infiltrates that were described as distinct from typical findings of proliferative, organizing, or fibrotic DAD; (c) statements that findings were "consistent with bacterial pneumonia"; or (d) direct visualization of bacteria within tissue [8, 9]. *Possible superinfection* was defined as a case in which histopathology was consistent with superinfection, but bacteria were not visualized in tissue, or detected by culture or PCR. *Potential superinfections* encompassed both *proven* and *possible superinfections*.

RESULTS

Potential Lung Superinfections

From 75 published postmortem studies, we identified 621 patients with COVID-19 for whom descriptions of lung histopathology were provided [8–82]. Ninety-six percent (72/75) of studies did not have a stated objective of specifically investigating superinfections. Histopathologic findings that were consistent with potential bacterial lung superinfections were reported in 32% (200/621) of patients (Table 1). These patients were from the United States (59 patients, 16 studies), Austria (27 patients, 3 studies), Germany (21 patients, 5 studies), Switzerland (12 patients, 3 studies), Brazil (12 patients, 2 studies), Italy (9 patients, 2 studies), Belgium (10 patients, 2 studies), Iran (10 patients, 2 studies), the Netherlands (7 patients, 1 study), the United Kingdom (5 patients, 2 studies), Spain (5 patients, 1 study), China (3 patients, 3 studies), Romania (2 patients, 1 study), Japan (1 patient, 1 study), and either the United States or Italy (17 patients, 1 study). At least 1 patient with a potential bacterial lung superinfection was included in 60% (45/75) of the studies. Relevant tissue samples were obtained at open autopsy (84.5%, 169/200) or by ultrasound-guided minimally invasive autopsy (12%, 24/200) or other biopsy method (7/200, 3.5%). Dates of COVID-19 cases were stated or inferred in 66 studies; in each of 536 cases, postmortem examinations were performed before the end of May 2020. Thirty percent (160/536) of patients in these studies had lung histopathologic findings consistent with potential bacterial superinfection.

Patients with potential bacterial lung superinfections ranged from 22–96 years of age; 66% (90/136) and 34% (46/136) of those for whom data were presented were men and women, respectively. Predominant symptoms were fever, cough, and dyspnea, which were first noted 0–100 days before death. Information on antibiotic treatment was provided in 53% (24/45) of studies. In these studies, 79% (75/95) and 21% (20/95) of patients were treated or not treated with antibacterial agents, respectively. Among 50 patients for whom specific treatment was listed, the most commonly prescribed antibiotics were beta-lactam/beta-lactamase inhibitors (48%, 24/50), macrolides (16%, 8/50), cephalosporins (12%, 6/50), carbapenems (6%, 3/50), clindamycin (4%, 2/50), linezolid (4%, 2/50), and vancomycin (2%, 1/50).

Histopathologic findings in patients with potential lung infections were consistent with bronchopneumonia, lobar pneumonia, or diffuse pneumonia (95%, 191/200), lung abscesses or empyema (3.5%, 7/200), and pulmonary septic thromboemboli (1.5%, 3/200) (Table 1). The most common histopathologic descriptions were neutrophilic infiltrations of alveoli in a manner distinct from that typically seen with DAD or explicit statements that findings were "consistent with bacterial pneumonia." For cases in which descriptions were provided, 73% (73/100) and 27% (27/100) of potential

Table 1. Postmortem Histopathology Consistent With Lung Superinfections in Patients With COVID-19[a]

Pt No. [Ref]	Lung Infxn, No. (%)	Case Details					Comments[c]
		Age(s), Sex	Clinical History, Time to Death[b]	Abx Treatment	Relevant Histopathology	Microbiology	
1 [10]	10/21 (48)	66–96 y, 80% M	Cough 50%, fever 38%, 25% dyspnea 0–9 d	Not stated	"Superimposed bacterial bronchopneumonia," ranging from "early" to "severe"	Gram-positive cocci in alveoli (1 pt)	Autopsies, pts from Switzerland, through April. Causes of death in 8/10 pts listed as "SARS-CoV-2-associated respiratory failure with superimposed bacterial bronchopneumonia." "Severe and extensive bronchopneumonia without typical features of DAD" described in 3 pts. 4 localized pneumonia, 6 severe or diffuse.
2 [11]	4/12 (33)	54–87 y, 50% M	Not stated	None	"No DAD but extensive granulocytic infiltration of alveoli and bronchi, resembling bacterial focal bronchopneumonia"	Not stated	Autopsies, pts from Germany, through April. Causes of death listed as pneumonia, pneumonia and septic encephalopathy, bronchopneumonia, purulent bronchitis. Not clear if pneumonia causing death ascribed to SARS-CoV-2 or bacteria. "Macroscopically differentiating viral pneumonia with subsequent DAD (a histologic diagnosis) from bacterial pneumonia was not always possible."
3 [12]	1/4 (25)	59 y, M	Fever 52 d	Not stated	"Abundant intra-alveolar neutrophilic infiltration, consistent with superimposed bacterial bronchopneumonia"	Not stated	Postmortem biopsy, pt from China, February or earlier. "Abundant intra-alveolar neutrophilic infiltration, consistent with superimposed bacterial bronchopneumonia."
4 [13]	1/2 (50)	42 y, M	Cough, fever, dyspnea 48 h	Not stated	"Acute bronchopneumonia, focal aspiration"	Postmortem lung tissue: *E. coli, P. mirabilis*	Autopsy, pt from USA, March. Cause of death listed as "complications of hepatic cirrhosis." "Acute bronchopneumonia with aspiration" listed as significant condition. Pt died in community.
5 [14]	2/3 (67)	70 y, W; 27 y, M	1) Vomit, abdominal pain, dyspnea 2 d; 2) cough, dyspnea 6 d	1/2, no details	"Focal areas of rich neutrophilic infiltration"	Not stated	Autopsies, pts from Romania, through May. Causes of death listed as "direct lung injury due to viral pneumonia." 1 death with pneumonia in community.
6 [15]	1/2 (50)	65 y, M	Fever, respiratory failure 16 d	Yes, no details	Alveolar wall destruction, diffuse inflammatory infiltrate, "concentrated inflammatory exudate filling the airspaces"	Not stated	Postmortem biopsies, pts from China, March or earlier. Histopathology "suggestive of an organizing phase of DAD complicated by bacterial pneumonia"; "acute DAD may favor the development of bacterial pneumonia."
7 [16]	3/10 (30)	22–78 y, M	Dyspnea, CVA (1), mechanical ventilation (1) 12–27 d	Not stated	"Interstitial neutrophilic infiltrate," "patchy acute bronchopneumonia," broad, aseptate hyphal co-infection in 1 pt	Not stated	Autopsies, pts from UK, through April. Causes of death DAD in 2 pts.
8 [17]	6/11 (55)	70–91 y, 83% M 6–11 d	Not stated	5/6: BL-BLI 4, carbapenems 2, macrolides 2	"Reactive neutrophilic infiltrates," "bronchopneumonia…ranging from (mostly) focal to confluent" in 6 pts, "adjacent to infraction" in 5 pts	Not stated	Autopsies, pts from Austria, through 14 April. Predominant causes of death DAD, respiratory insufficiency, and thromboses. Deaths included community cases. 2/11 received mechanical ventilation.
9 [18]	10/11 (91)	67–89 y, 50% M 8–20 d	Fever, chills, dyspnea 4–36 d	Not stated	DAD with "bronchopneumonia associated with purulent bronchitis"	Not stated	Autopsies, pts from Austria, through 13 May. "Most focal bronchopneumonia." Data here exclude 8 pts also included in [17].
10 [9]	1/4 (25)	78 y, W	Fever, chills, vomiting 12 h	None	"Focal inflammatory exudate with neutrophils"	Not performed	Autopsy, pt from Germany, through April. Patient was found dead at home. Likely cause of death was "inflammation associated pulmonary edema and acute cardiac failure." A second patient with ventilator-associated pneumonia due to *K. oxytoca* was diagnosed and treated antemortem, but relatively infrequent neutrophils on histopathology "argued against significant bacterial superinfection."
11 [19]	11/14 (79)	55–94 y, 64% M	SOB (11), fever (11), cough (10) 6–50 d	11/11: BL-BLI 8, clindamycin 2, carbapenems 1, macrolides 1	DAD with "superimposed acute bronchopneumonia," "dense accumulation of neutrophils within the airways and alveoli"	Postmortem cx: *S. aureus*, 4; *K. pneumoniae, P. aeruginosa*, 1 each	Autopsies, pts from Austria, through 14 May. Acute bronchopneumonia considered major cause of death in 2 pts.

Table 1. Continued

Pt No. [Ref]	Lung Infxn, No. (%)	Case Details					Comments[c]
		Age(s), Sex	Clinical History, Time to Death[b]	Abx Treatment	Relevant Histopathology	Microbiology	
12 [20]	8/17 (47)	53–77 y, all M	3–14 d, symptoms not stated	7/8, no details	"Acute pneumonia or bronchopneumonia"	Not stated	Autopsies, pts from Belgium, through April. Causes of death: MOF 4, septic shock 2, cardiogenic shock 1, respiratory failure 3, mesenteric ischemia 1. "It is difficult to conclude whether DAD reflected the natural time course of the viral disease or was secondary to superimposed complications, such as nosocomial infections."
13 [21]	1/1 (100)	93 y, W	Cough, prostration 20 d	Amp-sulbactam, ceftriaxone	"Acute bronchopneumonia," "alveolar space infiltration of numerous neutrophils," "bacterial colonies were detected"	Not stated	Autopsy, pt from Japan, April or earlier. Bronchopneumonia was felt to be likely secondary to primary viral infection and DAD.
14 [22]	4/12 (33)	Not stated	Not stated	Not stated	"Granulocyte-dominated focal confluent bronchopneumonia was dominant," "mixed forms of DAD and purulent pneumonia"	Not stated	Autopsies, pts from Germany, through 18 April. First 80 consecutive autopsies performed in Hamburg, but histopathology only reported for 12. Four pts had evidence of "superinfected bronchopneumonia (no bacteriologic diagnosis was made postmortem)."
15 [23]	3/14 (21)	73–84 y, all W	Respiratory distress 2, SOB, fever, cough, N/V 2–23 d	Not stated	"Areas of neutrophilic inflammation," "acute bronchopneumonia"	Not detected	Autopsy, pt from USA, through March. Only 1/3 had bronchopneumonia as ICD-10 coded diagnosis. 2 other patients with ICD-10 coded pneumonia did not have histopathologic evidence on autopsy.
16 [24]	1/1 (100)	76 y, W	Nasal congestion, chills, fever, hypoxia 11 d	Ceftriaxone, azithromycin	"Rare foci with neutrophilic and histiocytic infilrates in alveolar spaces"	Not stated	Autopsy, pt from USA, date unclear. Comfort measures only. Primary cause of death was "DAD due to SARS-CoV-2." "Focal pneumonic process, consistent with superimposed bronchopneumonia."
17 [26]	2/6 (33)	33 y, W; 70 y, M	Cough, cardiac arrest, duration not stated	Not stated	"Superimposed bronchopneumonia (likely bacterial infection)"	Not stated	Autopsies, pts from UK, through April. Bronchopneumonia superimposed on DAD. One patient found dead at home.
18 [27]	3/7 (43)	50–77 y, 100% M	Fever, cough, respiratory failure 6–31 d	Not stated	"Superimposed bacterial lobar pneumonia"	Not stated	Autopsies, pts from USA, April.
19 [28]	1/1 (100)	59 y, M	Cough 5 d	None	"Focal neutrophilic infiltration…in some airspaces and bronchial wall suggested the beginning of a secondary bacterial pneumonia"	Not stated	Autopsy, pt from Switzerland, April or earlier. Patient found dead at home. Cause of death "ARDS due to severe diffuse DAD as a result of severe infection with SARS-CoV-2."
20 [29]	5/10 (50)	64–90 y, not stated	Not stated	Not stated	"Minor neutrophil infiltration was indicative of secondary infection and/or aspiration"	Not stated	Autopsies, performed in 10 of 12 consecutive patients from Germany who died with SARS-CoV-2 infection, through 19 April. DAD was dominant histopathologic finding in all pts.
21 [30]	5/8 (63)	37–75 y, 80% M	Fever, cough, myalgia, dyspnea	Not stated	"Acute bronchopneumonia"	Not stated	Autopsies, pts from USA, dates unclear. Average of 5 sections of lung examined for each pt. All pts had evidence of DAD. Deaths occurred in community (2) and in-hospital (3) cohorts.
22 [31]	6/10 (60)	33–83 y, 50% M	Fever, dyspnea, cough most common 3–16 d	Not stated	"Secondary suppurative pneumonia," which was "intense" and "mild" in 5 and 1, respectively	Not stated	Ultrasound-guided minimally invasive autopsies, pts from Brazil, through April. Cases described as "secondary bacterial pneumonia." All pts had DAD.
23 [32]	1/10 (10)	Not stated	Not stated	Cefepime	"Focal acute inflammatory infiltrate suggestive of a secondary infection. The neutrophils…were partly degenerated and entrapped in fibrin, possibly representing NETs"	Not stated	Autopsy, pt from USA, through March. Meaning of histopathologic finding at left is unclear. "A notable finding was the absence of observed secondary infection in our patients. Although most of the patients received antibiotic therapy…. The absence of bacterial infection suggests that this was not the main cause of death."
24 [33]	1/1 (100)	31 y, W	Loss of consciousness	None	"In the alveolar exudate, there were… only scant PMNs and lymphocytes. Focal areas of intra-alveolar hemorrhage and bacterial proliferation were also present" "Liver microabscesses"	Postmortem: "mixed flora…on blood, lungs, liver, spleen and CSF"	Autopsy, pt from Switzerland, March or earlier. Death occurred at home. "An early phase of secondary bacterial infection was noticed within the alveoli, with margination of PMNs." Cause of death: "pulmonary changes related to SARS-CoV-2 and high fever without implication of a secondary bacterial infection."

Table 1. Continued

Pt No. [Ref]	Lung Infxn, No. (%)	Case Details					Comments[c]
		Age(s), Sex	Clinical History, Time to Death[b]	Abx Treatment	Relevant Histopathology	Microbiology	
25 [34]	3/7 (43)	46–75 y, 67% M	Fever 100%, dyspnea 67% 6–16 d	Cefepime, 1/3	"Marked intra-alveolar accumulation of neutrophil-rich inflammatory cells was observed, which is compatible with acute pneumonia"	Not stated	Needle biopsies, pts from Iran, dates unclear. Histopathologic findings "can be interpreted as acute pneumonia resulting from superimposed bacterial infection."
26 [35]	1/2 (50)	54 y, M	Dyspnea, cough 12 d	Vanco, pip-tazo	"Marked intra-alveolar acute inflammation focally involving all lobes except LLL, diagnostic of acute bronchopneumonia"	Blood: *Enterococcus faecalis*, coagulase-negative *Staphylococcus* Sputum: negative	Autopsy, pt from USA, dates unclear. "Superimposed acute bronchopneumonia." Cause of death: "SARS-CoV-2 infection occurring in the setting of diabetes and underlying cardiovascular disease leading to respiratory and subsequent multiorgan system failure."
27 [36]	4/8 (50)	Median, 73.5 y, 50% M	Fever, cough, dyspnea most common 7–13 d	Not stated	Diffuse or focal bronchopneumonia with filling of alveolar spaces by neutrophils	Immunostain and/or PCR: + *Streptococcus* spp. in 3 pts	Autopsies, pts from USA, dates unclear. Diffuse (1) and focal (3) bronchopneumonia.
28 [37]	2/2 (100)	72–73 y, M	Respiratory failure 1–4 d	None	"Intra-alveolar accumulation of neutrophils"	Not stated	Autopsies, pts from USA, through March. Immunostaining revealed prominent complement. "Tissue neutrophilia may be attributable to the neutrophil chemoattractant properties of complement" rather than bacterial bronchopneumonia.
29 [38]	5/38 (13)	32–86 y, not stated	Not stated	Not stated	Four pts had bacterial abscesses (1 or 2 per lung, <5 mm diameter)	Not stated	Autopsies in 38 consecutive pts from Italy, through 24 March. 4 bacterial abscesses "were presumed to have formed after hospital admission." No microbiology.
30 [39]	2/23 (9)	49 y, M (empyema), no other details	Not stated	None	"Significant neutrophilic infiltrate within alveoli" (1), "right pleura necroinflammatory infiltrate…confirming diagnosis of empyema (1)	Empyema postmortem cx: "mixed flora… consistent with postmortem contamination"	Autopsies, pts from USA, through April. Pt with empyema found dead at home.
31 [40]	17/68 (25)	48–95 y, 82% M	Dyspnea 82%, cough 53%, fever 41%	Abx 71%, no details	"Associated acute bacterial pneumonia"	Not stated	Autopsies, pts from Italy and USA, through 25 April. Pneumonia, "mostly bacterial" 14, lung abscess 1.
32 [41]	10/40 (25)	38–97 y, not stated	Not stated	Not stated	Bronchopneumonia listed as "minor microscopic pattern"	Not stated	Autopsies, pts from USA, through early May. 7 bacterial bronchopneumonias were identified. Bronchopneumonia and other "minor microscopic patterns" were "improbable causes of death."
33 [8]	2/8 (25)	Not stated	Symptoms not stated 7–25 d	Not stated	"Neutrophilic infiltrates" (1), "bronchopneumonia was extensive and necrotizing and associated with bacterial overgrowth" (1)	Not performed	Autopsies, pts from USA, through May. "Since culture results were not available, we cannot exclude artifactual postmortem bacterial overgrowth. The distribution of neutrophils in areas of acute bronchopneumonia differed from the neutrophilic component associated with acute DAD: more localized and peribronchiolar distribution of a more marked neutrophilic infiltrate in the former compared to more diffuse interstitial distribution of neutrophils with mild alveolar accumulation in the latter."
34 [42]	1/1 (100)	65 y, M	Fever, dyspnea 21 d	Antibiotics, but details not provided	"Purulent discharge in most areas of the alveolar spaces"	Not provided	Postmortem biopsy, pt from China, March or earlier. Died of multisystem organ failure. Death "might have been associated with uncontrolled secondary bacterial infection."
35 [43]	8/8 (100)	69–96 y, 87% M	Not stated 6–100 d	Not stated	"Acute bronchopneumonia"	Postmortem cx + 6/8 (*S. aureus* 3, *E. faecium* 1, *E. cloacae* 1, "usual flora" 1)	Autopsies, pts from USA, dates unclear. "Acute bronchopneumonia" cause of death in 7/8. "While acute bronchopneumonia is usually caused by bacterial infection, it might be possible this particular virus elicits an acute bronchopneumonia pattern, especially in cases that are negative by culture…. Negative cultures in cases might also be due to sampling as cultures were taken from periphery of the lungs before they were perfused with formalin and sectioned." Cases were seen with and without DAD.

Table 1. Continued

Pt No. [Ref]	Lung Infxn, No. (%)	Case Details					Comments[c]
		Age(s), Sex	Clinical History, Time to Death[b]	Abx Treatment	Relevant Histopathology	Microbiology	
36 [45]	4/9 (44)	44–66 y, 100% M	Fever, cough, dyspnea 100% 6–35 d	Azithromycin (3), BL/BLI (3), carbapenem (3), linezolid (2)	"Typical bacterial bronchopneumonia with bronchiocentric neutrophilic infiltrate" (3), large venous thrombus containing "small aggregates of mycotic spores" (1)	Respiratory cx: *P. aeruginosa* (2), *E. coli*, *S. aureus* (1 each)	Autopsies, pts from Italy, through 17 April. Bronchopneumonias occurred in setting of late fibrous (proliferative) DAD. Causes of death considered multifactorial.
37 [46]	12/30 (40)	Median, 69 y, 67% M	Cough 73%, Fever 67%, fatigue 43% 16–82 d	100%, but no details provided	"Secondary or coincident microorganism infections"	Sputum cx: *A. baumannii* (12), *K. pneunoniae* (7), *S. maltophilia* (2), *P. aeruginosa*, *E. coli*, *S. aureus* (1 each)	Ultrasound-guided minimally invasive autopsies, pts from USA, dates unclear. In 2 patients, bronchopneumonia was evident in absence of DAD.
38 [47]	5/18 (28)	Median, 61 y, 60% M	Fever most common, dyspnea, cough	Not stated	"Associated areas of bronchopneumonia with numerous neutrophils and focal necrosis"	Not stated	Autopsies and ultrasound-guided minimally invasive autopsies, pts from Spain, dates unclear. Bronchopnuemonia seen in settings of exudative, fibroproliferative, or fibrotic stage DAD.
39 [48]	6/10 (60)	Not stated	Not stated	Not stated	"Neutrophilic pneumonia was observed in...variable degrees"	Not stated	Ultrasound-guided minimally invasive autopsies, pts from Brazil, dates unclear.
40 [49]	3/7 (43)	Not stated	Not stated	Not stated	"Superimposed acute bronchopneumonia, focally necrotizing"	Antemortem respiratory and blood cx: *S. aureus* (1)	Autopsies, pts from USA, through May. *S. aureus* pneumonia and bloodstream infection diagnosed antemortem in 1 pt. Pneumonia not diagnosed antemortem in 2 pts.
41 [50]	2/4 (50)	51–73 y, M	Not stated, 39 d	Both received antibiotics, no details	Intra-alveolar PMNs and macrophages	Not stated	Autopsies, pts from Belgium, through May. Causes of death were ARDS. "Even though NETs may also be induced by bacterial-derived mediators during a secondary infection, we found a massive presence of NETs in each patient, regardless of the status of secondary infection. It is thus unlikely that the secondary infection on its own would be solely responsible for the massive and multifocal infiltration of NETs in our study."
42 [51]	7/18 (39)	41–78 y, 76% M	Not stated, median, 22 (5–44) d	All received antibiotics, no details	"Exudative bronchopneumonia with neutrophilic granulocyte infiltration of bronchi and surrounding parenchyma"	Not stated	Autopsies, pts from the Netherlands, through 18 May. DAD found in all pts, bronchopneumonia predominated in 3/7. Causes of death were respiratory failure due to COVID-19, or multisystem organ failure. One pt died of superimposed bacterial peritonitis due to abdominal surgery complications.
43 [52]	7/24 (29)	30–87 y, 80% M	Fever and cough most common, average, 13 (6–34) d	Not stated	"Supportive bronchopneumonia, alveolar spaces filled with neutrophils"	Not stated	Blind biopsies postmortem, pts from Iran, through April. Bronchopneumonias "most likely correspond to a superimposed bacterial infection." Biopsies in 5/7 pts showed overlapping features of DAD.
44 [53]	1/3 (33)	38 y, W	Chest pain, SOB, unknown duration	None	"Extensive neutrophilic inflammation within alveoli"	Not stated	Autopsy, pt from USA, dates unclear. Died shortly after presentation to hospital.
45 [54]	7/13 (54)	41–90 y, 77% M	Median, 22 (6–40) d	"Nearly all pts received pip-tazo as prophylaxis"	"Florid bronchopneumonia"	*P. aeruginosa* (3)	Autopsies, pts from Germany, through 23 May. Bronchopneumonia deemed like to be "the consequence of secondary infection." "Superinfections with *Pseudomonas*" diagnosed antemortem in 3/7 cases. COVID-19 considered cause of death in most pts.

Abbreviations: Abx, antibiotics; ARDS, acute respiratory distress syndrome; BL/BLI, β-lactam/β-lactamase inhibitor; COVID-19, coronavirus disease 2019; CSF, cerebrospinal fluid; CVA, cerebrovascular accident; DAD, diffuse alveolar damage; LLL, left lower lobe; NETs, neutrophil extracellular traps; PCR, polymerase chain reaction; PMNs, polymorphonucleocytes; Pt, patient; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOB, shortness of breath.

[a]In other postmortem studies that examined the lungs (n = 30 studies, 85 patients), there were no histopathologic findings described that were consistent with superimposed pneumonia [25, 44, 55–82]. Therefore, histopathologic findings consistent with superimposed pneumonia were reported in 32% (200/621) of postmortem examinations and in 60% (45/75) of published reports.

[b]Time from onset of symptoms to death.

[c]Dates of cases are presented as months of autopsy, 2020.

pneumonias were focal and diffuse/extensive, respectively. Histopathology-proven infections occurring with lung infections included central nervous system infections (2 patients), multisystem abscesses, liver abscesses, endocarditis, nonpulmonary septic thromobemboli, mediastinal lymphadenitis, and peritonitis (1 patient each).

Proven and Possible Lung Superinfections

Proven superinfections were identified by direct tissue visualization of bacteria, microbiologic cultures, and/or postmortem PCR in 25.5% (51/200) of patients with otherwise consistent histopathologic findings. Among the entire cohort, proven bacterial infections were identified in 8% (51/621) of patients. Pathogens identified by direct visualization, culture, and PCR are listed in Table 2.

Possible superinfections were identified in the remaining 74.5% (149/200) of patients, in whom histopathologic findings were consistent with an infection, but bacteria were not visualized in tissue or detected by culture or PCR. There were no significant differences in histopathologic findings among patients with proven or possible superinfections (other than in detection of pathogens), those with potential lung superinfections in the community vs hospital, those who received mechanical ventilation vs those who did not, those from different continents (data not shown), or those presenting in different months.

Lung Superinfections as Causes of Death

Lung superinfections were the cause of death of 16% (16/97) of patients with potential bacterial infections for whom a cause of death was assigned. In the remaining 84% (81/97) of cases, deaths were not due to bacterial superinfection. The most commonly attributed cause of death was respiratory failure due to COVID-19. Lung superinfections were the cause of death of 3% (16/621) of all patients who underwent postmortem examination for whom a cause of death was assigned.

DISCUSSION

This is the first comprehensive review of postmortem studies of persons with COVID-19 for histopathologic evidence of bacterial superinfections. The quality of data on superinfections was uneven, which likely reflected the fact that identifying such events was not a major objective or end point in 96% of studies. As such, detailed clinical, microbiologic, and histopathologic descriptions of these infections were often lacking, and accompanying discussions were largely cursory. Histopathologic findings that were consistent with potential lung superinfections were evident in 32% of patients. Lung infections were proven by visualization of bacteria in tissue, microbiologic cultures, or PCR in 8% of patients. In 24% of patients, lung superinfections were possible based on histopathologic findings, but causative organisms were not visualized or detected. Potential (ie, proven or possible) bacterial superinfections included pneumonia (95%), abscesses or empyema (3.5%), and septic emboli (1.5%). In 73% of pneumonias, histopathologic findings were focal, and, in many instances, they were of uncertain clinical significance (see descriptions in the Table 1 comments column). When causes of death were assigned, lung superinfections were deemed responsible in only 16% of patients with potential infections and 3% of all SARS-CoV-2-infected patients. Given the limitations cited above, the data must be interpreted with caution. Nevertheless, our review indicates that 8%–32% of persons who have died thus far with COVID-19 had superinfections of the lungs, but such infections were uncommonly the cause of death.

The findings here were broadly in keeping with data from COVID-19 clinical studies, in which bacterial superinfections were reported in ~16% of critically ill patients [2]. Seventy-nine percent of patients with possible lung superinfections in our review were treated with antibiotics, which is consistent with the 71% treatment rate in a living review of hospitalized COVID-19 patients [2]. With rare exception, postmortem studies and clinical reports were not designed to specifically

Table 2. Causes of Proven Bacterial Lung Infections in Postmortem Tissue Samples of Patients With COVID-19

Direct Visualization of Bacteria in Tissue, No.	Positive Culture Results for Bacteria, No.	Positive PCR Results for Bacteria, No.
Bacteria NOS, 24	*Acinetobacter baumannii*, 12	*Streptoococcus* spp., 3
	Staphylococcus aureus, 10	
	Pseudomonas aeruginosa, 10	
	Klebsiella pneumoniae, 8	
	Escherichia coli, 3	
	Stenotrophomonas maltophilia, 2	
	Enterococcus spp., 2	
	Proteus mirabilis, 1	
	Enterobacter cloacae, 1	
	Coagulase-negative *Staphylococcus*, 1	
	"Mixed flora," 3[a]	

Abbreviations: COVID-19, coronavirus disease 2019; NOS, not otherwise specified; PCR, polymerase chain reaction.

[a]"Mixed flora" typically are ascribed to postmortem contamination; these cases were not included as potential superinfections in our series.

detect or define superinfections [1]. A somewhat higher prevalence of bacterial lung infections in postmortem studies may reflect increased likelihood of these events among patients who die, or an overestimation of cases. In the absence of direct visualization or recovery of pathogens, superinfections would be overestimated in postmortem studies if histopathologic findings such as acute neutrophil infiltration of alveoli were caused by SARS-CoV-2 or other agents, rather than by bacteria. Conversely, bacterial infections may be understated in postmortem studies if tissue sections were from uninvolved areas of the lung. It is also possible that widespread empiric antibiotic treatment led to underdiagnosis of antemortem pneumonia, even if postmortem histopathologic findings were supportive of infection. We found bacterial lung superinfections identified by postmortem examination that were not suspected clinically [49], as well as cases that were suspected clinically but not confirmed by histopathology [9]. Taken together, the data attest to the challenges in diagnosing non-SARS-CoV-2 infections in patients with COVID-19, and in making sound treatment decisions in accordance with antimicrobial stewardship principles [1, 83].

Studies that sought etiologic agents of infection largely identified nosocomial pathogens that cause health care– and ventilator-associated pneumonia, including nonfermenting and fermenting gram-negative bacteria (most notably, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli*, *Stenotrophomonas maltophila*) and *Staphylococcus aureus* (Table 2). Postmortem cultures of tissues are susceptible to microbial contamination [4], but this possibility was mitigated in our study by the presence of supportive histopathology, recovery of plausible bacterial pathogens, and exclusion of results that described "mixed flora" or organisms "consistent with postmortem contamination." *Streptococcus* species or other bacteria that typically colonize the upper respiratory tract were identified uncommonly in COVID-19 postmortem examinations, which marks a difference with findings of autopsy studies of lungs from patients dying with superinfections during the 1918–1919 influenza pandemic [5]. In postmortem studies of influenza during the 1918–1919 and 1957 pandemics, *S. aureus*, Strepotococcs species, and tissue culture–negative pneumonias were prominent; the gram-negative pathogens described in patients with COVID-19 were rare. [5, 84]. It is possible that patients in our cohort were more likely to receive broad-spectrum antibiotics and undergo mechanical ventilation than patients with influenza in 1918–1919 and 1957, which may have contributed to our finding of greater incidence of pneumonias by gram-negative bacteria. Over the past 20 years, a growing body of experimental research has identified viral-mediated alterations to host cells and immune system function that promote pathogenesis of influenza-associated lung infections [85, 86]. It is unclear if DAD or immune system derangements caused by SARS-CoV-2 are also predisposing conditions for secondary pneumonia, or if these infections stem from risks associated with hospitalization or serious illnesses in general [15].

In most reports included in our review, superimposed pneumonia was observed in association with COVID-19-associated DAD. The intra-alveolar and peribronchial neutrophilic infiltrates characteristic of bacterial pneumonia are typically more extensive than observed during acute DAD, which usually exhibits diffuse but less intense interstitial and mild intra-alveolar neutrophil accumulations [8, 9]. Despite these distinctions, it was often difficult to distinguish between DAD complicated by a possible superimposed pneumonia and DAD that reflected the natural course of SARS-CoV-2 infection [20]. In keeping with histopathologic findings, transcriptional profiling of postmortem lung samples from patients with COVID-19 revealed enrichment of genes involved in neutrophil activation and neutrophil-mediated immunity, including those contributing to generation of neutrophil extracellular traps (NETs) [87]. NETs may be induced by bacterial-derived mediators, but they are well described in COVID-19 autopsies in the absence of lung superinfections [50]. Pulmonary neutrophilia may also be attributable to chemoattractant properties of complement deposition, which can be another histopathologic feature of COVID-19 [37].

We acknowledge that postmortem studies face inherent biases due to the selection of fatal cases, including potential for over-representation of severe pathology and descriptions of histopathologic and microbiologic patterns that may differ from those observed in disease survivors [4, 51]. Our review was limited to bacterial lung infections because they are the most common superinfections in COVID-19 case series [1], the majority of postmortem reports have focused on the respiratory tract, and histopathologic studies of other anatomic systems usually have not addressed superimposed infections. The overall prevalence of superinfections is higher than identified here, as bloodstream, urinary tract, skin and soft tissue, *Clostridiodes difficile,* and other nosocomial infections also occur in SARS-CoV-2-infected patients [1]. The vast majority of postmortem examinations were from COVID-19 epicenters during the early months of the pandemic. The incidence, outcomes, and clinical, microbiologic, and pathologic features of superinfections may change as management of COVID-19 evolves and strains on health care personnel and resources fluctuate. Scant data were presented on antimicrobial resistance (AMR) in postmortem studies. Nevertheless, the bacteria reported in studies are well recognized for their propensity to develop AMR. The impact of COVID-19 on AMR is unclear [88]. However, it is reasonable to assume that microbiology and susceptibility patterns will be in keeping with local epidemiology and that trends of emerging AMR pathogens (such as increasing prevalence of extended beta-lactamase-producing Enterobacteriaceae in the United States) will continue [1].

CONCLUSIONS

Postmortem histopathology data indicate that bacterial lung superinfections complicated a minority of COVID-19 cases globally over the first months of the pandemic, and they were uncommonly the cause of death. It is plausible that the features and impact of superinfections will change as the pandemic progresses, particularly as mortality rates have declined in hospitalized patients and as the roles of corticosteroids and other immunomodulatory drugs evolve [89]. Antimicrobial stewardship will continue to be a priority, as antibacterial use in SARS-CoV-2-infected patients is likely to remain in excess of superinfections [1, 83]. It is imperative that centers collect and publish their clinical, microbiology, antimicrobial prescribing, and AMR data, using rigorous, systematic testing strategies and clearly stated case definitions. There is a pressing need for well-designed prospective studies, particularly as COVID-19 treatment paradigms shift. The failure of many postmortem studies to discuss or seriously investigate superinfections is a major missed opportunity. In future studies, greater attention should be paid to identifying potential bacterial infections, including those of organs other than the lungs, and to coupling histopathologic findings with clinical data. Other priorities are to identify risk factors for superinfections, including those specific to SARS-CoV-2 infection, define relationships between timelines of superinfections and corresponding microbiology and AMR patterns, and understand the accuracy of antemortem diagnoses of pneumonia and their impact on antimicrobial usage and patient outcomes.

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