Microbiological Findings and Antibiotic Treatment of Pneumonia: a single-centre retrospective descriptive study

Master's thesis, Medicine

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Abstract

Background: Both national and regional guidelines are regularly published in order to ensure correct diagnosing and treatment of pneumonia contemporary with limiting unnecessary use of antibiotics. Recent studies have shown microbiological findings that question the recommendations in the Danish guidelines. This study aimed to report the aetiology, antibiotic treatment and guideline-adherence in the empirical management of patients hospitalised with pneumonia.

Methods: In this retrospective descriptive study, all adults hospitalised with pneumonia at the Emergency Department of Aalborg University Hospital, Denmark, in the period between November 2021 and June 2022 were included. Patients who were primarily admitted because of COVID-19 were excluded. Hospital records were reviewed, and the microbiological data and the antibiotic therapy were analysed.

Results: The study included 306 patients with a median age of 77 years. In total, 42% of the patients had chronic obstructive pulmonary disease (COPD), 16% had been hospitalised within the last 28 days and 8% were immunocompromised. The majority had a CURB-65 score below 2 (73%). In total, 97% had minimum one microbiological testing of which the proportion of positive findings was 26%. The most frequently identified pathogen was influenza A (22%). The dominant bacterial pathogen was *Haemophilus influenzae* (16%) followed by *Staphylococcus aureus* (10%). *H. influenzae* was the dominant bacterial pathogen amongst both COPD patients and non-COPD patients. *S. aureus* was the most frequently detected pathogen in patients with a CURB-65 score of 3-5 (23%). Regarding the antibiotic treatment, 40% of the immunocompetent patients with community-acquired pneumonia (CAP) did not receive correct empirical treatment in adherence to the regional guidelines. The major reason for non-adherence to guidelines was overtreatment with broad-spectrum antibiotics. At admission time, the most frequently prescribed empirical antibiotics were amoxicillin/clavulanic acid (32%), piperacillin/tazobactam monotherapy (21%) and penicillin monotherapy (18%), respectively. The median length of the antibiotic treatment was 8 days.

Conclusion: Our study showed that *H. influenzae* was the dominant bacterial finding amongst both COPD and non-COPD patients with pneumonia. Amoxicillin/clavulanic acid was the most frequently prescribed antibiotic at admission time. In total, 40% of the immunocompetent patients with CAP did not receive empirical antibiotic treatment in adherence to the regional guidelines. The main reason for non-adherence to guidelines was overtreatment with broad-spectrum antibiotics.

Introduction

Pneumonia is one of the most frequent reasons for hospitalisation. In Denmark, 15,000 people are hospitalised annually with pneumonia [1]. Pneumonia is associated with increased morbidity and mortality, and community-acquired pneumonia (CAP) is the most frequent infectious cause of death in Europe [2,3].

Furthermore, lower respiratory tract infections including pneumonia are the most frequent reasons for prescription of antibiotics in Europe [4]. However, antibiotic treatment is not entirely unproblematic due to the adverse events and antibiotic resistance which is a progressive threat to global health. Especially, broad-spectrum antibiotics are major drivers of antibiotic resistance [5]. In a report by the World Health Organization (WHO), antibiotic resistance is responsible for an estimated 33,000 deaths per year in Europe [6,7]. Consequently, several countries have issued guidelines for the use of antibiotics. Besides reducing the consumption of broad-spectrum antibiotics, adherence to guidelines also reduces the length of stay, the in-hospital mortality and is more cost-effective [8,9]. Hence, it is crucial that the treating physicians adhere to these guidelines. However, some studies have shown that lack of adherence to guidelines at hospitals is a common problem [10,11].

In Denmark and other Scandinavian countries, the empirical treatment for CAP depends on the severity of the pneumonia which is often assessed by the CURB-65 (confusion, urea, respiratory rate, blood pressure, age ≥65 years) scoring system. Mild and moderate CAP is empirically treated with penicillin G or V in order to mainly target *Streptococcus pneumoniae* as it is considered the most frequent bacterial cause of CAP [4,12,13]. However, other recommendations for antibiotic treatment of CAP exist in other countries. In the American, British and German guidelines, a more broad-spectrum antibiotic, amoxicillin, is recommended as the empirical treatment of mild CAP [14–16]. In Spain, monotherapy with quinolone is the empirical antibiotic drug for patients with CAP who require hospitalisation [17]. A reason for this difference in the recommendations between the Scandinavian countries and other countries may be the variation in the bacteriologic aetiology and the antibiotic resistance. The penicillin resistance of *S. pneumoniae* is 22.3 % in Spain whereas it is only 0.6% in Denmark [4,18].

Although, the empirical treatment of mild CAP in Denmark is penicillin in the purpose of ensuring initial coverage of *S. pneumoniae*, a recent study by Fally et al. (2021) reports *Haemophilus influenzae* as the most frequent bacteriological aetiology of CAP in Denmark [19]. However, a Danish study by Thønnings et al. shows that treatment of *H. influenzae* bacteremia with benzylpenicillin is associated with an increased 30-day mortality compared to treatment with aminopenicillins or cefuroxime [20]. These findings question the recommendations in the Danish guidelines for the management of CAP due to the potential resistance of *H. influenzae* to penicillin.

Hence, this study aimed to report the microbiological findings and antibiotic treatment of patients hospitalised with pneumonia. The current study also aimed to investigate whether the physicians in the Emergency Department of Aalborg University Hospital followed the regional antibiotic guidelines in the empirical treatment of CAP.

Methods

Study design and participants

This single-centre retrospective descriptive study included all patients ≥18 years admitted with pneumonia to the Emergency Department (ED) of Aalborg University Hospital, Denmark, in an 8-month period between November 1, 2021, and June 30, 2022. Pneumonia was defined in accordance with the Danish national guidelines and the guidelines of the North Denmark Region as a newly emerged infiltrate on chest radiograph and minimum one of the following symptoms or clinical findings: body temperature >38.0 °C, cough, exacerbated expectoration, dyspnoea, auscultatory rales or percussive dullness [12,21]. Hospital-acquired pneumonia (HAP) was defined as pneumonia developed ≥48 hours after hospital admission or within 28 days after discharge from a previous hospitalisation. Moreover, ventilator-associated pneumonia (VAP) was defined as pneumonia developed ≥48 hours after intubation. The patients were defined to have aspiration pneumonia if the diagnosis was suspected by the attending physician. CAP was defined as patients who did not meet the criteria for HAP, VAP or aspiration pneumonia.

Patients were also included if they were admitted due to other conditions, but at the same time met the criteria for pneumonia. However, patients who were primarily admitted because of COVID-19 were excluded. If a patient was COVID-19 positive but a concurrent bacterial or viral pneumonia was suspected by the attending physician, the patient was included in the study. If a patient was hospitalised with pneumonia more than once during the 8-month period, only the first admission was included in order to ensure the independence of the data.

All types of pneumonia including CAP, HAP, VAP and aspiration pneumonia were included. However, when analysing the adherence to antibiotic guidelines patients with HAP, VAP, aspiration pneumonia, active tuberculosis and immunocompromised patients were excluded. Patients were classified as immunocompromised if they had an infection with human immunodeficiency virus (HIV), had received chemotherapy or immunomodulating drugs within the last 28 days, had received corticosteroids (≥20 mg prednisolone-equivalent/day for more than 14 days), had neutrophil granulocytes <1.0 x 10^9/L, were immunocompromised after an organ transplantation or were splenectomised.

Data collection

All patients who had a chest radiograph at the ED were identified daily by a physician (LHM[1]) associated with the current study. This was done by looking up all hospitalised ED patients in the electronic health record system. The radiological description of the chest radiograph determined the presence of a newly emerged infiltrate. When patients with a newly emerged infiltrate were identified, each patient's hospital records were reviewed in order to exclude those who did not meet the criteria for pneumonia.

All data were collected from the hospital records by a medical student (SS[2]) associated with the current study. The data were managed in a database built by SS in the Research Electronic Data Capture (REDCap) software platform hosted in the North Denmark Region [22,23]. Information regarding comorbidity, penicillin allergy, smoking status, alcohol abuse, pneumonia symptoms, vital signs, biochemistry, arterial blood gas analysis, chest

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radiograph, microbiological findings and antibiotic treatment were recorded. Variables not mentioned in the hospital records were noted as not reported, except for co-morbidities, microbiological findings and antibiotic treatment which were recorded as absent if not mentioned. Microbiological findings from the following methods were reported: blood cultures; sputum cultures; tracheal aspirate cultures; bronchoalveolar lavage fluid (BAL) cultures; PCR detection of atypical pathogens (*Chlamydia pneumoniae*, *Chlamydia psittaci*, *Legionella pneumophila* and *Mycoplasma pneumoniae*) from sputum samples, tracheal aspirate samples and BAL samples; urinary antigen tests for *S. pneumoniae* (PUAT) and *L. pneumophila* (LPUAT); and PCR detection of respiratory viruses (influenza A and B, respiratory syncytial virus (RSV) and SARS-CoV-2 (COVID-19)) from oropharyngeal swab samples. The samples were analysed by the local Department of Clinical Microbiology. Only test results that came out as suitable were included. If the same microbiological pathogen was identified in more than one microbiological test, only one finding was reported.

Whether the empirical antibiotic therapy was prescribed in adherence to the antibiotic guideline, was assessed by SS based on the regional guidelines of the North Denmark Region for CAP. In the regional guidelines, the empirical antibiotic treatment was based on the severity of the pneumonia. Mild pneumonia was defined as a CURB-65 score of 0-2, moderate to severe pneumonia as a CURB-65 score of 3-5, and severe pneumonia as a CURB-65 score of 3-5 with minimum one of the following: involvement of more than one pulmonary lobe, severe hypoxia with oxygen saturation below 92% or sepsis [21]. If no CURB-65 score was documented by the attending physician, it was calculated based on the information in the hospital records. If the distribution of infiltrates on the chest radiograph was not reported, a single infiltrate was assumed. Whether a patient had sepsis was assessed through the quick sequential organ failure assessment score (qSOFA) (respiratory rate, blood pressure, confusion; sepsis if $\geq$2) [24]. Furthermore, when assessing guideline-adherence the attending physician's tentative diagnosis was also taken into account. However, if no antibiotics were given despite meeting the criteria of pneumonia, it was reported as non-adherent to the guidelines.

Statistical methods

All statistical analyses were performed by SS in Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC. Descriptive statistics were performed. Results were reported as counts (%) if categorical data and as medians with 25th to 75th interquartile range (IQR) if continuous data. To analyse differences between two groups, chi-square test was used for categorical data, and Mann Whitney U test was used for continuous data that was not normally distributed. Odds ratios (OR) with corresponding 95% confidence intervals (95% CI) were reported. A P-value <0.05 was considered statistically significant.

Systematic literature search

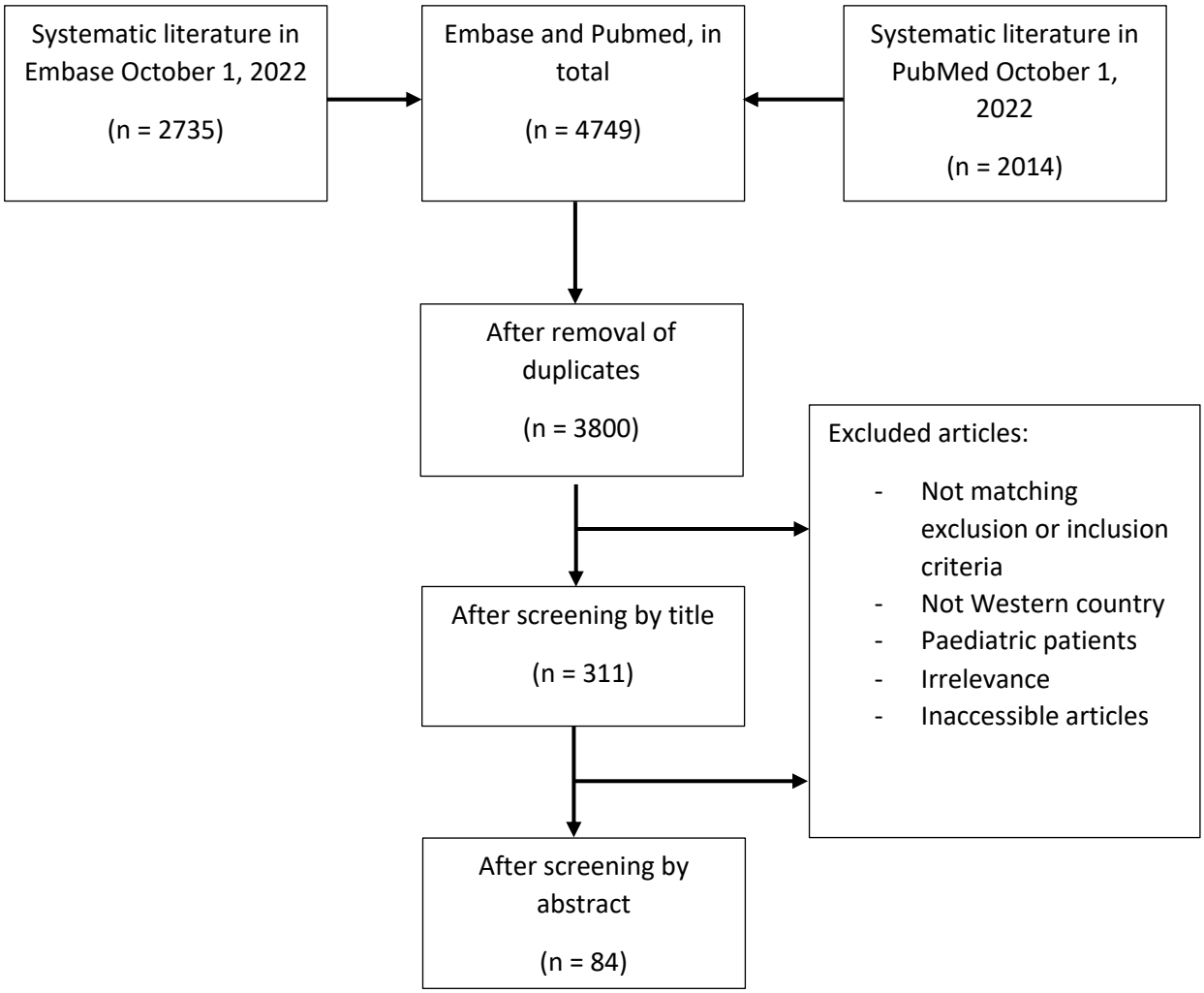
A systematic literature search was performed by SS October 1, 2022, in both Embase and PubMed. The search terms used for the systematic literature search are shown in Table 1. EmTree terms and MeSH terms were used when available. All references were managed in ProQuest® RefWorks software. An overview of the systematic literature search and exclusion of irrelevant studies are illustrated in Figure 1.

Table 1: Search terms for the systematic literature search

	AND					NOT	
OR	Community-acquired pneumonia	Epidemiological study Retrospective study Longitudinal study Cohort analysis Follow up	English [language] Danish [language]	2012-2022 [Publication date]	Humans	Infants Children	Covid-19 [Title]

AND, NOT, OR: Boolean operators

Figure 1: Flowchart of the systematic literature search



Ethics

The study was registered as a quality improvement study at Aalborg University Hospital and was approved by the legal department in North Denmark Region with the ID-number K2022-046.

Results

Patient characteristics

During the 8-month study period, 321 hospitalisations with pneumonia were identified of which 15 (5%) were readmissions and therefore excluded. In total, 306 patients were included in this study. The median age was 77 years, and the distribution of sex was balanced as 50% were women. In total, 22% of the patients were nursing home residents. Chronic obstructive pulmonary disease (COPD) patients comprised 42% of the study population. The majority of patients presented with a CURB-65 score $\leq$2 (73%). The CURB-65 score was only documented by the attending physicians in 12% of the hospital records. Furthermore, 79% of the patients were categorized as having CAP (Table 2). For the overall study population, the median length of stay was 5 days (IQR 3-7) and the 30-day all-cause mortality was 17%. The 30-day all-cause rehospitalisation was 22% of whom 52% met the criteria for a new pneumonia.

Table 2: Patient characteristics

Characteristic	Study population *N* = 306
Age, median (IQR)	77 (70 - 84)
Gender, female	153 (50%)
Nursing home resident	67 (22%)
Immunocompromised	26 (8%)
Co-morbidities	
COPD[1]	128 (42%)
Asthma	17 (6%)
Other chronic respiratory diseases[2]	31 (10%)
Chronic kidney disease	42 (14%)
Chronic heart disease	31 (10%)
Chronic liver disease	6 (2%)
Neoplastic disease	26 (9%)
Diabetes mellitus	66 (22%)
Smoking status	
Never smoked	64 (21%)
Currently smoking	60 (20%)
Ex-smoker	117 (38%)
Not reported	65 (21%)
Alcohol status	
None excessive alcohol consumption	198 (65%)
Excessive alcohol consumption	15 (5%)
Former excessive alcohol consumption	17 (6%)
Not reported	76 (25%)
Type of pneumonia	
Community-acquired pneumonia	241 (79%)
Hospital-acquired pneumonia	50 (16%)
Aspiration pneumonia	14 (5%)
Ventilator-associated pneumonia	1 (0%)
Chest radiograph	
Single infiltrate	136 (44%)
Infiltrates in >1 pulmonary lobe	118 (39%)
Distribution of infiltrates not reported	52 (17%)
CURB-65 score[3]	
0-2	223 (73%)
3-5	83 (27%)
Pneumonia severity index class	
1-2	44 (14%)
3	69 (23%)
4	124 (41%)
5	69 (23%)
qSOFA[4]	
0-1	267 (87%)
2-3	39 (13%)

Data are n (%), unless otherwise indicated
1) Chronic obstructive pulmonary disease
2) Interstitial lung disease, pulmonary cancer, lobectomy, asbestosis, bronchiectasis, emphysema, chronic bronchitis, sleep apnoea
3) Confusion, urea, respiratory rate, blood pressure and age ≥65 years
4) quick sequential organ failure assessment score

Microbiological findings

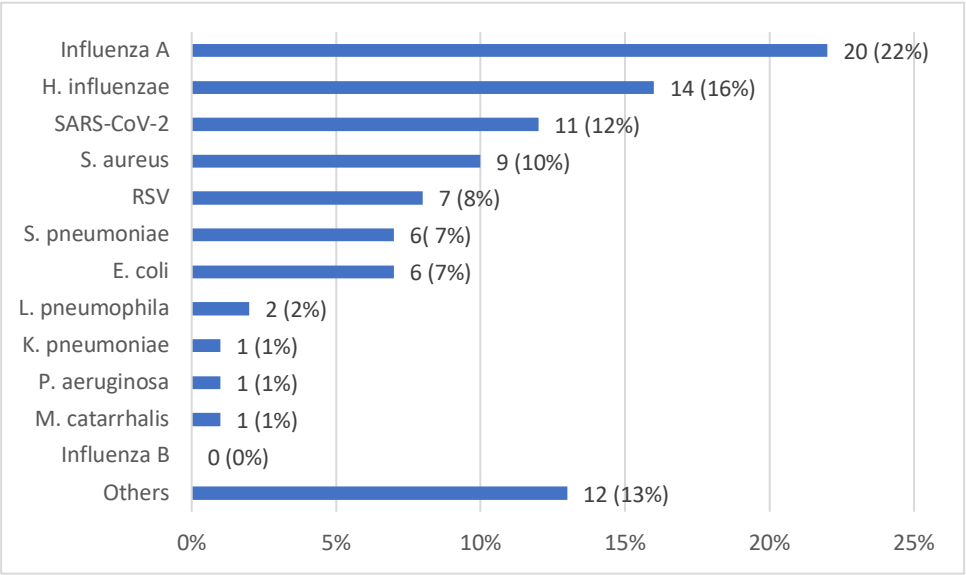
The vast majority of the patients were tested with minimum one microbiological test (97%). Exacerbated expectoration was present in 40% of the patients, while 28% had no exacerbated expectoration, and in the remaining 32%, the presence of exacerbated expectoration was not reported in the hospital records. Either sputum, tracheal aspirate or BAL cultures were performed for 35% of the patients. However, PCR detection of atypical pathogens were only performed for 15% of the patients. Of all patients with minimum one microbiological test, the proportion of positive findings was 26% (Table 3). The most dominant pathogen was influenza A which was identified in 22% of the patients. All cases with influenza A were detected between March and May 2022, of which 85% was found during a one-month period. The most frequently identified bacterial pathogen was *H. influenzae* (16%) followed by *Staphylococcus aureus* (10%). In total, five patients (6%) had a mixed bacterial-viral infection. Regarding *Escherichia coli*, 5/6 (83%) were found in blood cultures and only one in sputum cultures. The distribution details for the microbiological findings are shown in Figure 2.

Table 3: Microbiological tests

Microbiological test	Tests performed n (%)	Tests positive n (%)
Blood cultures	273 (89%)	19 (7%)
Sputum cultures	103 (34%)	29 (28%)
Tracheal aspirate cultures	5 (2%)	2 (40%)
Bronchoalveolar lavage fluid cultures	5 (2%)	1 (20%)
PCR for atypical pathogens[1]	41 (13%)	2 (5%)
Pneumococcal urinary antigen test	15 (5%)	0 (0%)
Legionella pneumophila urinary antigen test	15 (5%)	1 (7%)
Point of care virus PCR test[2]	260 (85%)	35 (13%)

1) PCR: polymerase chain reaction; atypical pathogens: *C. pneumoniae, C. psittaci, L. pneumophila and M. pneumoniae*
2) Tests for respiratory syncytial virus (RSV), influenza A virus, influenza B virus and SARS-CoV-2 (COVID-19).

Figure 2: Distribution of microbiological findings



Data are n (%)
Others: Yeast species (n = 3), aerobic gram-negative bacilli (n = 2), *Enterococcus faecalis* (n = 1), enterobacteriaceae species (n = 1), *Streptococcus mitis* (n = 1), *Abiotrophia defectiva* (n = 1), *Achromobacter xylosoxidans* (n = 1), Haemolytic group B Streptococcus (n = 1) and *Serratia marcescens* (n = 1)

Microbiological findings and subgroups

H. influenzae was the most frequent bacterial finding amongst both COPD patients (19%) and non-COPD patients (16%). Only 8% of the COPD patients and 7% of the non-COPD patients were identified with *S. pneumoniae*.

Regarding the CURB-65 score, *H. influenzae* was detected in 20% of the patients with a CURB-65 score of 0-2 but only in 9% of the patients with a score of 3-5. In contrast, *S. aureus* was the most frequently detected pathogen in patients with a CURB-65 score of 3-5 (23%) (Table 4).

Table 4: Microbiological findings and subgroups

Subgroups	n (%)
COPD patients	128 (42%)
Positive test	26 (20%)
Influenza A	6 (23%)
H. influenzae	5 (19%)
Non-COPD patients	178 (58%)
Positive test	55 (31%)
Influenza A	14 (25%)
H. influenzae	9 (16%)
S. aureus	7 (13%)
COVID-19	7 (13%)
Respiratory syncytial virus	6 (11%)
E. coli	5 (9%)
CURB-65 score	
0-2	223 (73%)
Positive test	59 (26%)
Influenza A	18 (31%)
H. influenzae	12 (20%)
Respiratory syncytial virus	6 (10%)
COVID-19	6 (10%)
S. pneumoniae	5 (8%)
3-5	83 (27%)
Positive test	22 (27%)
S. aureus	5 (23%)

Only findings ≥5 are reported

Antibiotic treatment

In total, 94% of the patients were given antibiotics at the time of admission. The most frequently prescribed empirical antibiotic was amoxicillin/clavulanic acid (32%) followed by piperacillin/tazobactam monotherapy (21%) and penicillin monotherapy (18%) (Table 5).

Table 5: Antibiotic treatment

Outcome	Study population *N = 306*
Most prescribed antibiotics at admission time	
Amoxicillin/clavulanic acid	93 (32%)
Piperacillin/tazobactam monotherapy	61 (21%)
Penicillin monotherapy	54 (18%)
Ampicillin/gentamicin	22 (7%)
Cefuroxime monotherapy or combination therapy	17 (6%)
Penicillin + clarithromycin	12 (4%)
Piperacillin/tazobactam + clarithromycin	8 (3%)
Others[1]	27 (9%)
Treatment duration, median days (IQR)	
Total antibiotic treatment	8 (6-10)
Intravenous antibiotic treatment	3 (2-6)

Data are n (%), unless otherwise indicated

1) Clarithromycin monotherapy, ciprofloxacin, roxithromycin, moxifloxacin, meropenem

Adherence to guidelines

In total, 60% of the immunocompetent patients with CAP received correct empirical treatment in concordance with the regional guidelines. COPD patients and patients with a CURB-65 score of 0-2 were more likely to receive correct empirical antibiotic treatment compared to non-COPD patients and patients with a CURB-65 score of 3-5, respectively (OR 2.37, 95% CI 1.29-4.41 and OR 2.62, 95% CI 1.35-5.11, respectively) (Table 6). The dominant reason for non-adherence to the guidelines was the prescription of broad-spectrum antibiotics in cases of mild or moderate pneumonia (Table 7). No statistically significant differences were found in the outcomes for guideline-adherent and guideline-non-adherent patients (P > 0.05) (Table 8).

Table 6: Adherence to guidelines

Subgroups	n/N (%)	OR (95% CI)
Immunocompetent CAP patients	222/306 (73%)	
Adherence to guidelines	134/222 (60%)	
COPD		
COPD patients	65/90 (72%)	2.37
Non-COPD patients	69/132 (52%)	(1.29-4.41)
CURB-65 score		
0-2	110/166 (66%)	2.62
3-5	24/56 (43%)	(1.35-5.11)

Table 7: Reasons for non-adherence to guideline

Reason	n (%)
Treatment not in accordance with the severity of the pneumonia	50 (57%)
Overtreatment with broad-spectrum antibiotics	36 (41%)
Undertreatment with narrow-spectrum antibiotics	14 (16%)
No antibiotics prescribed at admission time	11 (13%)
No clarithromycin added	10 (11%)
Wrong antibiotic class	8 (9%)
COPD treatment prescribed despite non-COPD patient	5 (6%)
Non-COPD treatment prescribed despite COPD patient	4 (5%)

Table 8: Guideline-adherence and outcome

Outcome	n (%)	P-value
Length of stay, median days (IQR)		
Adherence to guidelines	5	0.39
Non-adherence to guidelines	4	
30-day all-cause rehospitalisation		
Adherence to guidelines	28 (21%)	0.48
Non-adherence to guidelines	15 (17%)	
30-day all-cause mortality		
Adherence to guidelines	18 (13%)	0.46
Non-adherence to guidelines	15 (17%)	

Data are n (%), unless otherwise indicated

Discussion

Key findings

Our study was conducted to report the microbiological aetiology and antibiotic treatment of patients hospitalised with pneumonia. The study found that the most frequently identified pathogen was influenza A which almost comprised a fourth of the identified pathogens. Amongst the bacterial pathogens, *H. influenzae* was the most dominant finding in both COPD and non-COPD patients. Amoxicillin/clavulanic acid was the most prescribed antibiotic drug followed by piperacillin/tazobactam and penicillin. In total, 40% of the study population did not receive correct antibiotic treatment in concordance with the regional guidelines at admission time. The major reason for the lack of adherence to the guidelines was overtreatment with broad-spectrum antibiotics.

Comparison with the literature

Microbiological findings

In line with the findings of our study, a Danish cohort study comprising 2,264 CAP patients published in 2021 by Fally et al. also reported *H. influenzae* as the most frequently identified bacterial pathogen. However, Fally et al. reported *H. influenzae* as the dominant pathogen amongst both viruses and bacteria. In our study, 16% of the microbiological findings were *H. influenzae*, while it comprised 24% of the findings in the study by Fally et al [19]. Furthermore, a study by Gadsby et al. with 326 CAP patients from the UK, which used comprehensive molecular testing, also found *H. influenzae* as the dominant pathogen, but with an even higher frequency of 40%. Gadsby et al. reported rhinovirus as the most identified viral pathogen, which we did not test for in our study. Both Fally et al. and Gadsby et al. reported influenza A in 9% and 5% of the cases, respectively, which was in contrast to our findings of 22%. Another noticeable difference was the fact that both Fally et al. and Gadsby et al. found a higher proportion of *S. pneumoniae* (20% and 36%, respectively) compared to our study, in which *S. pneumoniae* only comprised 7% [25]. This difference may be attributable to the pneumococcal vaccination of citizens in Denmark and the implementation to the Danish childhood vaccination programme. According to the Danish Ministry of Health, approximately 80% of the citizens above 65 years were vaccinated with the pneumococcal polysaccharide vaccine (PPSV23) in Denmark since 2017 with the vaccination adherence increasing drastically during the COVID-19 pandemic [26]. This might explain the difference as Fally et al. and Gadsby et al. reported data from before the COVID-19 pandemic.

Nevertheless, most previously published studies from Western countries, including Scandinavian countries, reported *S. pneumoniae* as the dominant bacterial pathogen of CAP [4,27–34]. Although, the studies were published recently, many of them reported data from before 2012. Since our data was collected almost ten years later, a shift in the microbiological findings could have occurred meanwhile. Besides, two of the studies investigated the aetiology of CAP over time and reported an increasing prevalence of *H. influenzae* contemporary with a decreasing prevalence of *S. pneumoniae* [33,34]. Taking this course into account with our findings, it could indicate that *H. influenzae* will have a bigger impact in the near future, if not already.

Additionally, there was a discrepancy in the reporting of the most frequently identified pathogen as some studies reported a viral pathogen as the most frequent while other studies reported a bacterial pathogen. This difference could be explained by ongoing epidemics during the study period or annually outbreaks due to seasonal activity patterns of

respiratory pathogens. This might also be the case in our study as influenza A was solely detected during a two-month period in the spring. This was consistent with a study from Norway, where the viral findings varied considerably during the year with a significantly higher prevalence during winter and spring [32].

Surprisingly, *S. aureus* was the second-most identified bacterium in our study contrary to Fally et al. and Gadsby et al., who both found *S. pneumoniae* as the second-most identified bacterium. This could partially be explained by our inclusion of patients with HAP and aspiration pneumonia who comprised 16% and 5% of our study population, respectively. Previous studies showed that *S. aureus* was one of the two most common bacterial pathogens in patients with HAP [35,36]. A high prevalence of *S. aureus* was also reported in aspiration pneumonia [37]. Moreover, a previous study showed that secondary bacterial pneumonia caused by *S. aureus* was associated with influenza A infection, particularly among nasal carriers of *S. aureus* [38]. As influenza A was the most frequently identified pathogen in our study, this could also explain the high frequency of *S. aureus*.

Furthermore, we found a relatively high proportion of *E. coli* in the blood samples. However, it could be discussed whether *E. coli* found in blood was the actual aetiology of the pneumonia or if it was found due to a co-infection, for instance a urinary tract infection. This could also be discussed for some of the other bacterial findings e.g., the other Enterobacteriaceae species.

Microbiological findings and subgroups

Besides finding *H. influenzae* as the most commonly identified bacterial pathogen in COPD patients, it was also the most frequent amongst non-COPD patients. This is in conflict with the Danish guideline which recommends antibiotic treatment with penicillin to non-COPD patients with mild or moderate CAP. Unfortunately, Fally et al. and Gadsby et al. did not report the frequency of the pathogens amongst COPD patients and non-COPD patients, separately. However, a Norwegian study by Waagsbø et al. reported *S. pneumoniae* as the dominant bacterial pathogen in non-COPD patients [39]. The reason for this difference could be that there might be patients with undiagnosed COPD in our study since 58% of the study population were either current smokers or former smokers, but only 42% were diagnosed with COPD.

Regarding the CURB-65 score, *S. aureus* was the most frequently identified pathogen amongst patients with a CURB-65 score of 3-5 in our study. This was in line with previous studies which showed that CAP caused by *S. aureus* was associated with increased illness severity and mortality rate [40,41].

Antibiotic treatment

In our study, amoxicillin/clavulanic acid was the most prescribed empirical antibiotic drug as it was given to 32% of the patients. Similar to our results, a multicentre study performed in 10 European Union countries by Blasi et al. also reported amoxicillin/clavulanic acid as the most commonly administered empirical antibiotic drug [42].

Interestingly, only 18% of the patients in our study received penicillin monotherapy even though penicillin was the recommended antibiotic drug for mild and moderate CAP in the Danish guidelines. In a Danish study by Egelund et al., penicillin monotherapy was the most common prescription at admission time with 45% of the patients receiving it [4]. This difference could be explained by the fact that in our study COPD patients

comprised 42% of the study population but only 19% in the study by Egelund et al. This also explains the major proportion of patients receiving empirical treatment with amoxicillin/clavulanic acid in our study as amoxicillin/clavulanic acid is the empirical treatment for COPD patients with mild or moderate CAP. Another reason could be the fact that the patients in the study by Egelund et al. had less severe pneumonia compared to our study. Egelund et al. reported a CURB-65 score of 0-2 in 82% of the patients while in our study this number was only 73%. However, the duration of the antibiotic treatment in our study was similar to the study by Egelund et al. and another Danish study by Fally et al., in which the median total duration of antibiotic treatment was 10 days, the median duration of intravenous antibiotic treatment was 3 days, and the median length of admission was 5 days and 4 days, respectively [4,43].

Adherence to guidelines

In total, 60% of our study population was given empirical antibiotic treatment in accordance with the regional guidelines which was in line with many previously published studies (53-65%) [8,43–48]. In contrast to our study, some previous studies reported a significantly lower length of stay, mortality rate and readmission rate amongst patients receiving antibiotic treatment in concordance with the guidelines compared to those receiving non-concordant antibiotic treatment. A study by McCabe et al. found a reduced length of stay and in-hospital mortality amongst patients receiving guideline-adherent therapy [8]. Furthermore, a Norwegian study by Høgli et al. reported a decreased risk of 30-day readmission when prescribing empirical penicillin G/V monotherapy [30]. Hence, there is a great incentive to improve the guideline-adherence at our university hospital. Fally et al. showed that it is possible to improve the adherence to guidelines by implementing tailored interventions which led to an increase in guideline-adherence from 59% to 74% [43].

Strengths and limitations

Our study contained both strengths and limitations. A major strength of the study was our method of including patients. First, we identified all patients admitted to the ED with a newly emerged infiltrate on chest radiograph. Then, we excluded patients depending on whether the inclusion and exclusion criteria were met. By doing it in this way, we also ensured the inclusion of patients who were primarily hospitalised due to a co-infection or another co-morbidity, but at the same time were meeting the criteria for pneumonia. Some studies, including Egelund et al., identified patients with pneumonia by ICD-10 codes which might disregard patients, in whom a concurrent pneumonia was neglected due to other more conspicuous comorbidities [4]. Another strength might be the fact that we included all patients admitted with pneumonia at the ED, including patients discharged within 28 days from a previous hospitalisation, patients with aspiration pneumonia and patients with VAP, who altogether comprised more than a fifth of the study population. Thus, it better reflected the population being referred to a hospital. Our study was conducted at Aalborg University hospital, which is covering both urban and rural areas of the North Denmark region with approximately 217,000 inhabitants and providing both highly specialised and basic hospital functions. Thus, the study was considered to be representative in other Western countries. Moreover, it might be a strength that the hospital records were reviewed by only one person as the hospital records were very diverse due to the natural variation in the way physicians

journalise. Furthermore, the retrospective study design allowed us to collect the data independently of the study aim and thereby reducing the risk of information bias.

At the same time, the retrospective study design could also be a limitation as our data were collected from hospital records journalised by different physicians. Thus, our data depended on what each attending physician found necessary to document which might contribute to missing or misinterpretation of data. For instance, the CURB-65 score was only documented in 12% of the hospital records. Accordingly, we had to calculate the CURB-65 scores based on the information in the patient records, which could lead to discrepancy between our classification of the severity of the pneumonia and the physicians' judgement at the time of empirical prescribing. Besides, we only reported comorbidities that were documented in the hospital records, hence some comorbidities could be missing. In addition, the retrospective study design entailed that the microbiological tests were decided by the attending physicians. Hence, not all microbiological pathogens linked to pneumonia could be identified. For instance, no tests for rhinovirus were performed, which was a limitation since many previously published studies reported rhinovirus as one of the most identified pathogens in pneumonia [28,32,33].

A major limitation of the study was the small study population compared to other studies resulting in a high variability [19,27,28,33]. Furthermore, patients who were directly transferred to an intensive care unit (ICU), another hospital or another ward, and consequently not admitted to the ED, were unfortunately not included. This could contribute to selection bias as patients transferred directly to an ICU might be more severely ill. Another possible selection bias in our study was the fact that we only collected data from an 8-month period between November 2021 and June 2022, thereby missing data from the months of July to October. This might result in misleading microbiological findings due to seasonal activity patterns of some respiratory pathogens. Lastly, we did not take into account, whether the patients were given antibiotics prior to hospitalisation. Since the empirical antibiotic drug for pneumonia in the primary care is penicillin V, patients with *S. pneumoniae* might be discarded, resulting in selection bias.

Conclusion

In conclusion, our study showed that *H. influenzae* was the dominant bacterial finding in both COPD and non-COPD patients with pneumonia. If this finding is proven correct, the recommended empirical treatment of pneumonia in the Danish guidelines should be re-evaluated. Furthermore, amoxicillin/clavulanic acid was the most frequently prescribed antibiotic drug at admission time. In total, 40% of the immunocompetent patients with CAP did not receive empirical antibiotic treatment in adherence to the regional guidelines. The main reason for non-adherence to guidelines was overtreatment with broad-spectrum antibiotics. Hence, there is room for improvement of the guideline-adherence in order to achieve a better patient outcome and slow down the growing antibiotic resistance.

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