Bacterial superinfections among persons with coronavirus disease 2019: A comprehensive review of data from postmortem studies

Cornelius J. Clancy¹, Ilan S. Schwartz², Brittany Kula², M. Hong Nguyen¹

¹Division of Infectious Diseases, Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, United States

²Division of Infectious Diseases, Department of Medicine, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada

Corresponding author: Cornelius J. Clancy, M.D.
867 Scaife Hall,
3550 Terrace Street,
Pittsburgh, PA USA 15203
412-648-8510
cjc76@pitt.edu

Alternative corresponding author: M. Hong Nguyen, M.D.
867 Scaife Hall,
3550 Terrace Street,
Pittsburgh, PA USA 15203
412-383-5193
mhn5@pitt.edu

Summary: In published postmortem studies, 32% of patients with COVID-19 had lung histopathology consistent with potential bacterial superinfections (proven, 8%; possible, 24%). Bacterial superinfections of the lungs were responsible for only 3% of deaths among COVID-19 patients.
Abstract.

**Background.** Limited clinical data suggest ~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 26 September 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 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. 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; most common agents were beta-lactam/beta-lactamase inhibitors (48%), macrolides (16%), cephalosporins (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.
order, pathogens included *Acinetobacter baumannii*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. Lung superinfections were causes 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.

**Key words:** Covid-19; SARS-CoV-2; superinfections; bacteria; postmortem
Introduction.

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 healthcare- 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 endpoints. 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 under-utilized 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 1918-19 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, which have defined diffuse alveolar damage (DAD) as the histopathologic hallmark of 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 26 September 2020 using 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 (CJC and/or ISS) contacted 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 one patient with a potential bacterial lung superinfection was included in 60% (45/75) of 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 prior to 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 deaths. 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 pneumonias were focal and diffuse/extensive, respectively. Histopathology-proven infections occurring with lung infections included central nervous system infections (2 patients), multi-system abscesses, liver abscesses, endocarditis, non-pulmonary 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); and 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, in 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, in 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 endpoint 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 (i.e., 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 comments, Table 1). 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 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.

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 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 over-estimation of cases. In the absence of direct visualization or recovery of pathogens, superinfections would be over-estimated 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 under-stated in postmortem studies if tissue sections were from uninvolved areas of lung. It is also possible that widespread empiric antibiotic treatment led to under-diagnosis of ante-mortem 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 healthcare- and ventilator-associated pneumonia, including non-fermenting and fermenting Gram-negative bacteria (most notably, Acinetobacter baumannii, Pseudomonas aeruginosa, Klebsiella pneumoniae, Escherichia coli, Stenotrophomonas maltophilia) and Staphylococcus aureus (Table 2). Postmortem cultures of tissues are susceptible to microbial contamination,[4] but this possibility was mitigated in our study by 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 1918-19 influenza pandemic.[5] In postmortem studies of influenza during 1918-19 and 1957 pandemics, S. aureus and tissue culture-negative pneumonias were prominent, but other agents 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 were patients with influenza in 1918-19 and 1957, which may have contributed to 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 COVID19-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).[88] 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, since 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 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 healthcare 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.[87] 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 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 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 patients’ outcomes.
Source of funding.

There was no funding for this study.

Patient consent.

Data in this paper were publically available. There was no need for the authors to consent patients.

Conflicts of interest.

Dr. Clancy has been awarded investigator-initiated research grants from Astellas, Merck, Melinta, and Cidara for studies unrelated to this project, served on advisory boards or consulted for Astellas, Merck, the Medicines Company, Cidara, Scynexis, Shionogi, Qpex and Needham & Company, and spoken at symposia sponsored by Merck and T2Biosystems. Dr. Schwartz has served on an advisory board for AVIR Pharma. Dr. Kula has no potential conflicts. Dr. Nguyen has been awarded investigator-initiated research grants from Astellas, Merck, Melinta and Cidara for projects unrelated to this study, and served on advisory boards for Astellas, Merck, the Medicines Company, Scynexis and Shionogi.
Table 1. Postmortem histopathology consistent with lung superinfections in patients with COVID-19*

| Pt n [Ref] | Lung infxn (n, %) | Age(s), Sex | Clinical history, Time to death** | Abx treatment | Relevant histopathology | Microbiology | Comments*** |
|------------|------------------|-------------|----------------------------------|--------------|------------------------|-------------|-------------|
| 1 [10]     | 10/21 (48%)      | 66-96 y     | Cough 50%, fever 38%, 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     | 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          | 1/2              | 42 y M      | Cough, fever,                     | Not stated   | “Acute bronchopneumonia” | Not stated | Autopsy, pt from US, March. Cause of death listed as “complications of...” |
| Study | Deaths | Study Population | Clinical Presentation | Laboratory Findings | Autopsy Findings |
|-------|---------|------------------|-----------------------|--------------------|------------------|
| 1.13  | (50%)   | 17               | Dyspnea 48 hours      | Focal aspiration   | Lung tissue: *E. coli, P. mirabilis* hepatic cirrhosis. “Acute bronchopneumonia with aspiration” listed as significant condition. Pt died in community. |
| 1.14  | (67%)   | 5                | 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" Autopsies, pts from Romania, through May. Causes of death listed as “direct lung injury due to viral pneumonia.” 1 death with pneumonia in community |
| 1.15  | (50%)   | 6                | 65 y M                | Fever, respiratory failure 16 d Yes, no details | Alveolar wall destruction, diffuse inflammatory infiltrate, “concentrated inflammatory exudate filling the airspaces” 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” |
| 1.16  | (30%)   | 7                | 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 Autopsies, pts from UK, through April. Causes of death DAD in 2 pts |
| 1.17  | (55%)   | 8                | 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 Autopsies, pts from Austria, through 14 April. Predominant causes of death DAD and respiratory insufficiency, and thromboses. Deaths included community cases. 2/11 received mechanical ventilation |
| 1.18  | (91%)   | 9                | 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]. |
| 1.19  | (25%)   | 10               | 78 y W                | 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 |
| No. | Data | Age | Gender | Symptoms | Treatment | Diagnosis | Autopsy Details |
|-----|------|-----|--------|----------|-----------|-----------|-----------------|
| 11  | 11/14 (79%) | 55-94 y, 64% M | SOB (11), Fever (11), cough (10), 6-50 d | DAD with “superimposed acute bronchopneumonia” “Dense accumulation of neutrophils within the airways and alveoli” | Postmortem cx: S. aureus, 4; K. pneumoniae, 1 each | Autopsies, pts from Austria, through 14 May. Acute bronchopneumonia considered major cause of death in 2 pts. |
| 12  | 8/17 (47%) | 53-77 y, all M | 3-14 d, symptoms not stated | “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  | 1/1 (100%) | 93 y W | Cough, prostration, 20 d | “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  | 4/12 (33%) | 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  | 3/14 (21%) | 73-84 y, all W | Respiratory distress 2, SOB, fever, cough, N/V, 2-23 d | “Areas of neutrophilic inflammation” “acute bronchopneumonia” | Not detected | Autopsy, pt from US, 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  | 1/1 | 76 y W | Nasal | Ceftriaxone, | Not stated | Autopsy, pt from US, date unclear. Comfort measures only. Primary |
| Reference | Cases | % of Total | Age | Gender | Symptoms | Duration | Findings | Cause of Death | Methodology |
|-----------|-------|------------|-----|--------|----------|----------|----------|---------------|-------------|
| [24]      | 1     | (100%)     |     |        |          |          | azithromycin histiocytic infiltrates in alveolar spaces | cause of death was “DAD due to SARS-CoV-2.” “Focal pneumonic process, consistent with superimposed bronchopneumonia” | Autopsies, pts from UK, through April. Bronchopneumonia superimposed on DAD. One patient found dead at home |
| [26]      | 1     | (33%)      | 33 y W, 70 y M | Not stated | 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 |
| [27]      | 1     | (43%)      | 50-77 y | 100% M | Fever, cough, respiratory failure, 6-31 d | Not stated | “Superimposed bacterial lobar pneumonia” | Not stated | Autopsies, pts from US, April. |
| [28]      | 1     | (100%)     | 59 y M | Not stated | 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” |
| [29]      | 1     | (50%)      | 64-80 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 |
| [30]      | 1     | (63%)      | 37-75 y | 80% M | Fever, cough, myalgia, dyspnea | Not stated | “Acute bronchopneumonia” | Not stated | Autopsies, pts from US, 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. |
| [31]      | 1     | (60%)      | 33-83 y | 50% M | Fever, dyspnea, cough most common, 3-16 d | Not stated | “Secondary suppurative pneumonia”, which was “intense” or “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. |
| [32]      | 1     | (10%)      | Not stated | Not stated | Cefepime | Not stated | “Focal acute inflammatory infiltrate suggestive of a” | Not stated | Autopsy, pt from US, through March. Meaning of histopathologic finding at left is unclear. “A notable finding was the absence of observed...” |
secondary infection. The neutrophils...were partly degenerated and entrapped in fibrin, possibly representing NETs”

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.”

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”

Needle biopsies, pts from Iran, dates unclear. Histopathologic findings "can be interpreted as acute pneumonia resulting from superimposed bacterial infection”

Autopsy, pt from US, 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”

Autopsies, pts from US, through March. Immunostaining revealed
| [37] | (100%) | failure 1-4 d | neutrophils | prominent complement. “Tissue neutrophilia may be attributable to the neutrophil chemoattractant properties of complement” rather than bacterial bronchopneumonia |
| 29 | 5/38 (13%) | Not stated | Not stated | Four pts had bacterial abscesses (1 or 2 per lung, <5 mm diameter) | Not stated |
| 30 | 2/23 (9%) | 49 y M (empyema) | Not stated | 32-86 y | Not stated |
| 31 | 17/68 (25%) | Dyspnea 82%, cough 53%, fever 41% | Abx 71%, no details | Not stated |
| 32 | 10/40 (25%) | Not stated | Not stated | Not stated |
| 33 | 2/8 (25%) | Symptoms not stated. 7-25 d | Not stated | Not stated |
| 34 | 1/1 | 65 y M | Fever, dyspnea | Antibiotics, “Purulent discharge in most |

Autopsies in 38 consecutive pts from Italy, through 24 March. 4 bacterial abscesses “were presumed to have formed after hospital admission.” No microbiology

Autopsies, pts from US, through April. Pt with empyema found dead at home.

Autopsies, pts from US, through April. Pt with empyema found dead at home.

Autopsies, pts from US, through 25 April. Pneumonia, “mostly bacterial” 14; lung abscess 1

Autopsies, pts from US, through early May. 7 bacterial bronchopneumonias were identified. Bronchopneumonia and other “minor microscopic patterns” were “improbable causes of death”

Autopsies, pts from US, 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”

Postmortem biopsy, pt from China, March or earlier. Died of...
| Study | N (%) | Age | Gender | Duration | Clinical Findings | Pathologic Findings | Cause of Death | Additional Information |
|-------|-------|-----|--------|----------|------------------|---------------------|---------------|------------------------|
| 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 US, 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. |
| 36 [45] | 4/9 (44%) | 44-66 y | 100% M | Fever, cough, dyspnea | 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 multi-factorial. |
| 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. pneumoniae (7), S. maltophilia (2), P. aeruginosa, E. coli, S. aureus (1 each) | Ultrasound-guided minimally invasive autopsies, pts from US, 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. Bronchopneumonia seen in settings of exudative, fibroproliferative or fibrotic stage DAD. |
| No. | Date | % Male | Age (y) | Symptoms | Chest Radiograph | Outcome | Diagnosis | Details |
|-----|------|--------|---------|----------|-----------------|---------|-----------|---------|
| 39  | 6/10 | 60%    | Not stated | Not stated | "Neutrophilic pneumonia was observed in...variable degrees" | Not stated | Ultrasound-guided minimally invasive autopsies, pts from Brazil, dates unclear. |
| 40  | 3/7 | 43%    | Not stated | Not stated | "Superimposed acute bronchopneumonia, focally necrotizing" | Antemortem respiratory and blood cx: S. aureus (1) | Autopsies, pts from US, through May. S. aureus pneumonia and bloodstream infection diagnosed antemortem in 1 pt. Pneumonia not diagnosed antemortem in 2 pts. |
| 41  | 2/4 | 50%    | 51, 73 y M | 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  | 7/18 | 39%    | 41-78 y, 76% M | Not stated, Median 22 d (5-44 d) | "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  | 7/24 | 29%    | 30-87 y, 80% M | Fever and cough most common. Average 13 d (6-34 d) | "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  | 1/3 | 33%    | 38 y W | Chest pain, SOB, unknown duration | None | "Extensive neutrophilic inflammation within alveoli" | Not stated | Autopsy, pt from US, dates unclear. Died shortly after presentation to hospital. |
| 45  | 7/13 | 54%    | 41-90 y, 77% M | Median 22 d (6-40 d) | "Nearly all pts received pip-" | "Florid bronchopneumonia" | P. aeruginosa (3) | Autopsies, pts from Germany, through 23 May. Bronchopneumonia deemed like to be "the consequence of secondary infection." |
tazo as prophylaxis”

“Superinfections with Pseudomonas” diagnosed antemortem in 3/7 cases. COVID-19 considered cause of death in most pts.

*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.

**Time from onset of symptoms to death.

***Dates of cases are presented as months of autopsy, 2020.

Abbreviations:  COVID-19 – coronavirus disease 2019; SARS-CoV-2 – severe acute respiratory syndrome coronavirus-2; Pt – patient; n – number; Ref – reference; Abx – antibiotics; y: years; M - man; W – woman; d – days; DAD – diffuse alveolar damage; ARDS – acute respiratory distress syndrome; BL/BLI – β-lactam/β-lactamase inhibitor; CSF – cerebrospinal fluid; CVA – cerebrovascular accident; PCR – polymerase chain reaction; US – United States; UK – United Kingdom; DAD – diffuse alveolar damage; LLL – left lower lobe; PMNs – polymorphonucleocytes; NETs - neutrophil extracellular traps; spp - species
Table 2. Causes of proven bacterial lung infections in postmortem tissue samples of patients with COVID-19

| Direct visualization of bacteria in tissue, n | Positive culture results for bacteria, n | Positive PCR results for bacteria, n |
|---------------------------------------------|----------------------------------------|------------------------------------|
| Bacteria NOS, 24                            | Acinetobacter baumannii, 12             | Streptococcus 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\(^1\)                   |                                    |

\(^1\) "Mixed flora" typically are ascribed to postmortem contamination; these cases were not included as potential superinfections in our series.

n: number; NOS: not otherwise specified; spp.: species
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