Bacterial and Fungal Growth in Sputum Cultures from 165 COVID-19 Pneumonia Patients Requiring Intubation: Evidence for Antimicrobial Resistance Development and Analysis of Risk Factors

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Research

Keywords: SARS-CoV-2, COVID-19, Pneumonia, Bacterial superinfection, Sputum culture, Antibiotic resistance, Antimicrobial stewardship

Posted Date: September 24th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-79487/v1

Version of Record: A version of this preprint was published at Annals of Clinical Microbiology and Antimicrobials on September 25th, 2021. See the published version at https://doi.org/10.1186/s12941-021-00472-5.

Abstract

Background: Coronavirus SARS-CoV-2 causes COVID-19 illness which can progress to severe pneumonia. Empiric antibacterials are often employed though frequency of bacterial superinfection is debated and concerns raised about selection of bacterial antimicrobial resistance. We evaluated sputum bacterial and fungal growth from 165 intubated COVID-19 pneumonia patients. Objectives were to determine frequency of culture positivity, risk factors for and outcomes of positive cultures, and timing of antimicrobial resistance development.

Methods: Retrospective reviews were conducted of COVID-19 pneumonia patients requiring intubation admitted to a 1,058-bed four community hospital system on the east coast United States, March 1 to May 1, 2020. Length of stay (LOS) was expressed as mean (standard deviation); 95% confidence interval (95% CI) was computed for overall mortality rate using the exact binomial method, and overall mortality was compared across each level of a potential risk factor using a Chi-Square Test of Independence. All tests were two-sided, and significance level was set to 0.05.

Results: Average patient age was 68.7 years. Eighty-three patients (50.3% of total) originated from home, 10 from group homes (6.1% of total), and 72 from nursing facilities (43.6% of total). Mortality was 62.4%, highest for nursing home residents (80.6%). Findings from 253 sputum cultures overall were evaluated and did not suggest acute bacterial or fungal infection in 89 (54%) of 165 individuals sampled within 24 hours of intubation. Cultures $\geq$ one week following intubation did grow potential pathogens in 72 (64.9%) of 111 cases with 70.8% consistent with late pneumonia and 29.2% suggesting colonization. Twelve (10.8% of total) of these late post-intubation cultures revealed worsened antimicrobial resistance predominantly in *Pseudomonas*, *Enterobacter, or Staphylococcus aureus*.

Conclusions: In severe COVID-19 pneumonia, a radiographic ground glass interstitial pattern and lack of purulent sputum suggest antibacterials are not needed. Discontinuation of empiric antibacterials should be considered after 48 hours in absence of sputum to culture or results reported "without growth" or "normal flora." Continuing longterm hospitalisation and antibiotics are associated with sputum cultures reflective of hospital-acquired microbes and increasing antimicrobial resistance.

Trial registration: Not applicable as this was a retrospective chart review study without interventional arm.

Background

As of mid-July 2020 the world remains engulfed by a pandemic. Coronavirus SARS-CoV-2 causes COVID-19 disease typically presenting with fever, cough, fatigue and dyspnea [1]. Pulmonary symptoms may follow direct viral invasion and later immune-mediated "cytokine storm" [2, 3]. In severe COVID-19, clinical features often are consistent with sepsis and septic shock [4]. Lung pathology reflects viral injury, bacterial superinfection, or immune-mediated endothelitis and microthrombosis [5, 6]. In the United States, COVID-19 infections and associated hospitalisations, intensive care unit (ICU) utilization, and ventilator usage are increasing [7]. This fall potential resurgence of influenza in the northern hemisphere could pose challenges in diagnosis and management of individuals with fever and respiratory disease.

Respiratory viral infections, especially influenza, are associated with bacterial and fungal superinfection [8–10]. This has also been noted in previous coronavirus outbreaks of Severe Acute Respiratory Syndrome (SARS) [11] and Middle Eastern Respiratory Syndrome (MERS) [12]. However, there is relatively little data on prevalence and severity of bacterial and fungal superinfections in COVID-19. Severe COVID-19 with pulmonary infiltrates and a septic picture progressing to respiratory failure commonly leads to antimicrobial agents directed at bacterial superinfection [13]. Use of immunosuppressants such as tocilizumab and dexamethasone [14, 15] to combat COVID-19 cytokine storm

also contributes to empiric antibacterial and antifungal therapy [16] with concerns about potential development of antimicrobial resistance (AMR) [17, 18].

Some preliminary data suggest bacterial and fungal superinfection may be less common in COVID-19 pneumonia than in influenza [19]. However, superinfecting or colonizing microorganisms have not been well-described for the former. Current data is largely from China with little from Europe or the United States [20]. Larger study numbers, greater geographic distribution, and longer follow up of patients has been suggested [21, 22]. Optimal pneumonia management in COVID-19 patients would reduce prolonged antibiotic courses, restrain development of multidrug-resistant pathogens, and conserve hospital resources [23].

Methods

Study setting

The Main Line Health System (MHLS) consists of five hospitals just northwest of Philadelphia, Pennsylvania, in the mid-Atlantic United States. The system's four acute care teaching hospitals total 1,058 beds including 138 ICU beds. MLHS hospitals began seeing COVID-19 in early March 2020. MLHS had 801 total COVID-19 discharges by May 1, 2020; individual hospitals saw 121 to 323 discharges.

Ethical approval and data collection

After Institutional Review Board approval, we compiled a list of patients with positive nasopharyngeal polymerase chain reaction (PCR) assays for SARS-CoV-2 virus who were intubated and admitted to ICU between March 1 and May 1, 2020, inclusive. Cases were reviewed individually online. Data analysis used FileMaker$^{(R)}$ database software on secure computers. Of 188 total patients, 23 were excluded due to lack of positive SARS-CoV-2 PCR within study dates (3 patients), no radiographic evidence of pneumonia during admission (3), death within 48 hours of admission (13), palliative care chosen on admission (1), and ICU admission due to non-COVID-19-related critical illness, e.g. acute gastrointestinal bleeding (2) and valvular heart disease (1). Cases meeting study criteria were reviewed from admission until discharge or death; one patient was still hospitalised after 90 days when study follow up was discontinued.

At the time of most cases, protocol called for 5 days hydroxychloroquine and azithromycin as potential treatment for COVID-19. Of 165 patients reviewed, 123 required vasopressor, 54 were given tocilizumab, and 7 received extracorporeal membrane oxygenation (ECMO).

Definitions and data analysis

Each sputum culture obtained or ordered was evaluated; cultures within 48 hours of each other with identical results were considered a single culture. Results were categorized as NO SPUTUM OBTAINED, ORDERED/NOT DONE, WITHOUT GROWTH, CONTAMINATED, or based on ORGANISM(S) RECOVERED. Clinical significance was defined:

Pneumonia on admission without intubation: radiographic evidence of pneumonia within 72 hours of admission but ≥ 4 days prior to intubation; treated with antibiotic course.

Pneumonia within 24 hours of intubation: radiographic evidence of pneumonia during the 24 hours before or after intubation; treated with antibiotic course.

Late pneumonia: radiographic evidence of worsening pneumonia occurring more than 7 days since any prior pneumonia diagnosis and treatment; treated with new antibiotic course.

Colonization: growth of organism(s) other than normal oral flora +/- yeast without radiographic evidence of a change in infiltrate appearance; no antibiotic course.

Antibiotic course: antimicrobial therapy ≥ 5 days directed against documented or suspected respiratory pathogen(s); completed or interrupted by patient death / change to palliative care.

Development of antimicrobial resistance (AMR): Sputum isolation later in a patient's hospitalisation of the same organism with significantly increased AMR profile compared with earlier isolate.

Sputum cultures were judged unlikely to be clinically significant if no sputum was obtained, culture was without growth, or only normal oral flora +/- yeast was isolated.

Statistical Methods

Length of stay (LOS) is described as mean (standard deviation) and categorical variables are described as frequency or percentage. A 95% confidence interval (95% CI) was computed for overall mortality rate using the exact binomial method, and overall mortality was compared across each level of a potential risk factor using a Chi-Square Test of Independence. All tests were two-sided, and significance level was set to 0.05. Data was analyzed in Stata/MP 15.1 (StataCorp LP., Texas, USA).

Results

Demographics of study population and clinical outcomes

Table 1 shows characteristics and clinical outcomes for 165 patients studied. Overall mortality was 62.4% (95% CI: 54.6, 69.8%). Men constituted 55.8% of patients; mortality was 57.6% for men compared with 68.5% for women (p = 0.152). Mortality increased with increasing age and patients admitted from home had a mortality of 45.8% compared with 70% in those coming from group homes (p = 0.148) and 80.6% from nursing homes (p = < 0.001). History of hypertension, obesity (body mass index > 30), smoking-related issues, and diabetes mellitus were common but not significantly associated with mortality.

Sputum culture findings

Results of 253 sputum cultures obtained are shown in Fig. 1. Approximately one-third of cultures grew only normal oral flora (n = 83, 32.8%) and an additional group grew only yeast or normal flora plus yeast (n = 33, 13.0%). Three cultures grew *Aspergillus* species not felt to represent infection by patient history, while 12 (4.7%) were "without growth." While not definitive, we posit based on chart review that almost all of these culture findings were not clinically significant.

A single Gram-positive bacterium was recovered from an additional 47 (18.6%) sputum cultures; these were predominantly *Staphylococcus aureus*, methicillin-susceptible (MSSA) (28, 11.1%) and methicillin-resistant (MRSA) (15, 5.9%). Growth of a single Gram-negative bacterium constituted 51 cultures (20.2%) with *Pseudomonas aeruginosa* being most prevalent (n = 25, 9.9%). Cultures growing two or more bacterial species were noted in 23 instances (9.1%), predominantly combinations of Gram-positive and Gram-negative organisms (14 cases) and Gram-

negative flora only (8 cases) with one culture having only Gram-positive flora. *Staphylococcus aureus* and *Pseudomonas aeruginosa* were the most common bacteria found in mixed cultures.

Significance of sputum culture timing related to pneumonia diagnosis and intubation

In Table 2, sputum results are correlated with timing of cultures relative to hospital admission and intubation and likely clinical significance. Some patients were not producing sputum for submission to the laboratory. Sputum culture orders were associated with signs and symptoms of infection, including fever, cough, and leukocytosis, and a radiographic study showing a new infiltrate or worsening of prior findings but occasionally were not carried out.

Admission radiographic and culture findings

Thirty-three patients had chest X-rays (CXRs) showing pneumonia upon admission but did not require intubation until four or more days later (range = 4 to 11 days). The majority were not producing sputum (n = 26, 78.8%) while 4 (12.1%) sputum cultures yielded normal flora only. One culture grew MRSA and one was judged contaminated. Admission CXRs for patients not requiring intubation initially revealed 30 (90.9%) had only interstitial "ground glass" opacities while the remaining 3 (9.1%) included alveolar airspace disease. The MRSA isolate was from a nursing home resident and judged clinically relevant and treated. Notably, 18 (54.5%) of these patients received intravenous antibiotics in addition to hydroxychloroquine and/or azithromycin directed at COVID-19.

Observations at time of intubation

All 165 patients studied were judged to have pneumonia within 24 hours of intubation. No sputum was cultured in 25 (15.2%) cases, while there was no growth in 11 (6.7%), normal oral flora only in 62 (37.6%), and yeast +/- normal oral flora in 16 (9.7%). Thus 114 (69.1% of study patients) did not have culture data supporting a diagnosis of bacterial infection at intubation. However, the remaining 51 (30.9% of study patients) did grow a potential pathogen, primarily bacterial (n = 48, 94.1% of potential pathogens) though *Aspergillus* species were isolated in three (5.9% of potential pathogens). *Staphylococcus aureus* was the most common solitary bacterial isolate upon intubation with methicillin-susceptible strains (n = 17) more common than methicillin-resistant ones (n = 6) by about a factor of almost three to one (33.3% and 11.8% of all potential pathogens respectively). *Escherichia coli* (n = 4, 7.8%) and *Pseudomonas aeruginosa* (n = 3, 5.9%) were the most common of a variety of solitary gram-negative potential pathogens. Polymicrobial growth was seen in 10 cultures (19.6% of those with potential pathogens); MSSA, MRSA, and *Pseudomonas aeruginosa* were most commonly represented.

Late pneumonias after intubation and sputum colonisation

Given extended hospitalisations (mean (SD) LOS of all patients = 19.9 days (14.4), range 2–90 days) and intubation and other invasive procedures, situations suggestive of new infection were not uncommon. There were 80 episodes possibly consistent with late pneumonia after intubation; most patients only had one episode, but 7 patients had two, 4 patients had three, and 1 patient had five. In 29 instances (36.3% of those suggestive of late pneumonia), culture results were 4 (5% of total) no sputum obtained or sent, 13 (16.3% of total) normal oral flora only, and 12 (15% of total) yeast +/- normal flora. With regard to potential pathogens isolated, the remaining 51 (63.8% of late pneumonias) cultures included 17 (33.3% of positives) with *Staphylococcus aureus*, now more equally divided between MSSA and MRSA (9 vs. 8). *Pseudomonas aeruginosa* (n = 14, 27.5% of positives) was the leading solitary gram-negative potential pathogen in late pneumonia.

Cultures judged to have sputum colonizers were found in 31 instances after intubation; these had a similar distribution of normal and potentially pathogenic microbial flora with *Pseudomonas* species most commonly recovered.

Development of antimicrobial resistance (AMR) during hospitalisation

Notably, in 12 patients (n = 11 late pneumonias and n = 1 colonization) increasing antimicrobial resistance was observed during the course of the hospitalisations; see Table 3. Organisms associated with pneumonia included *Pseudomonas aeruginosa* (n = 7) and *Enterobacter* spp. (n = 2) which demonstrated increased beta-lactam and/or carbapenem resistance and MSSA transitioning to MRSA (n = 2). One *Klebsiella* isolate acquired tetracycline resistance but was judged to be a colonizer. Of the 11 late pneumonia patients, only four (36.4%) had been on antibacterial agents prior to hospital admission. However, all of the late pneumonia patients and the colonization patient in this group had received antibacterials around the time of Intubation. In each case of late pneumonia, when susceptibility data became available antibiotics were modified to cover the new resistance patterns.

Discussion

We reviewed critically ill COVID-19 inpatients with respiratory failure requiring intubation. Mortality rate was 62.4% (95% CI:54.6%, 69.8%) reflecting many patients' chronic health problems and advanced age. Nursing home residency was associated with the highest mortality; younger patients from home also had prolonged hospital stays and significant mortality. In most patients not intubated within three days of admission, lack of sputum production or growth of normal oral flora and variations was associated with a ground glass appearance of CXR infiltrates suggesting viral pneumonia. Around intubation, a sizeable fraction of cultures (69.1%) were still not suggestive of bacterial infection. However, *Staphylococcus aureus*, predominantly MRSA, *Pseudomonas aeruginosa*, and various enteric Gram-negative bacteria were also recovered. MRSA recovery was associated with group and nursing home residency and the highest overall mortality rate compared with other sputum isolates. Beyond one week following intubation, both new episodes of suspected pneumonia and instances of colonization had the same spectrum of culture results. However, methicillin-resistance became more common among *Staphylococcus aureus* and *Pseudomonas aeruginosa* also was more common which could reflect early treatment with a non-pseudomonal beta-lactam +/- azithromycin as well as the ICU environment. Significantly, 12 cultures (10.8%) out of 111 beyond one week of intubation grew organisms, predominantly *Pseudomonas aeruginosa*, that had developed increased antimicrobial resistance. Contrary to expectations, most worsening of AMR was in patients from home rather than nursing home residents. This probably reflects the earlier and higher mortality of individuals from nursing homes. These individuals were more likely to grow *Staphylococcus aureus* and/or *Pseudomonas aeruginosa* from sputum at the time of intubation but there were relatively few longterm survivors. Development of AMR occurred late (average = 29.5 days, range = 11 to 58 days) after admission likely explaining the difference of our findings from studies that followed hospitalised patients for much shorter periods of time. Most episodes (54.5–100% depending on type) of suspected pneumonia in our study patients were treated with 5 days or more of broad spectrum antibiotics contributing to worsening AMR.

Our findings show a higher percentage of patients with bacterial and fungal growth in sputum cultures than some reports [24]. Our patients were sicker than in a study of hospitalised but not intubated patients and there was longer patient follow up [22]. Microorganisms recovered in our study were similar in some regards to published data [22] but with relatively few *Streptococcus pneumoniae, Haemophilus*, and *Moraxella* isolates compared with a Chinese study [25]. Testing was not done for *Mycoplasma pneumoniae* which was a common superinfecting pathogen in one

review [26]. Also, the three *Aspergillus* isolates did not represent invasive disease which was a concern of several prior published reviews [26, 27]. Our study does suggest that following admission and intubation, COVID-19 pneumonia patients have the same predisposition to colonization and infections due to nosocomial pathogens well-known in hospital-acquired and ventilator-associated pneumonias. The literature on bacterial sputum cultures in COVID-19 report high rates of antibiotic use [28, 29]. We observed this as well and demonstrated antimicrobial resistance development in over 10% of bacterial isolates late in patients' hospitalisations; this had been predicted [30] but also has been a topic of considerable debate [31, 32, 33, 34].

Strengths of our study include large size and extended follow up. This data from the United States allows comparison with Asia and Europe. Our health system is not a large tertiary referral center, so our experience may be in line with similar facilities in suburban areas of the US which are becoming the pandemic epicenter. Our mix of patients ranging from "healthy" individuals coming from home to older, debilitated individuals residing in nursing facilities may also guide management based on populations served.

Limitations of our study include lack of use of diagnostic tools targeting atypical bacterial infections, e.g. mycoplasma, and the lack of procalcitonin values. Influenza and respiratory syncytial virus studies were done in a minority of patients as infections with these pathogens had waned in our area by the spring. Only some patients received tocilizumab which could influence mortality data. Hydroxychloroquine and azithromycin are no long being given routinely to COVID-19 patients; remdesivir was not available during the study time frame and dexamethasone was not yet considered standard of care.

Conclusions

Based on our findings in severe COVID-19 pneumonia, we recommend: (1) empiric antibacterials should be used sparingly in patients presenting without sputum production and with a radiographic ground glass interstitial pattern; (2) discontinuation of empiric antibiotics should be considered after 48 hours in patients without sputum to culture despite adequate access or who have no growth or "normal flora / yeast" in cultures if the clinical situation allows; suspected aspiration pneumonia is an exception; (3) with longer duration of hospitalisation, sputum cultures increasingly reflect hospital-acquired microbial flora so length of stay and "clinical trajectory" are critical in deciding to use antibiotics and selection of agents; (4) culture results, antibiotic use, and clinical outcomes in COVID-19 patients should be reviewed periodically with changes guided by principles of antimicrobial stewardship.

Abbreviations

AMR = antimicrobial resistance, CI = confidence interval, CXR = chest X-Ray, Enteric GNRs = Enteric Gram-negative rod bacteria, ICU = intensive care unit, LOS = length of stay, MERS = Middle Eastern Respiratory Syndrome, MLHS = Main Line Health System, MRSA = Methicillin-resistant *Staphylococcus aureus,* MSSA = Methicillin-susceptible *Staphylococcus aureus,* PCR = polymerase chain reaction, SARS = Severe Acute Respiratory Syndrome, SD = standard deviation

Declarations

Ethics approach:

Prior to study initiation, permission for the retrospective review was requested from the Main Line Health System Institutional Review Board; this was granted on May 6, 2020 (MLHS IRB F/N-E20-3943B)

Consent for publication:

Not applicable

Availability of data and materials:

The datasets generated and/or analysed during the current study are not publicly available per the MLHS Institutional Review Board due to the chance they may contain identifiable protected health information but are available from the corresponding author on reasonable request such as for editorial review.

Competing interests:

HHL is on the speakers' bureau of DaiichiSankyo Co.; DY, LSP, and LK have no conflicting interests to declare.

Funding:

This study was a voluntary work on the part of the authors and no funding was involved.

Authors' contributions:

All authors participated in the study design, data collection / analysis, and manuscript writing / editing.

Acknowledgments:

Ms. Buckley has granted permission to be listed in the acknowledgments

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Tables

Due to technical limitations, tables are only available as a download in the Supplemental Files section.

Figures

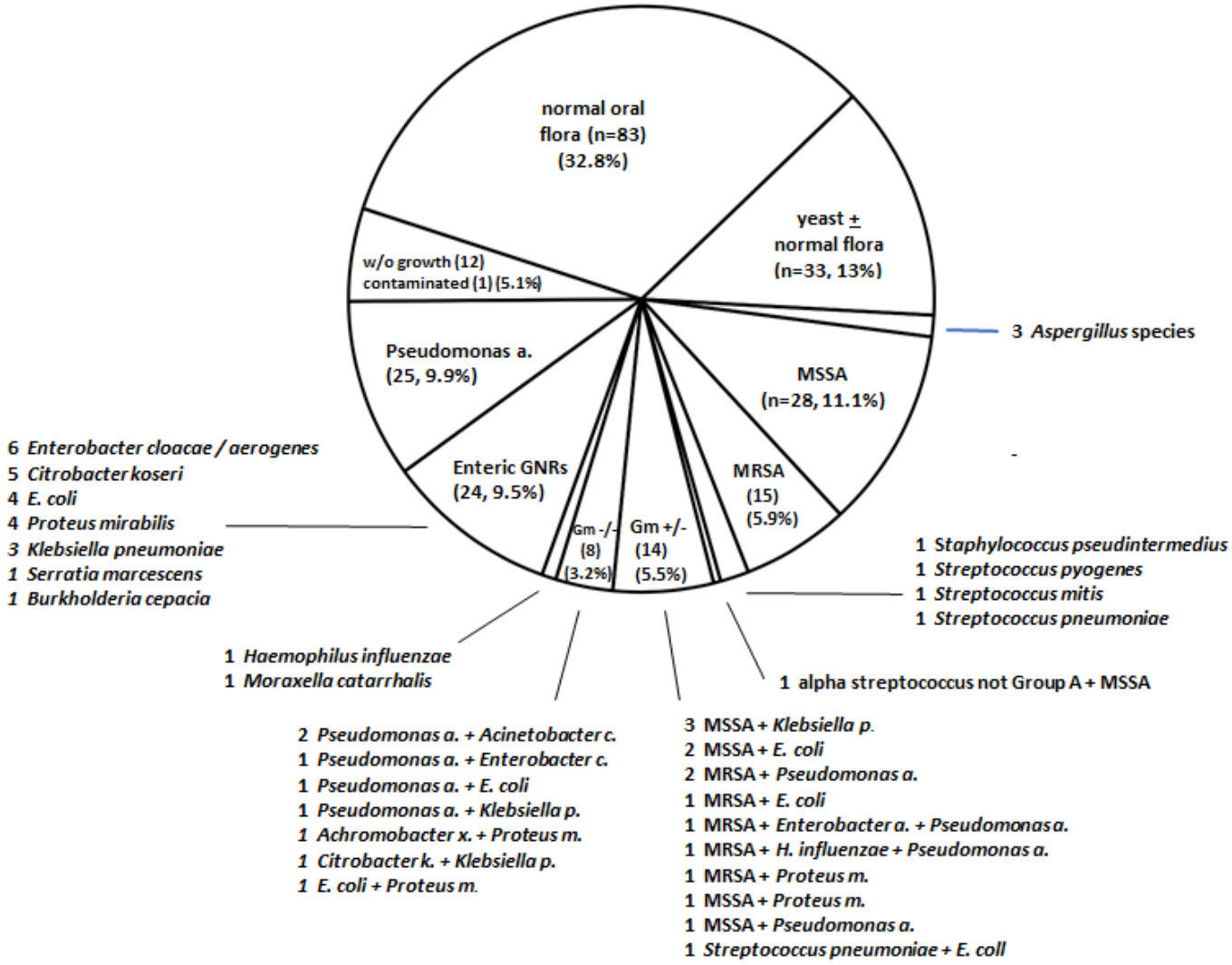

Figure 1

Distribution of all 253 sputum culture results from 165 patients with COVID-19 requiring intubation, March1 to May 1

Supplementary Files

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- Tables.docx