Graduate thesis

NTNU
Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences

Cecilia Eide Songstad

# Non-ventilator hospital-acquired pneumonia at a tertiary care university hospital in Norway

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Supervisor: Bjørn Waagsbø
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# Abstract

**Introduction**. Non-ventilator hospital aquired penumonia (nvHAP) continues to represent one of the most common nosocomial infections. The clinical diagnosis is difficult in part, and the infection is associated with increased costs and antibiotic utilization. In this study we describe the diagnostic and management features of nvHAP in a university hospital in Norway.

**Materials and methods**. This observational retrospective study included adult patients with non-ventilator hospital aquired pneumonia as a secondary diagnosis over a six-month period. NvHAP diagnosis was defined by the emergence of pneumonia symptoms at least 48 hours beyond admission, and which was not incubating at the time of admission. We used simple descriptive statistics to assess patient characteristics, diagnostic aspects, and antimicrobial therapy.

**Results**. Of 417 hospital admissions with pneumonia as a secondary diagnosis, 110 nvHAP cases were included. Clinical features such as cough, fever and dyspnea were documented in the medical journal in 41.8 %, 50.9 % and 21.8 % of cases, respectively. Radiological investigations were performed in 98 (89.1 %) of the included cases, and in 60 episodes (61.2 %) a pneumonia infiltrate was detected. Respiratory cultures were obtained in 15 (13.6 %) of included cases, of which 1 (0.9 %) culture-positive incident with a reliable pathogen was recovered. Empirical antimicrobial therapy was initiated in all cases included and remained empiric throughout the course due to consistently low sampling frequencies. The most frequently prescribed empiric antimicrobial agent was a 3$^{rd}$ generation cephalosporin followed by penicillins, together accounting for 91 (82.7 %) of all empiric regimens. In 57.8 % of episodes the regimen was altered once, while for the rest of the cases antimicrobial therapy remained unchanged throughout the course. De-escalation from narrow-spectrum and broad-spectrum regimens was performed in 24.1 % and 60.7 % of episodes, respectively. Initial narrow-spectrum regimens were escalated to broad-spectrum regimens in 12.9 % of episodes, and 7.1 % of initial broad-spectrum regimens were transferred to other broad-spectrum regimens.

**Conclusions**. Symptoms of HAP were infrequently observed and in considerable proportions absent or undocumented. Microbiological sampling was scarce, making antimicrobial therapy above all empiric and targeted therapy close to non-existing. Efforts to track, report, prevent, diagnose, and manage nvHAP seem necessary for building awareness and adhere to clinical practice guidelines.

# Sammendrag

**Introduksjon**. Ikke-ventilatorassosiert sykehuservervet pneumoni (nvHAP) er stadig en av de mest vanlige sykehuservervede infeksjoner. Å stille den kliniske diagnosen kan være vanskelig, og infeksjonen er assosiert med økte kostnader og økt bruk av antibiotika. I denne studien beskriver vi diagnostikk og håndtering av nvHAP ved et universitetssykehus i Norge.

**Materiale og metode**. Denne retrospektive observasjonsstudien inkluderte voksne pasienter med ikke-ventilatorassosiert sykehuservervet pneumoni som bidiagnose over en 6-måneders periode. NvHAP-diagnosen ble definert som utvikling av pneumonisymptomer minst 48 timer etter innleggelse i sykehus, som ikke var under inkubasjon på innleggelsestidspunktet. Vi benyttet deskriptiv statistikk for å vurdere pasientkarakteristika, diagnostiske aspekter og antimikrobiell behandling.

**Resultater**. Av 417 sykehusinnleggelser med pneumoni som bidiagnose ble 110 tilfeller av nvHAP inkludert i studien. Kliniske symptomer som hoste, feber og dyspné ble dokumentert i pasientjournaler i henholdsvis 41.8 %, 50.9 % og 21.8 % av tilfellene. Radiologiske undersøkelser ble utført i 98 (89.1 %) av inkluderte tilfeller, og i 60 (61.2 %) av dem ble det funnet et pneumonisk infiltrat. Man oppnådde mikrobiologiske luftveisprøver i 15 (13.6 %) av inkluderte tilfeller, hvorav de ble påvist 1 (0.9 %) positiv kultur med pålitelig patogen. Empirisk antibiotikabehandling ble startet i alle inkluderte episoder, og behandlingen forble empirisk gjennom hele forløpet grunnet konsekvent lav prøvetakingsfrekvens. Det hyppigst forskrevne antibiotikum var et 3. generasjons cefalosporin, etterfulgt av penicilliner. Sammen utgjorde disse 91 (82.7 %) av empiriske regimer. I 57.8 % av tilfellene ble behandlingsregimet endret én gang, mens regimet forble uendret gjennom forløpet for de resterende. Deeskalering fra smalspektrede og bredspektrede regimer ble gjennomført i henholdsvis 24.1 % og 60.7% av tilfellene. Eskalering fra smalspektret til bredspektret behandlingsregime ble utført i 12.9 % av inkluderte tilfeller, og 7.1 % av bredspektrede regimer ble overført til andre bredspektrede regimer.

**Konklusjon**. Symptomer på HAP ble i liten grad observert, og i betydelig grad var symptomer fraværende eller ikke dokumentert i pasientjournal. Mikrobiologisk prøvetaking var knapp og medvirket til at antimikrobiell behandling ble i hovedsak empirisk, og at målrettet behandling ble tilnærmet ikke-eksisterende. Tiltak for å spore, rapportere, forebygge, diagnostisere og håndtere nvHAP synes nødvendige for å skape bevissthet rundt og etterlevelse av nasjonale retningslinjer.

# Acknowledgements

I wish to express my deepest gratitude to my supervisor Bjørn Waagsbø for his invaluable patience and guidance throughout this project, and for always being available. Without his assistance and dedicated involvement, this paper would have never been accomplished.

## Keywords

Hospital-acquired pneumonia, non-ventilator pneumonia, nosocomial pneumonia, expectorate, induced sputum, antimicrobial therapy.

# Introduction

## Definitions and classification

Hospital-acquired or nosocomial pneumonia encompasses both ventilator-associated (VAP) and nonventilator pneumonia (nvHAP). In both circumstances the lower respiratory tract is invaded by hospital-acquired pathogens with symptoms developing 48-hours beyond intubation or admission, respectively (1). Historically, VAP has attracted more attention than NV-HAP in terms of clinical studies. This may be linked to population homogeneity of the former and heterogeneity of the latter.

In previous guidelines, a third subgroup was outlined in addition to VAP and NV-HAP, namely healthcare-associated pneumonia (HCAP) (2). HCAP was applied to circumstances where pneumonia occurred in patients that frequently encountered hospital facilities, such as nursing home residents, out-patient follow-ups, dialysis management and many more. It was believed that circumstances like these were associated with increased risk of acquiring multidrug-resistant pathogens, of which many could be related to hospital settings. Later, several studies denied this association, and HCAP was abandoned in later guidelines (1, 3).

## Epidemiology

HAP and VAP continue to represent the most common nosocomial-associated infections. NvHAP affects approximately 1 in every 100 hospitalized patients and has a crude mortality rate of 15-30%. It is also associated with prolonged hospitalization, and increased costs and antibiotic utilization (4, 5).

## Pathogenesis and etiology

Microorganisms that have colonized the oropharyngeal tract are introduced to the lower respiratory tract through microaspiration. Depending on the number and virulence of the microbe, as well as the host defense response, pneumonia may develop (6).

## Diagnostics

Diagnostic guidelines were defined by IDSA and ATS in 2016 (3) and recommend a clinical diagnosis based upon a new lung infiltrate plus clinical evidence that the infiltrate is of infectious origin. This includes the new onset of fever, purulent sputum, leukocytosis and decline in oxygenation. While these clinical features support the diagnosis of HAP, no individual sign or symptom nor any combination of signs and symptoms have been found to be highly sensitive or specific for the diagnosis. Therefore, the clinical diagnosis of nvHAP is difficult in part (6).

Obtaining respiratory cultures noninvasively is recommended, and the guidelines suggest that definitive treatment should be based upon culture results rather than empiric therapy. Although there is a lack of evidence demonstrating improved clinical outcomes with respiratory cultures in suspected nvHAP patients, obtaining cultures will allow antibiotic therapy to be tailored to the recovered organisms (5).

## Management

The IDSA- and ATS-guidelines suggest that patients with suspected nvHAP be treated according to culture and antimicrobial susceptibility testing results, rather than being treated empirically. They also highlight the importance of using routinely updated institutional antibiograms to determine the best empiric antimicrobial regimens based on local distribution of pathogens and their antimicrobial susceptibilities. The goal is to choose antibiotics that target specific pathogens associated with HAP or VAP as narrowly as possible. In addition to local antibiograms, patient-specific risk factors, such as prior IV antibiotic use within 90 days and need for ventilatory support for septic shock, should be used to identify patients at risk for MDR organisms who may necessitate coverage of MRSA or double coverage for *Pseudomonas aeruginos*a until susceptibilities are available (3, 5).

Recommendations from several international guidelines state that the management of nvHAP and VAP should be based on a combination of clinical state, such as sepsis, comorbidity, and risk factors for infections with MDR aetiology. In Norwegian hospitals HAP is commonly caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus* or Enterobacterales spp. The occurrence of micro-organisms such as Acinetobacter spp. and MRSA is rare in Norway, and empiric coverage for these is considered not to be necessary. International guidelines recommend a therapy duration of 5-8 days in patients that respond well to therapy and that are not immunocompromised. In patients with hospital stays of less than 5 days, HAP is often caused by the same microbes that cause CAP. Some international guidelines recommend that low-risk patients in this group be treated the same as CAP patients (7).

## Antimicrobial policy in Norway

Antimicrobial resistance governance in Norway was recently ranked highest among 114 countries around the world (8). In this study, countries were awarded an antimicrobial resistance governance score, based on several criteria and domains such as policy design, implementation tools, and monitoring and evaluation practices. The study implies that the strategies for antimicrobial resistance management is well established in Norway, including antimicrobial policy.

Updated clinical practice guideline recommendations on antimicrobial therapy are available for both primary healthcare services and hospital settings at a national level in Norway. All recommendations aim

to provide clinicians with rational, empirical regimens of choice for most infectious syndromes. The Directorate of Health has provided this service since 2013, in close collaboration with clinicians throughout the country. Revised guideline recommendations were available from 2020 throughout 2022. Recommendations stated in the clinical practice guidelines are considered normative. This means that clinicians are obligated to recognize and utilize the appropriate recommendation to the specific infection being treated. Exceptions are allowed for all circumstances. However, this requires careful consideration and documentation.

In nonventilator, hospital-acquired pneumonia, cefotaxime is regarded as first-line antimicrobial therapy according to current recommendations in Norway (7). However, several considerations apply. Firstly, the diagnosis should preferably rely on clinical, biochemical, microbiological, and imaging studies. Secondly, reasonable steps should be taken to rule out non-infectious, and non-bacterial conditions. Thirdly, if the diagnosis is confirmed, amoxicillin-clavulanate should be attempted in mild cases. And fourthly, in early hospital-acquired pneumonia, recommendations for community-acquired pneumonia should be evaluated.

In this observational study, we aimed to identify and describe cases diagnosed with nvHAP in a single-center teaching university hospital in Norway. Of special interest was diagnostic and management features, among these the antimicrobial therapy as compared to Norwegian clinical practice guidelines.

# Materials and methods

## Study setting

The study was conducted at a single-center, tertiary care, teaching university hospital in Norway. The hospital operates around 1,000 beds for inhabitants in the southern part of Trøndelag county. In addition, the hospital carries out a variety of regional functions.

## Study design

A joint study group of investigators was established to plan and carry out the study, and to analyze the retrieved data. The overall study design was observational, and all data were collected retrospectively.

## Study population

We used an in-patient hospital administrative system to identify cases that met criteria for eligibility. Search criteria were limited to ICD-10 codes between J12 to J18.9 as a secondary diagnosis on discharge letters from January throughout June 2022. All identified cases were presented to the study group in an anonymized excel spreadsheet.

Several exclusion criteria were applied to prevent heterogenicity in the study population. Of these were admissions with hospital days outside of the study time limit, patient transfers between hospitals, criteria to secure true hospital-acquired infections, criteria to detect viral etiology, specific medical departments, and data inconsistency.

Included cases in the study were diagnosed with hospital onset pneumonia documented as a secondary diagnosis in the discharge letter. This means that all included cases were ascribed with another primary discharge diagnosis, and that pneumonia occurred as a hospital-acquired, complicating disease, in addition to the primary cause of the hospitalization. All cases were aged above 16 years.

All patients admitted to the hospital in the study period that met the inclusion criteria were analyzed according to methods described in the statistics section.

## Data collection

All data were collected retrospectively. We used the standard patient administrative documentation program Doculive to retrieve data on patient characteristics, diagnostics, and HAP management. Of particular focus were microbiological-, radiology-, biochemical-, and clinical diagnostics, as well as

instituted antimicrobial therapy. The collected data were placed and assessed in a spreadsheet before statistical analyses.

## Definitions

Non-ventilator, hospital-acquired pneumonia was defined by the emergence of pneumonia symptoms in the hospitalized patient, at least 48-hours beyond admission, and which was not incubating at admission. All included cases were ascribed with this diagnosis on the official discharge letter. We excluded all cases that were invasively ventilated before, during or after the diagnosis and management of nvHAP.

Empirical antimicrobial therapy was defined from initiation until targeted antimicrobial therapy was instituted. Targeted antimicrobial therapy was defined as the transition to pathogen-directed antimicrobial therapy in accordance with the antimicrobial susceptibility test.

Antimicrobial therapy days were recorded as days, and not hours. If 50 % or more of the prescribed daily doses were administered, we defined this as a complete antimicrobial day.

## Statistical analyses

When assessing the collected data, we used simple descriptive statistics to delineate patient characteristics, diagnostics, and antimicrobial therapy. All statistics were performed using Microsoft Excel 2016.

## Ethical consideration

The study conducted was approved by the hospital administration, patient confidentiality official, and by the regional ethics committee (REK number 516837). The retrospective and observational nature of the study led the committee to conclude that patient consent was unnecessary among study participants. All data retrieved remained anonymous throughout the study period and were saved on secure servers within hospital environments.

# Results

## Exclusions and inclusions

Based on the applied search criteria, a total amount of 417 hospital admissions were identified in the 6-month period. Among these, 307 (73.6 %) met one or more exclusion criteria, and were discarded. Consequently, 110 (26.4 %) patients were eligible for inclusion according to established criteria. Reasons for exclusions are presented in table 1.

*Table 1. Overview of identified, excluded, and included number of cases.*

| Admissions evaluated for inclusion | n (%) | n (%) |
|---|---|---|
| Admissions identified according to search criteria | 417 (100.0) | |
| Exclusions | 307 (73.6) | |
| ▪ Community-acquired pneumonia | | 102 (33.2) |
| ▪ Hospital stay <48 hours | | 67 (21.8) |
| ▪ Hospital departments not included | | 44 (14.3) |
| ▪ Outside of timeframe | | 25 (8.1) |
| ▪ Viral infection with suspected superinfection | | 25 (8.1) |
| ▪ Data lacking | | 22 (7.2) |
| ▪ Invasive ventilated HAP | | 9 (2.9) |
| ▪ Hospital transfer | | 8 (2.6) |
| ▪ Aspiration pneumonia | | 5 (1.6) |
| Inclusions | 110 (26.4) | |

## Patient characteristics

A total of 110 admissions with 110 individual patients were successfully included in the study. Of these 49 were men and 61 were women, with mean age of 70,0 (95 % CI, 66.5 – 73.5) and 72,4 (95 % CI, 70.0 – 74.9), respectively. For all inclusions the mean age was 71,4 years (range 43 to 92), median was 74 years, and mode was 59 years.

We observed 98 in-hospital survivors and 12 case fatalities. There were no statistically significant differences among patient characteristics in terms of survivors or fatalities. Patient characteristics for inclusions are presented in table 2.

Reason for hospitalization was assessed for all inclusions. Among these, cancer was most frequently reported, followed by cardiovascular event or respiratory event. About 89 % of included cases were acutely admitted to hospital, and about 11 % were planned admissions to their respective department.

Cases undergoing surgery during the hospital stay was also assessed. Almost half of included cases did not receive planned or acute surgery before developing nvHAP, whereas proportions that underwent 1, 2 or 3 or more procedures were 28 %, 17 % and 5 %, respectively.

*Table 2. Overview of patient characteristics of included cases.*

| | | Survivors | Non-survivor | Total | *p*-value |
|---|---|---|---|---|---|
| **Cohort** | | | | | |
| **Cohort, n (%)** | | 98 (89.1) | 12 (10.9) | 110 | |
| | Age, mean (95% CI) | 71.3 (69.1-73.5) | 72.1 (65.4-78.8) | 71.4 (69.3-73.4) | |
| | Age, median (IQR) | 74 | 75 | 74 | |
| | Male gender, n (%) | 44 (44.9) | 5 (41.7) | 49 (44.5) | 0.911 |
| **Cause of admittance, n (%)**[#] | | | | | 0.711 |
| | Infection (B) | 1 (1.0) | - | 1 (0.9) | |
| | Malignant tumors (C) | 25 (25.5) | - | 25 (22.7) | |
| | Neurological diseases (G) | 2 (2.0) | - | 2 (1.8) | |
| | Circulatory system (I) | 19 (19.4) | 5 (41.7) | 24 (21.8) | |
| | Respiratory system (J) | 16 (16.3) | 3 (25.0) | 19 (17.3) | |
| | Digestive system (K) | 13 (13.3) | - | 13 (11.8) | |
| | Skin and subcutaneous tissue (L) | 4 (4.1) | - | 4 (3.6) | |
| | Musculoskeletal system and connective tissue (M) | 1 (1.0) | 1 (8.3) | 2 (1.8) | |
| | Genitourinary system (N) | 2 (2.0) | - | 2 (1.8) | |
| | R* | 2 (2.0) | - | 2 (1.8) | |
| | Injury, poisoning, external causes (S-T) | 13 (13.3) | 3 (25.0) | 16 (14.5) | |
| **Admission type, n (%)** | | | | | NA |
| | Acute | 86 (87.8) | 12 (100) | 98 (89.1) | |
| | Elective | 12 (12.2) | - | 12 (10.9) | |
| **Surgery, n (%)** | | | | | 0.693 |
| | 0 procedures | 50 (51.0) | 4 (33.3) | 54 (49.1) | |
| | 1 procedure | 24 (24.5) | 7 (58.3) | 31 (28.2) | |
| | 2 procedures | 18 (18.4) | 1 (8.3) | 19 (17.3) | |
| | ≥3 procedures | 6 (6.1) | - | 6 (5.5) | |

#Cause of admittance classified by ICD10-code

*Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified

The calculation of incidence was based on official data from the national patient admission registry. Table 3 summarizes the incidences from selected departments.

*Table 3. Incidence according to departments*

| Department | Orkdal | Trondheim | Total | Admissions | Incidence | Incidence pr 100.000 inhabitants |
|---|---|---|---|---|---|---|
| **Medical departments** | | **39** | **39** | **3 995** | **1.0 %** | **976** |
| **Surgical departments** | **5** | **16** | **21** | **5 362** | **0.4 %** | **392** |
| **Orthopedic department** | **3** | **11** | **14** | **1 801** | **0.8 %** | **777** |
| **Oncology depertment** | | **11** | **11** | **1 007** | **1.1 %** | **1 092** |
| **Cardiology department** | | **9** | **9** | **3 102** | **0.3 %** | **290** |
| **Medical department** | **8** | | **8** | **1 894** | **0.4 %** | **422** |
| **Department of neurosurgery** | | **3** | **3** | **862** | **0.3 %** | **348** |
| **Department of dermatology** | | **2** | **2** | **237** | **0.8 %** | **844** |
| **Nerulogical department** | | **2** | **2** | **1 999** | **0.1 %** | **100** |
| **ENT department** | | **1** | **1** | **812** | **0.1 %** | **123** |
| **Total** | **16** | **94** | **110** | **21 071** | **0.5 %** | **522** |

## Diagnostic characteristics

Major clinical features of pneumonia, regardless of disease acquisition, are cough, fever and dyspnea. In the data recorded we observed that clinical features were documented in the medical journal in 41.8 %, 50.9% and 21.8 % of cases, respectively. Figures 1 and 2 summarize the observed clinical features.

*Figure 1. Observed clinical features in absolute numbers.*

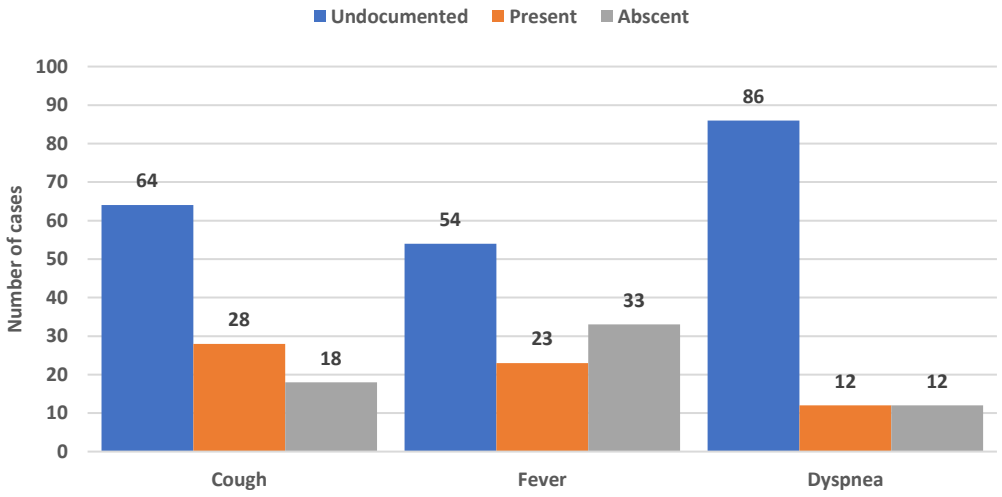
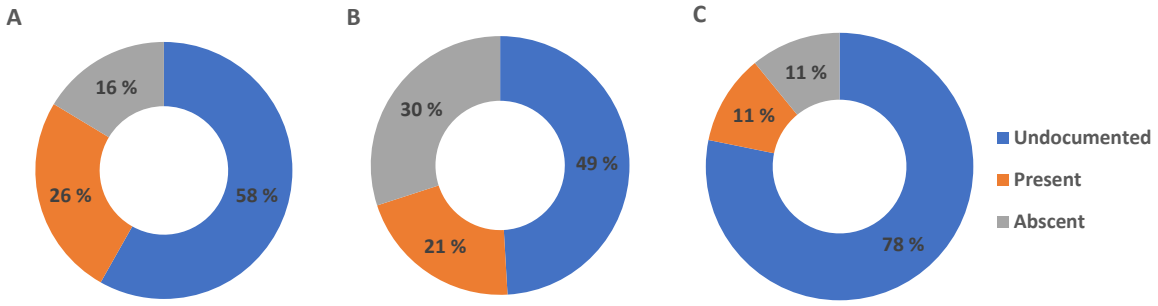


*Figure 2. Observed clinical features in proportions (%). A: Cough, B: Fever, C: Dyspnea.*




Radiological investigation of pneumonia is traditionally easy to perform and is generally recommended. Of the included cases of nvHAP, we observed that 98 (89.1 %) patients underwent at least one radiological investigation, and that a radiologically confirmed or highly suspected pneumonia infiltrate was detectable in 60 episodes (61.2 %). Mode of imaging studies and radiological findings are summarized in figures 3 and 4.

*Figure 3. Mode of imaging studies performed.*

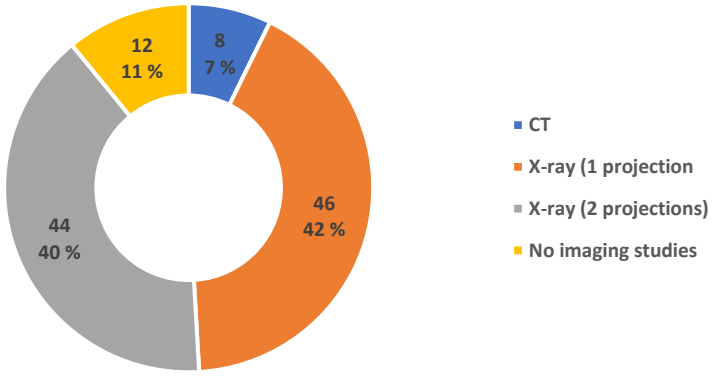
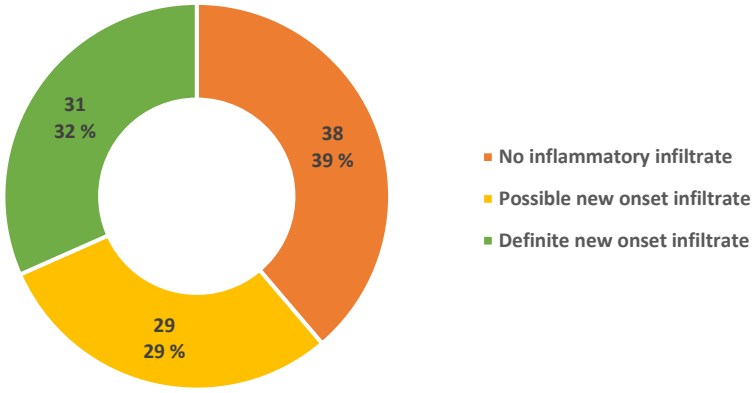
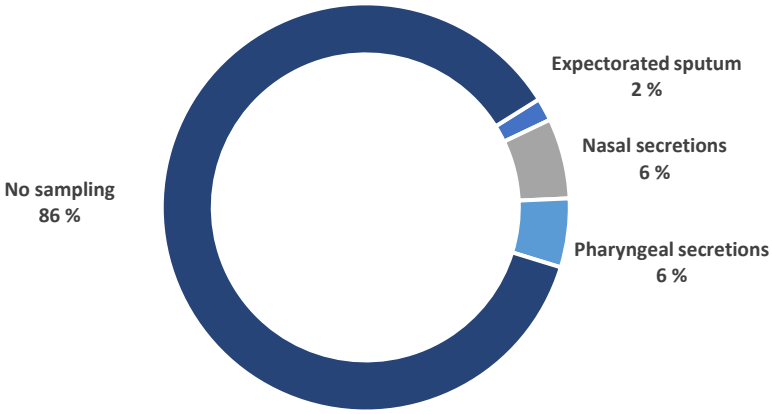


*Figure 4. Radiological findings.*




Microbiological confirmation of pneumonia is warranted for many reasons. Especially for the timely transition to targeted antimicrobial therapy, de-escalation strategies, and for pneumonia episodes with resistant microorganisms. In the data recorded, we observed that lower respiratory tract samples for microbiological confirmations were collected and analyzed on 2 of 110 included cases (1.8 %). Upper respiratory tract sampling was performed in 13 of 110 episodes (11.8 %), of which 7 were collected from the pharyngeal and 6 from the nasopharyngeal mucosa. We were unable to recover data on nvHAP-episodes that were planned for, and possibly underwent sampling procedures, but for any reason were unable to produce a representative respiratory tract secretion for analysis. Figure 5 summarizes the data on microbiological samples.

*Figure 5. Sampling of secretions for microbiological analyses.*



Diagnostic yield of microbiological samples was universally low. Of the 15 nvHAP-episodes that underwent sampling of respiratory secretions for microbiological analyses, we recovered 1 culture-positive incident with a reliable pathogen, whereas 7 were culture negative, and 7 yielded oral cavity flora.

## Disease severity

According to several clinical practice guideline recommendations, both diagnostic and management approaches should preferably rely on a disease severity assessment. Especially, disease severity as presented in the emergency room setting. Table 4 summarizes the clinical data observed to address disease severity at presentation.

*Table 4. Observed clinical variables.*

| Parameter | Count | Mean | 95% CI |
|---|---|---|---|
| **Systolic blood pressure (mmHG)** | **94** | **137** | **133-141** |
| **Diastolic blood pressure (mmHG)** | **94** | **74** | **71-75** |
| **Heart rate (pr minute)** | **79** | **84** | **82-87** |
| **Respiratory rate (pr minute)** | **47** | **18** | **17-19** |
| **Oxygen saturation (%)** | **72** | **96** | **95-97** |

We were unable to calculate some of the frequently used indicators and scores for pneumonia patients in the emergency room settings, like NEWS2-score or Pneumonia severity index.

Because of universally undocumented status on cerebral functions, we were unable to calculate CRB65-score. If this status was assumed to be normal, meaning that Glasgow coma scale were assumed to be 15 for all included nvHAP-episodes, the CRB-65 score would have been as presented in table 5.

*Table 5. Frequencies of calculated CRB65-scores.*

| CRB65 | Count | Frequency |
|---|---|---|
| **0-1** | **39** | **86,7 %** |
| **2** | **6** | **13,3 %** |
| **3-4** | **0** | **0,0 %** |
| **Total** | **45** | **100,0 %** |

Cases with nvHAP that were admitted to intensive care facilities were not the objective of this study and were therefore excluded from the study.

## Empirical antimicrobial therapy

Empirical antimicrobial therapy was initiated to all included cases on suspicion of lower respiratory tract infection. The mean number of days before empirical antimicrobial therapy was initiated was 4.9 days (95 5 CI 4.1 – 5.6), whereas mode was 2 days. The proportions of included cases that were initiated on oral or intravenous antimicrobial therapy were 27.3 % and 72.7 % respectively. In 42.2 % of included cases the empirical antimicrobial therapy was unchanged throughout the course, whilst in the remaining proportion the initiated regimen was altered to a new regimen. No included cases were transitioned to more than one new regimen.

Prescribed regimens were narrow-spectrum β-lactams in monotherapy in 51 of 110 (46.6 %) episodes. The addition of gentamicin to narrow-spectrum β-lactam regimens was initiated in 3 of 110 (2.7 %) episodes. Broad-spectrum antimicrobial regimens were initiated to the remaining proportion which constituted 56 of 110 (50.9 %) episodes, of which cefotaxime and piperacillin-tazobactam constituted 85.7 % and 14.3 %, respectively. Table 6 summarizes the initiated empirical regimens.

*Table 6. Distribution of initiated antimicrobial therapy.*

| Empirical regimens | Number | Frequency |
|---|---|---|
| **Phenoxymethylpenicillin** | **6** | **5,5 %** |
| **Amoxicillin** | **20** | **18,2 %** |
| **Benzylpenicillin** | **17** | **15,5 %** |
| **Benzylpenicillin + gentamicin** | **3** | **2,7 %** |
| **Trimethoprim-sulfametoxazole** | **8** | **7,3 %** |
| **Cefotaxime** | **48** | **43,6 %** |
| **Piperacillin-tazobactam** | **8** | **7,3 %** |
| **Total** | **110** | **100,0 %** |

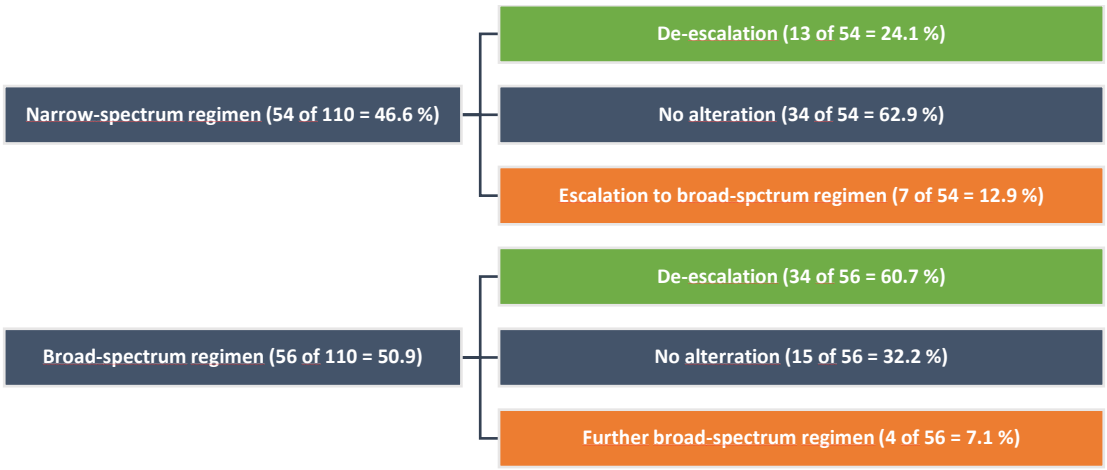
## De-escalation strategies

Because of consistently low sampling frequencies of respiratory tract secretions, the timely transition to targeted pathogen-directed antimicrobial therapy was not observed. Hence, antimicrobial therapy that was initiated to all included episodes of nvHAP remained empirical throughout the course.

Transition to new regimens throughout the infection course was initiated to 57.8 % of included episodes. Of the episodes that initially received narrow-spectrum regimens, 13 of 54 (24.1 %) were de-escalated to oral β-lactam regimens, mainly phenoxymethylpenicillin. However, in 7 of 54 (12.9 %) episodes escalation to broad-spectrum regimens were performed, of which all received cefotaxime. Of the episodes that initially received broad-spectrum regimens, 34 of 56 (60.7 %) episodes were de-escalated to narrow-

spectrum regimens, mainly amoxicillin. In 4 of 56 (7.1 %) episodes, broad-spectrum regimens that were initially prescribed were transferred to other broad-spectrum regimens, mainly ciprofloxacin. Figure 6 summarizes the initiated antimicrobial regimens.

*Figure 6. Proportions of empirical antimicrobial regimens.*




## Duration of therapy

Duration of antimicrobial therapy was assessed for all included episodes. Antimicrobial therapy initiated for other or unspecific reasons before hospital admission was not included in these calculations.

*Table 7. Duration of initiated antimicrobial regimens.*

| Initial regimen | Secondary regimen | Mean total duration | 95 % CI |
|---|---|---|---|
| **Narrow-spectrum** | **Narrow-spectrum** | **12.5** | **10.8 - 14.2** |
| | **No alteration** | **7.2** | **6.3 - 8.2** |
| | **Broad-spectrum** | **9.0** | **6.1 - 11.8** |
| **Broad-spectrum** | **Narrow-spectrum** | **12.4** | **11.3 - 13.6** |
| | **No alteration** | **6.9** | **5.3 - 8.6** |
| | **Broad-spectrum** | **10.2** | **8.7 - 11.7** |

## Outcomes

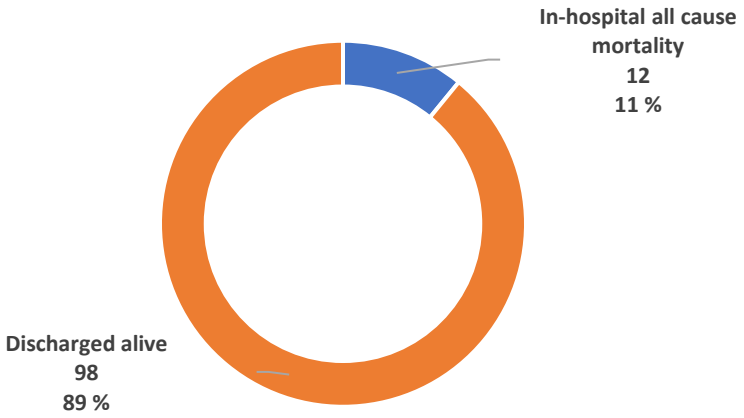
Disease outcomes were assessed for all included nvHAP episodes. We observed death from any cause during the hospital stay to 12 of 110 episodes, which constituted 10.9 %. The remaining proportion, counting 98 of 110 (89.1 %) included episodes, was discharged alive. The mean duration from the initiation of antimicrobial therapy until in-hospital, all-cause mortality was 9.5 days. The mean duration of days between cessation of antimicrobial therapy until in-hospital, all-cause mortality was 5.3 days.

For patients that were deceased 5 of 12 (41.7 %) were evaluated by an infectious disease specialist during the course of therapy.

Among deceased inclusions, 50 % received narrow-spectrum regimens, of which one was oral amoxicillin. This patient deceased two days after antimicrobial therapy was discontinued. Mean duration of narrow-spectrum antimicrobial therapy until in-hospital, all-cause mortality was 14.1 days.

Among patients with nvHAP that received broad-spectrum antimicrobial therapy initially and later deceased, all received cefotaxime for a mean duration of 8.2 days.

*Figure 7. In-hospital, all-cause mortality.*



# Discussion

Studies that target hospital-acquired pneumonia are scarce, especially nvHAP cases. Here, we report epidemiological, diagnostic, and management features, as well as outcomes from a single-center, university teaching hospital in Norway.

The calculated incidence of nvHAP in our study was 0.5 %, which corresponded to 522 per 100.000 inhabitants. Accumulated in-hospital antimicrobial therapy days for nvHAP were 1.060. Compared to earlier studies (9-13), our estimated nvHAP incidence was slightly lower. The incidence of nvHAP is interesting for many reasons. A recent commentary states that nvHAP is one of the most frequently observed healthcare-associated infections and is associated with considerable morbidity. However, nvHAP is rarely tracked, reported, or actively prevented by most hospitals. Call for action initiatives and research needs were recently published (4).

New onset of cough, fever, and dyspnea was infrequently observed in patients ultimately diagnosed with and treated for nvHAP in our study, reaching only 26 %, 21 % and 11 %, respectively. Moreover, these three cardinal symptoms were completely absent in considerable proportions. Interestingly, clinical symptoms often reported from pneumonia cases were frequently undocumented in our study, which is particularly surprising. This hampers representative and reproducible data. It is, however, a known characteristic of observational studies with retrospective data collection. Cardinal symptoms are, however, frequently reported in previously studies (3), but no specific symptoms or sets of signs or symptoms have been found to be highly sensitive or specific for the HAP diagnosis (14, 15).

Vital signs are routinely documented and evaluated in hospitalized infections. The observed parameters in our study indicated that both cardiovascular and oxygenation status were predominantly preserved. Disease severity assessments were uniformly undocumented in included nvHAP episodes. Internationally, disease severity assessments are frequently reported by the use of CRB65-score or pneumonia severity index (PSI). The lack of data made such calculations unpredictable or impossible. When analyzing our data, we assumed normal cerebral functions and a Glasgow coma scale at 15 points. In addition, both CRB65 and PSI are developed and validated for community-acquired cases only (16, 17), and the application to hospital-acquired infections is questionable. The findings of our study raise some concern that the nvHAP diagnosis ascribed to included cases in fact is trustworthy. It is likely to assume that an unknown proportion of included cases received a nvHAP diagnosis and antimicrobial therapy for other infectious and non-infectious reasons. We also observed that the absence of clinical signs and undocumented clinical signs, correlated with radiographically unconfirmed cases.

For ventilator-associated pneumonia, efforts to secure a microbiological confirmation is recommended from both European (1) and North American guidelines (3). However, the approach to sample representative respiratory secretions differs, as the former encourage invasive, and the latter non-invasive techniques. For nvHAP, clear recommendations are lacking, although semi-quantitative cultures seem to be preferred over qualitative ones (3). In Norway however, clinical practice guidelines offer specific recommendations to secure blood cultures and expectorated or induced sputum for nvHAP (7). This is in line with other guideline recommendations from Sweden (18) and Great Britain (19), and some comprehensive online resources like BMJ Best Practice (20), and UpToDate (6).

Norwegian guideline recommendations favor a third-generation cephalosporin as empirical antimicrobial therapy for uncomplicated nvHAP cases (7). However, this should preferably apply to confirmed cases only. For mild cases, oral amoxicillin-clavulanate should be evaluated, and for early onset nvHAP, recommendations for community-acquired pneumonia should be evaluated. In cases with respiratory failure, sepsis, or high risk of AMR-pathogen, Norwegian guideline recommendations favor piperacillin-tazobactam as an antipseudomonal regimen. In our study, we did not observe the use of amoxicillin-clavulanate for mild cases, although a considerable number of included cases were estimated to be non-severe. We were also unable to confirm that recommendations for community-acquired pneumonia should preferably be used to early onset episodes. In addition to this, no risk assessments for AMR-pathogens were documented.

The choice of empirical antimicrobial therapy was cefotaxime in nearly 44 % of included nvHAP episodes in our study. Based on the available data, including severity assessments and the lack of microbiological confirmations, this number probably indicates that cefotaxime is overprescribed. In Norway, prevalence of AMR-pathogens remain low, especially for methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum β-lactamase producing gram negatives (ESBL), and pneumococci with decreased penicillin-susceptibility (21). For these reasons broad-spectrum antimicrobial regimens have traditionally been considered unjustified in Norway, which is mirrored in national clinical practice guidelines (7).

Targeted therapy is justified according to several previously published guidelines and commentaries (3, 22, 23). The timely transition to targeted, pathogen-directed antimicrobial therapy at the time point when antimicrobial susceptibility tests are being reported, has proved beneficial as compared to the continuation of empirical therapy. Firstly, no increased mortality is observed (24-26). Secondly, no increased risk of re-infection is observed (24, 26). And thirdly, no increased ICU length of stay has been observed (24, 27). In our study, microbiologically confirmed cases were non-existing, except for one episode only. The

small number of included nvHAP cases, to which efforts to sample lower respiratory tract secretions were documented, deprives targeted antimicrobial therapy.

According to national (7) and international guideline recommendations (1, 3), 7 days of antimicrobial therapy seem warranted for most nvHAP cases. This recommendation is based on two meta-analyses that comprise six randomized clinical trials which included over 1.000 patients with nvHAP or VAP (3, 28). The main findings were that 7-8 days of antimicrobial therapy was non-inferior to 10-15 days. Longer courses have not proved beneficial and may contribute to the emergence of AMR (3, 25). We observed that therapy duration exceeded 7 days for most included cases in our study, even in the absence of more complicated disease like bacteremia, empyema, abscess or metastatic infection. A promising tool to aid the decision to discontinue antimicrobial therapy is the use of procalcitonin (29, 30). However, procalcitonin is infrequently used at our hospital.

Survivors of nvHAP risk additional hospitalizations. In some studies, 30-day readmission rates peak 20 % (9-13). While crude mortality previously has been reported for VAP episodes, data on nvHAP episodes are scarce. We estimated in-hospital, all-cause mortality at 10.9 % which is surprisingly high. Unfortunately, we were unable to report re-admission rates. Factors that are associated with increased mortality are disease severity, bacteremia, severe underlying comorbidity, AMR-pathogens, multilobular-, cavitating- or rapidly progressing infiltrates, and delayed effective antimicrobial therapy (3, 25, 31). A very prominent finding in our study is the few occurrences of such factors. However, cases admitted to the ICU were excluded in our study.

# Conclusion

Non-ventilator HAP is a frequent entity in hospital settings that might benefit from increased attention. The aim of the study was to identify and describe cases diagnosed with nvHAP in a university hospital in Norway. Diagnostic and management features, such as antimicrobial therapy and adherence to Norwegian guidelines, were of particular interest.

In patients diagnosed with nvHAP, cardinal symptoms are infrequently observed and often completely absent or undocumented in medical journals. Absent or undocumented clinical signs also correlates with radiographically unconfirmed cases, making the nvHAP diagnosis questionable in some included cases. Norwegian clinical practice guidelines offer specific recommendations for respiratory tract sampling for nvHAP. Yet sampling frequencies are surprisingly low, and microbiologically confirmed cases are predominantly lacking, depriving targeted antimicrobial therapy.

In the management of nvHAP Norwegian guidelines recommend cefotaxime as first-line antimicrobial therapy in confirmed cases. In mild or early-onset cases narrow-spectrum antimicrobial therapy should be evaluated, however cefotaxime is the most frequently prescribed antimicrobial agent. Therapy duration frequently exceeds the recommendation of 7 days, although this duration is considered to be non-inferior to longer courses. Available data indicate an overall low disease severity in included cases, suggesting that cefotaxime is overprescribed, and therapy duration is too long-lasting.

Ultimately, efforts to thoroughly track, report, prevent, diagnose, and manage nvHAP seem necessary for building awareness and adhere to clinical practice guidelines.

## Declaration of interest statement

We declare no conflict of interests.

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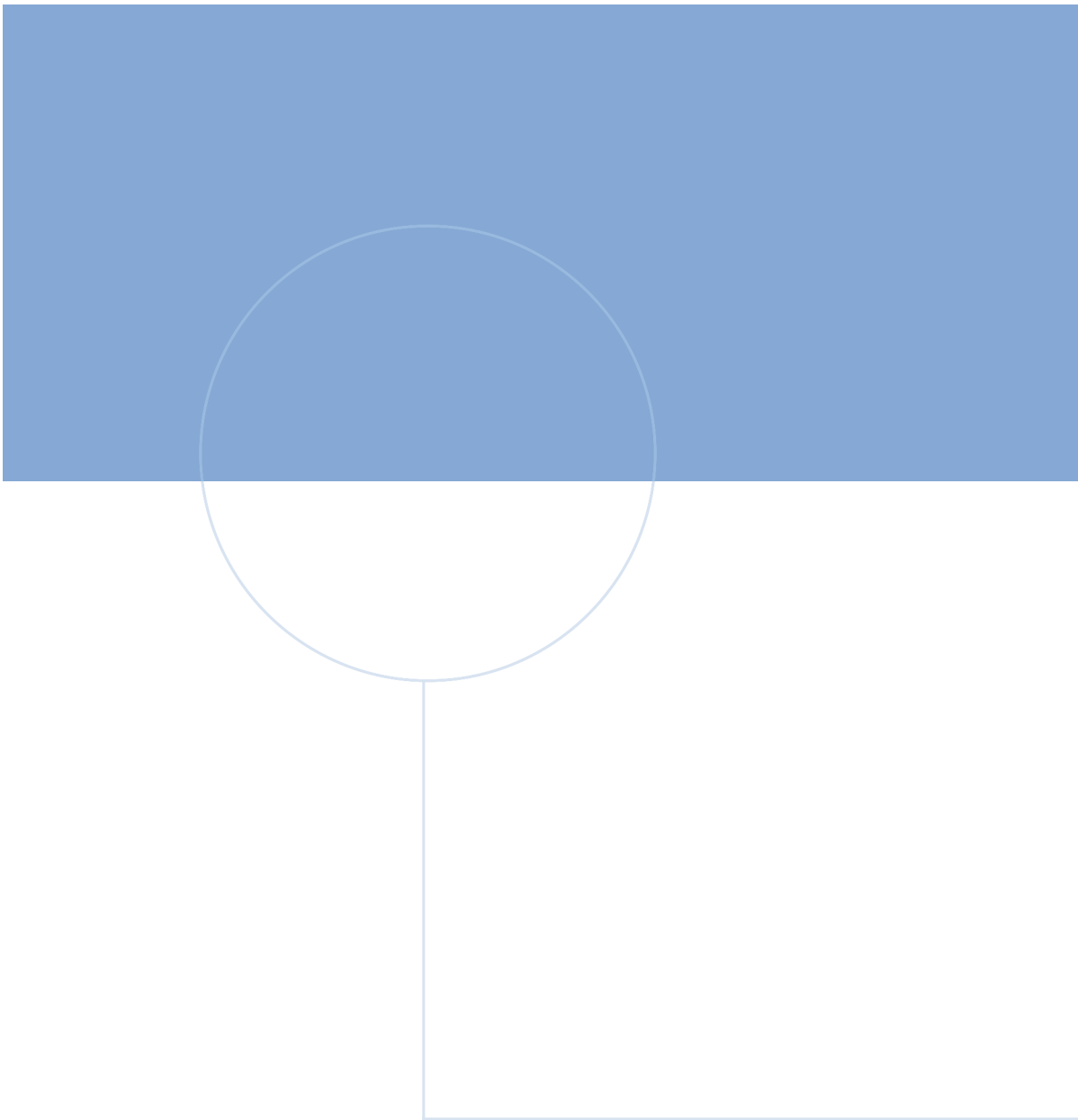

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