

Original Article

Aetiology of pneumonia in patients in the intensive care unit treated with chlordiazepoxide

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ABSTRACT

INTRODUCTION. Research on pneumonia in patients undergoing treatment for alcohol withdrawal symptoms (AWS) is sparse. This study describes the microbiological aetiology in this patient group within an intensive care unit (ICU).

METHODS. We conducted a retrospective, observational study at Copenhagen University Hospital, Bispebjerg, Denmark. Patients admitted to the ICU between 1 June 2017 and 31 December 2020 who had received at least 200 mg of chlordiazepoxide for AWS within the preceding days were identified through electronic health records. Admissions presenting with clinical symptoms of pneumonia were included in the study.

RESULTS. A total of 76 patients with 88 admissions met the inclusion criteria. We identified 58 bacterial species, with the most common being *Staphylococcus aureus* (n = 14; 24%), *Haemophilus influenzae* (n = 12; 21%) and *Streptococcus pneumoniae* (n = 11; 19%). In the overall ICU population, excluding our cohort study, 516 bacterial samples from the lower airways were identified. The prevalence rate in the study period for *S. aureus* was 25.6% (n = 132), for *H. influenzae* 8.3% (n = 43) and for *S. pneumoniae* 8.5% (n = 44).

CONCLUSIONS. Pneumonia was prevalent in patients with AWS in the ICU, and it had a predominantly bacterial aetiology. The most frequently isolated bacteria were *S. aureus*, *H. influenzae* and *S. pneumoniae*. Notably, the prevalence of *S. aureus* in our study cohort was similar to that in the overall ICU population at the study site.

FUNDING. None.

TRIAL REGISTRATION. The study was approved by the Hospital Board of Directors as a quality study.

In 2018, a total of 9,695 individuals were registered with one or more alcohol-related hospital contacts in the Capital Region of Denmark, which has a population of approx. 1.8 million [1, 2]. Alcohol withdrawal symptoms (AWS) are handled in a standardised manner, involving symptom-triggered benzodiazepine treatment, with chlordiazepoxide being the first-line drug.

Chlordiazepoxide is a long-acting benzodiazepine with a half-life of 5-30 hours. It is metabolised into active metabolites characterised by having a particularly long half-life of up to 200 hours [3].

Several studies have proven a correlation between alcohol intake and increased risk of pneumonia [4]. The negative impact of alcohol on immune system activity is highly multifactorial but includes localised impairment of the respiratory system through reduced ciliary clearance, alveolar oxidative stress leading to reduced efficacy of alveolar macrophages and decreased recruitment of circulating polymorphonuclear leukocytes [5-7].

Additionally, the oropharyngeal flora has been found to differ between heavy drinkers and non-drinkers, primarily by a higher presentation of anaerobic bacteria, possibly altering the frequency with which different organisms cause pneumonia [8]. Furthermore, heavy alcohol consumption increases the risk of aspiration due to its sedative effect, while potential oversedation due to benzodiazepine treatment for AWS encompasses an additional risk [9, 10].

Despite this, few studies have investigated the microbiological aetiology of pneumonia in patients with high alcohol intake and fewer still in patients undergoing benzodiazepine treatment for AWS, which prompted our investigation.

Thus, our primary outcome was microbiological aetiology in patients admitted to our intensive care unit (ICU) with symptoms clinically interpreted as pneumonia who had been treated for AWS with chlordiazepoxide within ten days before admission.

Secondary outcomes were sex, age, BMI, alcohol intake, habitual benzodiazepine intake, concurrent disease, antibiotics administered, mechanical ventilation, time spent intubated, hospital length of stay and ICU length of stay.

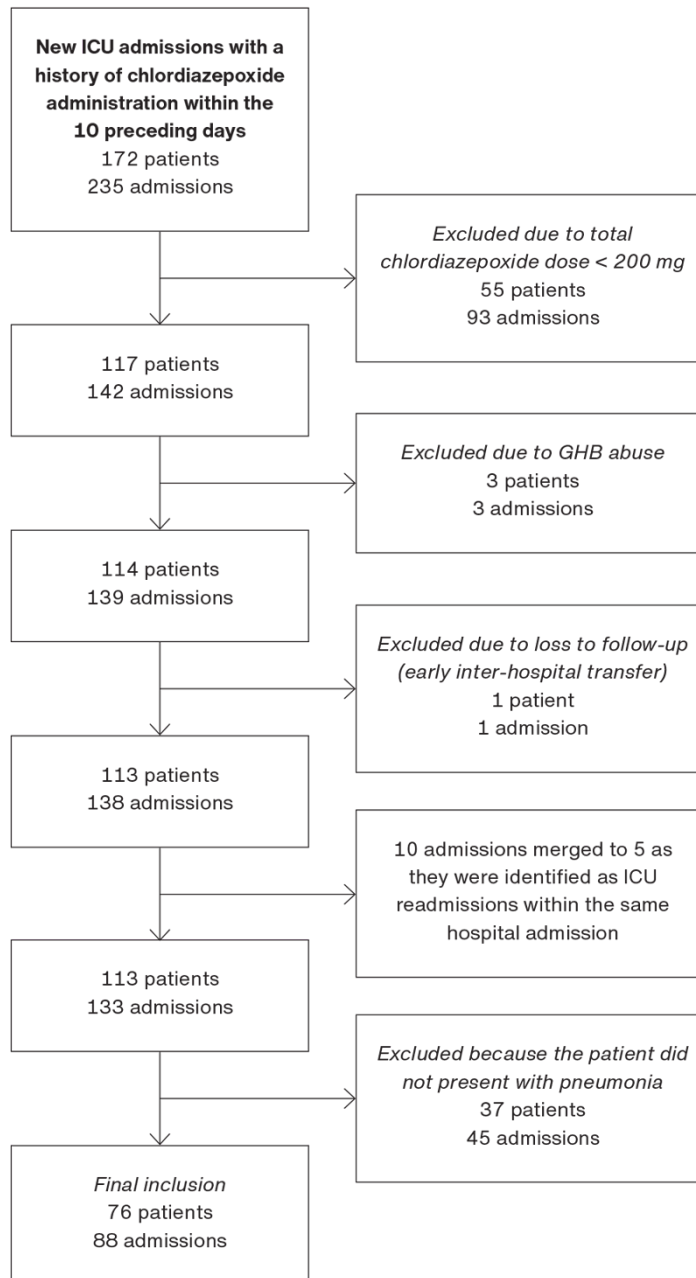
Methods

This retrospective, observational study was conducted at the ICU at Copenhagen University Hospital, Bispebjerg and Frederiksberg. This general ICU primarily treats medical patients, with a significant proportion of neurological cases and, to a lesser extent, post-surgical admissions.

Our hospital's emergency department serves 430,000 urban citizens, receiving approximately 82,000 visits and admitting 10,000 patients annually [11]. In the inclusion period, our ICU saw 2,986 admissions.

The data used in this study originate from a study on respiratory failure requiring mechanical ventilation among patients receiving chlordiazepoxide for AWS [12]. Patients were included over approximately 3.5 years, from 1 June 2017 to 31 December 2020. Patients were identified in the hospital's electronic health record (EHR) system, and data were entered in a REDCap (Vanderbilt University, Nashville, USA) database. All inpatient records on patients admitted to the ICU (regardless of diagnosis) involving any chlordiazepoxide administration within ten days prior to ICU admission were identified. Only admissions with administration of at least 200 mg of chlordiazepoxide and presenting symptoms of pneumonia were included in this study (**Figure 1**). Pneumonia was defined at the discretion of the treating ICU physician based on their clinical judgment.

FIGURE 1 Inclusion/exclusion.



GHB = γ -hydroxybutyric acid; ICU = intensive care unit.

The inclusion criteria were:

- Admission to the ICU
- History of chlordiazepoxide administration within ten days preceding admission to the ICU
- Age 18 or above.

The exclusion criteria were:

- < 200 mg chlordiazepoxide administered within ten days preceding admission to the ICU

- Current γ -hydroxybutyric acid (GHB) abuse

Absence of clinical symptoms interpreted as pneumonia.

Patients with concurrent GHB abuse were excluded due to the need for high amounts of benzodiazepine doses required for AWS treatment.

All in-hospital drug administrations were recorded in the electronic health record (EHR) at the point of prescription by a physician and administration by a nurse.

Baseline information on alcohol consumption, benzodiazepine use, comorbidities, mechanical ventilation, length of stay and antibiotics used was extracted from the patients' EHR by a designated department physician.

Comorbidities were grouped into psychiatric disorders (e.g. anxiety, depression, schizophrenia), pulmonary disease (e.g. COPD, asthma, fibrosis), cardiac disease (e.g. ischaemic heart disease, New York Heart Association Classification (NYHA) > 2, arrhythmia), hepatic disease (e.g. cirrhosis, hepatitis C), pancreatic disease (e.g. pancreatitis, pancreatic insufficiency) and neurologic disease (e.g. stroke sequelae, peripheral nerve disease, epilepsy). Hypertension and diabetes were registered independently, whereas all other comorbidities were categorised as "other".

Alcohol and benzodiazepine intake were patient-reported and categorised as daily or periodic, with alcohol additionally being counted in estimated daily units. Registered intakes of 0-1 units daily were dismissed as incorrect and not included.

All patients underwent microbiological sampling upon admission to the ICU, where most cultures from the respiratory system were obtained by tracheal aspirate or bronchoalveolar lavage, with the remainder being sputum.

All positive respiratory cultures were included, regardless of the sample collection method used.

Positive microbiological culture results from respiratory samples collected in the ICU during the inclusion period were retrieved from the Department of Clinical Microbiology at Copenhagen University Hospital, Hvidovre, for reference to our study population. Results originated from a database search of all positive samples related to airways and were screened for duplicates, defined as identical organisms identified within 30 days in the same patient. Microbiological culture results concerning admissions included in the study were excluded from the results. We did not compare reference results with admission-specific details and therefore do not know when samples were taken during admission.

Viral results and certain organisms requiring specialty examination/handling (e.g., *Mycobacterium tuberculosis*) were not obtained for the reference group.

Trial registration: The study was approved by the Hospital Board of Directors as a quality study.

Results

We identified 172 patients with 235 admissions matching the inclusion criteria by EHR screening. After exclusion, 76 (44.2%) patients with 88 (37.4%) admissions were included in the study.

Positive respiratory microbiological results were present in 56 (73.7%) of patients. The inclusion procedure is depicted in Figure 1. Patient characteristics are presented in **Table 1**.

TABLE 1 Patient ($N_p = 76$) and admission ($N_a = 88$) characteristics.

Males, n (%)	71 (93)
Age	
Mean ($\pm$ SD), yrs	57 ($\pm$ 10.6)
Groups, n (%):	
< 30 yrs	1 (1)
30-39 yrs	4 (5)
40-49 yrs	12 (16)
50-59 yrs	24 (32)
60-69 yrs	29 (38)
$\geq$ 70 yrs	6 (8)
BMI	
Mean, kg/m ²	24.45
Groups, n (%):	
< 18 kg/m ²	6 (8)
18-< 25 kg/m ²	35 (48)
25-< 30 kg/m ²	25 (34)
$\geq$ 30 kg/m ²	7 (10)
Subtotal	73
Daily alcohol intake, mean (Q1-Q3) ^a , U ^b	20.8 (12-25)
Habitual daily benzodiazepine consumption, n (%)	11 (14)
Comorbidities, n (%)	
Psychiatric	32 (42)
Pulmonary	26 (34)
Cardiac	14 (18)
Hepatic	21 (28)
Pancreatic	6 (8)
Neurologic	10 (13)
Diabetes mellitus	9 (12)
Hypertension	12 (16)
Other	21 (28)
Patients with $\geq$ 1, total	68 (89)
Hospital length of stay, mean (Q1-Q3) ^a , days	22.1 (12.3-28.3)
ICU, length of stay, mean (Q1-Q3) ^a , days	9.2 (4.5-11.3)
Chlordiazepoxide administered, mean (Q1-Q3) ^a , mg	920.3 (443.8-1.200)
Mechanical ventilation, share of admissions, n/N (%)	72/88 (82) ^c
Non-invasive ventilation, n/N (%)	15/88 (17)
Invasive ventilation, n/N (%)	58/88 (66)
Continuous positive airway pressure, n/N (%)	18/88 (20)
Time spent intubated on ventilator, average (Q1-Q3) ^a , days	6.5 (2.5-8.6)
Reason(s) for ICU admission, share of admissions, n/N (%)	
Respiratory insufficiency ^d	44/88 (50)
Agitation	3/88 (3)
Somnolenced	40/88 (45)
Other	40/88 (45)

ICU = intensive care unit; SD = standard deviation.

a) Interquartile range.

b) 1 U = 12 g pure ethanol; the mean alcohol intake was calculated across all 88 admissions.

c) 10 admissions included both invasive and non-invasive ventilation.

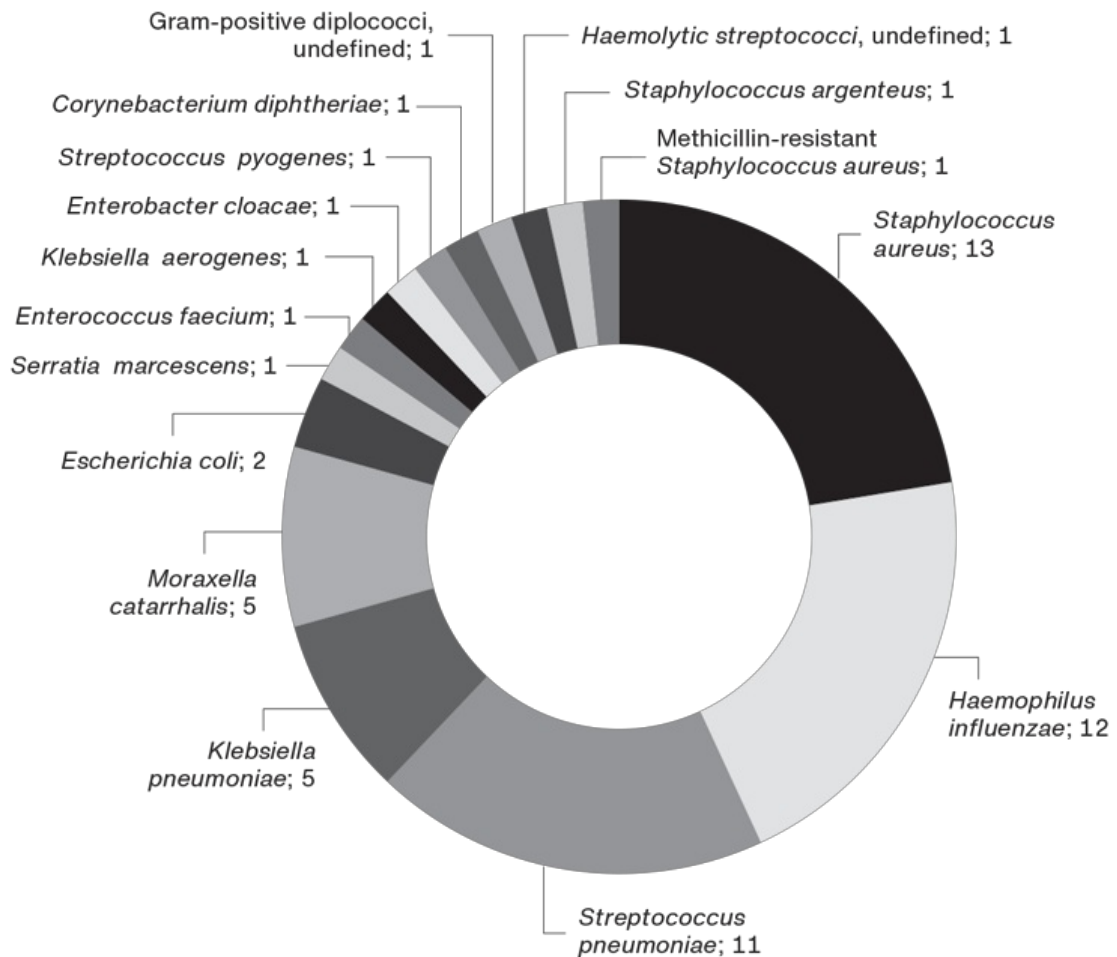
d) Respiratory insufficiency and somnolence were mostly concurrent factors; if multiple indications for admittance to the ICU unit were present, they were each noted and counted.

Estimated daily alcohol intake spanned from three to 55 units daily, with the mean being 20.8 units, corresponding to 249.6 g of ethanol.

Chlordiazepoxide administration varied considerably from 200 to 4,500 mg. The mean dose was 920.3 mg.

Microbiological findings included 58 bacterial cultures, 16 fungi and three viral samples. The bacteria most commonly identified were *Staphylococcus aureus* (n = 14; 24%), *Haemophilus influenzae* (n = 12; 21%) and *Streptococcus pneumoniae* (n = 11; 19%). Complete bacterial results are illustrated in **Figure 2**.

FIGURE 2 Bacterial results in the study population. Positive bacterial results concerning all included admissions between 1 June 2017 and 31 December 2020, involving ≥ 200 mg chlordiazepoxide administered up to ten days prior to admission to the intensive care unit.



Sixteen samples contained yeast, primarily candida species ($n = 10$). Three viruses were identified once each: SARS-CoV-2, influenza B and a rhinovirus.

Twenty admissions included ≥ 2 unique microbiological results, whereas 28 admissions did not include a positive microbiological result from the respiratory system.

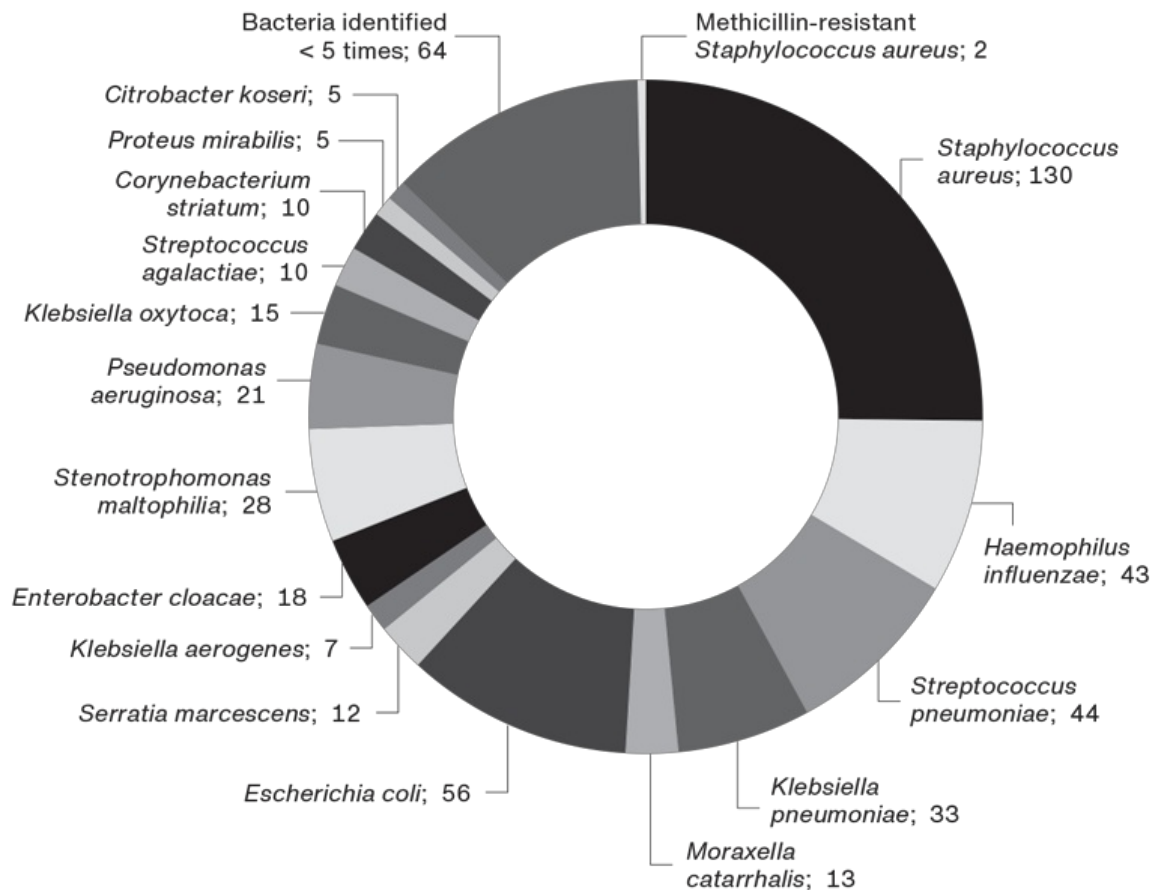
The antibiotics used during an individual patient's admission varied from single-drug therapies to combination treatments involving up to six different drugs.

Piperacillin/tazobactam was administered in 62 (70%) admissions, rendering it the most widely prescribed antibiotic, followed by metronidazole ($n = 36$; 41%), meropenem ($n = 26$; 30%), ciprofloxacin ($n = 23$; 26%), cefuroxime ($n = 17$; 19%) and clarithromycin ($n = 11$; 13%). Thirteen additional antibiotics were prescribed, but were each used in fewer than ten admissions.

The microbiological results for positive airway samples in the entire ICU population during the inclusion period, excluding the study population, consisted of 913 samples from 666 individuals with a total of 1,140 identified organisms. Bacterial samples comprised 516 results, with the remaining 624 results being fungi, primarily consisting of *Candida albicans* ($n = 205$; 32.9%), *C. tropicalis* ($n = 58$; 9.3%), *C. glabrata* ($n = 43$; 6.9%) and *C.*

dublinsiensis (n = 38; 6.1%). Bacterial results are depicted in Figure 3.

FIGURE 3 Bacterial results in the reference population. Positive bacterial results concerning all intensive care unit admissions between 1 June 2017 and 31 December 2020, excluding results related to an admission included in the chlordiazepoxide group.



Discussion

Our results revealed that most infections were caused by gram-positive bacterial infections, predominantly *S. aureus* and *S. pneumoniae*, whereas the gram-negative bacteria *H. influenzae*, *Klebsiella pneumoniae* and *Moraxella catarrhalis* accounted for slightly more than a third of infections in ICU patients treated with chlordiazepoxide for AWS, displaying clinical symptoms of pneumonia. Comparing the chlordiazepoxide group with the overall department microbiological results, we found no difference in *S. aureus* prevalence. However, *S. pneumoniae*, *H. influenzae* and *K. pneumoniae* were considerably less prevalent in the overall department population.

Several studies have reported the microbiological aetiology of pneumonia in ICU patients. Walden et al. conducted a large epidemiological survey in 2014 investigating microbiological aetiology in patients with sepsis and community-acquired pneumonia (CAP) admitted to European ICUs. They found *S. pneumoniae* in 28.6% of patients, with *S. aureus* and *H. influenzae* contributing only 5.9% and 4.8%, respectively [13], suggesting that the high prevalence of pneumonia with *S. aureus* in our study group may be nosocomial and possibly due to heavy sedation with chlordiazepoxide. Alternatively, it may be due to an increased representation of *S. aureus*

infections in people with an AWS-inducing alcohol intake. However, this hypothesis does not correlate with the equal percentage of *S. aureus* infections in our reference population.

A potential nosocomial source of *S. aureus* infections in our study group seems to be supported by a 2009 study conducted by Koulenti et al., focusing on nosocomial pneumonia, which, in concordance with our results, identified *S. aureus* in 32.3% of patients in European ICUs [14].

Studies of patients with alcoholism, pneumonia and bacterial aetiology are few. However, in 2019, a large American study led by Gupta et al. found *S. pneumoniae*, *S. aureus* and *K. pneumoniae* in 46%, 32% and 4.1%, respectively, in positive cultures from patients with AWS diagnosed with CAP [15]. It should be noted that their study was not conducted in the ICU and had a positive culture rate of 14.6% in the AWS group, whereas our study included at least one positive culture in 68% of patients. The study by Gupta did, however, include significantly more patients than our study. Thus, they reported data from 137,496 patients, of whom 4,752 were considered to have alcohol use disorder and 1,005 patients presented with AWS.

Considering our most prevalent finding, *S. aureus*, our results are overall in line with studies performed elsewhere, with the notable exception of the study by Walden et al. *S. pneumonia* findings, however, were lower in our population than in both the CAP- and AWS-oriented studies. Finally, *H. influenzae* was more prevalent among our patients than in the studies referenced above.

Regarding the use of benzodiazepines and risk of pneumonia, two large studies demonstrated an increased risk, with one finding a dose-response relationship between benzodiazepines and pneumonia [16, 17]. Neither study, however, found an association between chlorthalidone and risk of pneumonia, as the observed effect was primarily linked to shorter-acting benzodiazepines. While several other studies have investigated the risk of pneumonia and benzodiazepine usage, we were unable to find any including microbiological results.

A strength of the present study was the relatively large positive culture rate along with precise information regarding chlorthalidone dosing, antibiotics used, admittance/discharge and use of mechanical ventilation. Additionally, we consider microbiological reporting in this particular patient group a strength, as this is a vulnerable population that has historically been neglected in medical research.

Our study also has some limitations; most importantly, its retrospective, single-centre design, which reduces the generalisability of our results. Pneumonia was defined at the discretion of the treating physician rather than by verification of new infiltrates on chest X-ray combined with relevant symptoms, as is otherwise the gold standard. This may result in reporting non-causative organisms as pathogens for pneumonia.

Since we did not record symptom onset, we were unable to distinguish between CAP, hospital-acquired pneumonia and ventilator-associated pneumonia, which limits comparability with other studies. Furthermore, we chose not to exclude patients who, in addition to their suspected pneumonia, displayed clinical signs of infection outside of the pulmonary system. Thus, antibiotics used by the treating clinician might not have been solely aimed at pneumonia, and might have been prescribed before pneumonia developed, possibly affecting the aetiology of pneumonia.

Finally, the COVID-19 pandemic may have impacted our study, as a national lockdown was imposed during the final inclusion year.

Conclusions

This retrospective, single-centre, observational study showed that patients admitted after treatment with chlorthalidone for AWS frequently displayed symptoms clinically interpreted as pneumonia. They often had

positive airway cultures, and the most frequent bacterial aetiologies were *S. aureus*, *H. influenzae*, *S. pneumoniae*, *K. pneumoniae* and *M. catarrhalis*.

S. aureus was found with the same frequency as in the ICU background population.

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