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# Dissertation Abstract

## Empiric Antibiotic Treatment and Diagnostic Imaging for Pneumonia

### Background

Antimicrobial resistance (AMR) is a threat to global health. A pivotal driver of AMR is the indiscriminate prescription of broad-spectrum antibiotics, which is largely attributable to diagnostic uncertainties about the specific pathogen and foci of the infection. Pneumonia is an infection frequently seen in the emergency department (ED), where timely and accurate diagnosis is crucial, not only to tailor the treatment but also to combat AMR. Danish guidelines for community-acquired pneumonia (CAP) recommend beta-lactamase-sensitive penicillin and adding a macrolide or fluoroquinolone to provide coverage for *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae* (LMC) pathogens in patients with high severity score. However, the efficacy of the current strategy in providing specific and comprehensive antibiotic treatment is still unknown.

The chest X-ray (CXR) remains the primary imaging method for CAP. While standard-dose computed tomography (SD-CT) provides greater details and is considered the gold standard in imaging, its use is limited by the significant radiation involved. Emerging diagnostic imaging modalities include ultralow-dose CT (ULD-CT) and focused lung ultrasound (FLUS). ULD-CT is a modification of traditional SD-CT, limiting radiation exposure while maintaining adequate image clarity. FLUS, particularly when conducted by skilled operators using advanced ultrasound equipment, has been shown to have high sensitivity and specificity rates for the diagnosis of CAP. Nonetheless, the rise in handheld ultrasound (HHUS) devices and the relative scarcity of experienced FLUS operators warrants an examination of the accuracy of FLUS when performed by newly certified operators using HHUS. In light of these challenges and given that often antibiotic treatment is commenced in the ED, this thesis seeks to evaluate current initial antibiotic prescription patterns arising from uncertain diagnoses and diagnostic imaging accuracy for CAP in the ED and imaging's potential to reduce diagnostic uncertainty.



### HVAD VED VI?

Empirisk antibiotikabehandling af CAP i akutområder er ofte præget af diagnostisk usikkerhed, og standard CXR har begrænset nøjagtighed sammenlignet med SD-CT.

*Fact box (in Danish)*

### Objectives

The overarching aim of this thesis was to evaluate current antibiotic prescription patterns and explore the accuracy of various diagnostic imaging techniques for CAP. The specific objectives were to:

1. examine empiric antibiotic therapy for patients with CAP and estimate the prevalence of prescriptions arising from uncertain diagnoses (Study 1)
2. examine the precision of applied severity-based antibiotic guidelines for empirical treatment of LMC pneumonias (Study 1)
3. estimate the diagnostic accuracy of the following imaging modalities for opacities consistent with CAP and compare them with the accuracy of CXRs, with SD-CT as reference standard:
  - FLUS using HHUS by newly certified operators (Study 2)
  - ULD-CT (Study 3)
4. evaluate the efficacy of the current standard imaging modality, CXR, versus the highest potential of imaging, SD-CT, in enhancing diagnostic certainty for CAP

### Methods

Study 1 was a register-based cross-sectional analysis of nontraumatic patients presenting to hospitals in the Re-

gion of Southern Denmark over a 2-year period. The antibiotics prescribed to all patients discharged with a diagnosis of pneumonia were identified. In addition, for cases with a credible CAP pathogen, the percentage of LMC pneumonia cases that were prescribed antibiotics with LMC coverage, as well as the percentage of patients who were prescribed antibiotics with LMC coverage and who had LMC pneumonia, were calculated.

Studies 2 and 3 were multicenter cross-sectional studies with data prospectively collected from patients admitted to the EDs with suspected pneumonia. Study 2 examined the diagnostic accuracy of FLUS conducted by newly certified operators using HHUS devices, while Study 3 examined the diagnostic accuracy of ULD-CT. Each modality was compared with the CXR, against SD-CT used as the reference standard. Additionally, the Cohen's kappa coefficient and agreement of CXR and SD-CT with expert diagnosis were compared.

### Results

Study 1 was based on a sample of 13,352 patients diagnosed with pneumonia and prescribed empiric antibiotic therapy within 24 hours. The most frequently prescribed antibiotic was piperacillin/tazobactam ( $n = 4,488$ , 34%), followed by beta-lactamase-sensitive penicillin ( $n = 3,324$ , 25%). Only 37% (CI [28, 47]) of patients with LMC pneumonia were covered by the empirical antibiotic treatment, while only 12% (CI [8, 15]) of patients treated with antibiotics with LMC coverage actually had LMC pneumonia. Of non-LMC pneumonia cases, 22% (CI [20, 24]) were prescribed antibiotics with LMC coverage.

Studies 2 and 3 were based on a sample of 325 patients with suspected pneumonia. The results of Study 2 show that FLUS has a sensitivity of 32% and a specificity of

### PERSPEKTIVERING

Implementering af ULD-CT som alternativ til CXR kan øge diagnostisk sikkerhed, men yderligere diagnostiske tiltag bør overvejes, især i forbindelse med behandling af LMC-pneumonier.

*Fact box (in Danish)*

81%, while ULD-CT has a sensitivity of 84% and a specificity of 83% to detect opacities consistent with CAP. In contrast, CXR has a sensitivity of 69% and a specificity of 69%. These findings show that compared with CXR, FLUS has a significantly lower sensitivity, while ULD-CT has a significantly higher sensitivity and specificity. Cohen's kappa for CXR agreement with expert diagnosis was 0.31, corresponding to a moderate agreement of 64% with expert diagnosis. For SD-vii CT, Cohen's kappa was 0.37, corresponding to a moderate agreement of 69% with expert diagnosis. The kappa value was significantly higher for SD-CT compared to CXR ( $p < 0.001$ ).

### Conclusion

Empiric antibiotic therapy for patients diagnosed with CAP is based on a significant degree of diagnostic uncertainty. Severity-based antibiotic guidelines' ability to provide specific and adequate coverage for LMC pneumonia is low. When conducted by newly certified operators using HHUS devices, FLUS has low sensitivity compared with CXR for visible lung opacities consistent with CAP. ULD-CT shows superior diagnostic accuracy and is a promising alternative to CXR. However, our findings suggest a modest potential for increased diagnostic certainty with imaging techniques beyond CXR, highlighting the need for additional diagnostic measures beyond imaging.

### Conflict of Interest

The author declares that they have no conflicts of interest.

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### HVAD TILFØJER AFHANDLINGEN?

ULD-CT viser højere diagnostisk nøjagtighed sammenlignet med CXR, mens FLUS med HHUS udført af nyuddannede operatører har lavere sensitivitet.

*Fact box (in Danish)*