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Limited value of sputum culture to guide antibiotic treatment in a Danish emergency department

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ABSTRACT

Introduction: Antibiotics resistance is increasing worldwide. The Region of Southern Denmark developed an antibiotic stewardship to reduce the use of broad-spectrum antibiotics in hospitals including microbiological diagnostics of sputum samples. The aim of this study was to evaluate the implementation of the stewardship in the emergency department (ED) concerning management of pulmonary infections. The objectives were: 1) to investigate whether the empirical therapy was prescribed correctly, 2) to identify the quality and results of pre-antibiotic sputum collection and 3) to investigate whether the antibiotic treatment was revised based on the microbiological results.

Methods: This was a quality assessment study. Patient files from patients discharged with either pneumonia or acute exacerbation of chronic pulmonary disease were reviewed, and written feedback was provided to the doctors, focusing on the regional guideline.

Results: Among the 257 medical records audited, the guideline was followed in 89% of the cases. Pre-antibiotic sputum samples were collected from 47% of the patients and 79% of these had sufficient quality for cultivation. None of the empirical antibiotic treatments were revised based on the microbiological results but some were revised based on other clinical parameters.

Conclusions: Sputum samples had no clinical value for adjustment of the antibiotic treatment. Improvements of sputum sample collection and faster microbiological diagnostics are needed for sputum analysis to have any impact on the antibiotic treatment of patients with a pulmonary infection in the ED.

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Trial registration: not relevant.

Lower respiratory tract infections (LRTI) are a major cause of antibiotic prescriptions from emergency departments (ED) [1], and treatment success is challenged by antibiotic resistance [2].

The growing concern over overuse of antibiotics and the focus on a targeted antibiotic treatment to prevent resistance has culminated in antibiotic stewardship programmes. These programmes often recommend the collection of sputum to identify causative pathogens so that physicians can adjust antibiotic therapy if necessary [3-6]. The Region of Southern Denmark's (RSD) guidelines recommend that pneumonia be targeted through an initial antibiotic treatment combined with sputum collection, cultivation and microbiological examination. The

guidelines recommend that the results are available within 48 hours to ensure that antibiotic treatment may be adjusted as necessary [1].

The aim of this study was to evaluate the effect of the RSD guidelines in the ED when treating LRTI. Our objectives were: 1) to investigate whether empirical therapy was prescribed according to guidelines, 2) to identify the quality and results of the sputum collections, and 3) to investigate whether the initial antibiotic treatment was adjusted in accordance with the microbiological results.

METHODS

Study design and setting

An audit was performed on all patients admitted with LRTI at a 50-bed ED at the Hospital of Southern Jutland, Aabenraa, with a hospital service area including approximately 150,000 inhabitants. Admitted patients were referred to the hospital by either a general practitioner or a doctor from the ED.

Selection of patients

The study included all patients discharged from the hospital with a diagnosis of pneumonia or acute exacerbation of chronic pulmonary disease (AECOPD) who received antibiotic treatment. The patients were identified using the hospital's electronic administrative system. Patients were excluded if they were less than 18 years of age, had severe immunodeficiencies, e.g., patients with uncontrolled HIV (a CD4 count below 200/µl), received immunosuppressive therapy apart from glucocorticoids below 20 mg/day of prednisolone, were admitted directly to the intensive care unit, had been treated with antibiotics before admission or had more than one infection as the RSD guidelines did not include these patient groups.

The Region of Southern Denmark's antibiotic guidelines

The guidelines recommend that all patients who require treatment with antibiotics due to pneumonia/AECOPD deliver a sputum sample before treatment is initiated. If this is not possible within 30 minutes of arrival, nurses are obliged to perform a tracheal aspiration. The transport of specimens to the laboratory for cultivation should

occur at least twice daily. A PCR analysis is included if patients are suspected of having "atypical pathogens", i.e. Legionella pneumophila, *Mycoplasma pneumoniae* or *Chlamydia pneumoniae* infection, either by history, a CURB-65 score > 2 points or an X-ray of the chest with > 1 pulmonary infiltrate. Empirical antibiotic treatment should be prescribed within four hours of arrival (**Table 1**) and be revised according to microbiological results within 48 hours of the first antibiotic dose [1].

TABLE 1 / The Region of Southern Denmark antibiotic stewardship: respiratory infections.

Infection	Drug	Dose	Duration, days
Pneumonia			
Community-acquired:			
Mild: CURB-65 score 0-2	Benzylpenicillin	1.2 g (2×10^6 IU) IV × 4	5
	Or phenoxymethylpenicillin	0.6 g (1×10^6 IU) p.o. × 4	
	In the case of penicillin allergy: clarithromycin	500 mg IV/p.o. × 2	
Moderate: CURB-65 score 3-5	Benzylpenicillin	1,2 g (2 × 106 IU) IV × 4	7
	+ clarithromycin	500 mg IV × 2	
	In the case of penicillin allergy: cefuroxime	1.5 g IV × 3	
	+ clarithromycin	500 mg IV × 2	
Severe[a]: CURB-65 score 3-5	Piperacillin/tazobactam	4 g/0.5 g IV × 3	7
	+ clarithromycin	500 mg IV × 2	
	In the case of penicillin allergy: cefuroxime	1.5 g IV × 3	
	+ clarithromycin	500 mg IV × 2	
Hospital-acquired	Piperacillin/tazobactam	4 g/0.5 g IV × 3	7
	In the case of penicillin allergy: cefuroxime	1.5 g IV × 3	
Aspirational	Treated as mentioned above based on type of pneumonia and severity Patients treated with cefuroxime in the case of penicillin allergy should also receive metronidazol 1-2 g/day divided on 2-3 doses IV or supplement		-
Acute exacerbation of COPD[b]	Amoxicillin/clavulonic acid	500 mg/125 mg p.o. × 3	5
	In cases with NIV-/mechanical ventilation or where p.o. treatment is impossible: piperacillin/tazobactam	4 g/0.5 g IV × 3	7
	In the case of penicillin allergy: cefuroxime	1.5 g IV × 3	7

COPD = *chronic obstructive pulmonary disease*; CURB-65 = confusion, urea, respiratory rate, blood pressure, ≥ 65 yrs of age; IU = international units; NIV = non-invasive ventilation; p.o. = peroral(ly).
a) Severe pneumonia is defined by CURB-65 score ≥ 3 and radiological involvement of several lung lobes or hypoxia with O_2 saturation < 92%, or sepsis.
b) Antibiotic treatment is only indicated if the patient is clinically affected and has the symptoms: increased purulence of sputum, dyspnoea and expectoration.

Sputum sample analyses

Sputum samples were heat fixed and gram stained. Sputum with ten or more squamous epithelial cells/low-power field (× 10) was rejected for analysis.

Samples judged useful by microscopy were collected with a cotton swab and sown with three steps spread on a 5% blood agar plate with one staphylococci line, one optochin-disc and one chrome-agar orientation plate. The blood agar was incubated at 35 °C in CO_2 and the chrome-agar orientation plate at 35 °C. Anaerobic plates were incubated in an anaerobic cabinet. After 1-2 days of incubation, the pathogens were identified, and a bacterial antibiotic resistance test was performed indicating whether the material was useful and including a description of the identified bacterial flora. PCR analysis was performed if atypical pathogens or clinically severe pneumonia was suspected.

Optimising clinical practice related to the Region of Southern Denmark's antibiotic guidelines

During implementation of the RSD guidelines, attention was focused on information and training of ED doctors and relevant departments for admitted ED patients.

Training consisted of lectures emphasizing that no patient should receive antibiotics before a blood sample and a dedicated attempt for a sputum sample had been collected. In addition, all clinicians received a pocketbook version of the RSD guidelines. Nursing staff received simulation and bedside training in obtaining a representative sputum sample and performing tracheal aspiration.

Written feedback was given by two study assistants to the doctors prescribing the empirical antibiotic treatment to inform whether or not treatment was in accordance with the RSD guidelines. An infection disease specialist evaluated and adjusted this feedback before it was given to the prescribing doctor. All written feedback was sent through the electronic patient file system and included encouragement to follow the RSD guidelines.

Data sources, outcomes and analyses

The data were collected from all patients discharged with a diagnosis of AECOPD or pneumonia from 11 December 2017 to 13 May 2018. An audit of the patient files enabled inclusion of the time of arrival to the ED and departure from the hospital. The following outcomes were explored:

1. Correct prescription of the empirical antibiotic therapy

2. The quality and results of the pre-antibiotic sputum collection

3. Adjustment of antibiotic treatment based on the microbiological results.

The data were collected, and descriptive statistics were used to summarise the results.

Ethical considerations

The regional ethical committee of Southern Denmark considered the study a quality assurance project (no S-20172000-186). The study was approved by the Hospital of Southern Jutland ED management team. The data were registered by the Danish Data Protection Agency (no.17/44190).

Trial registration: not relevant.

RESULTS

Patient characteristics

Among the 257 medical records audited, 87 (34%) were excluded due to lack of antibiotic treatment, co-infection or illnesses making adherence to the antibiotic guidelines difficult, e.g., cancer or chemotherapy. A total of 170 records were included in this study. The mean age of the population was 74 years and the population included 92 men (54%) and 78 women (46%).

The 170 medical records consisted of 135 (79%) patients diagnosed with pneumonia and 35 (21%) patients diagnosed with AECOPD.

Correct prescription of the empiric antibiotic therapy

Based on the RSD guidelines (Table 1), 151 (89%) of the patients had the correct empiric antibiotic therapy prescribed. The remaining 19 (11%) patients were treated incorrectly according to RSD guidelines with no valid medical reason for the choice of the alternative empirical therapy. For example, a community-acquired non-severe pneumonia was treated with piperacillin/tazobactam or cefuroxime instead of penicillin as required by the RSD guidelines.

The quality and results of pre-antibiotic sputum collection

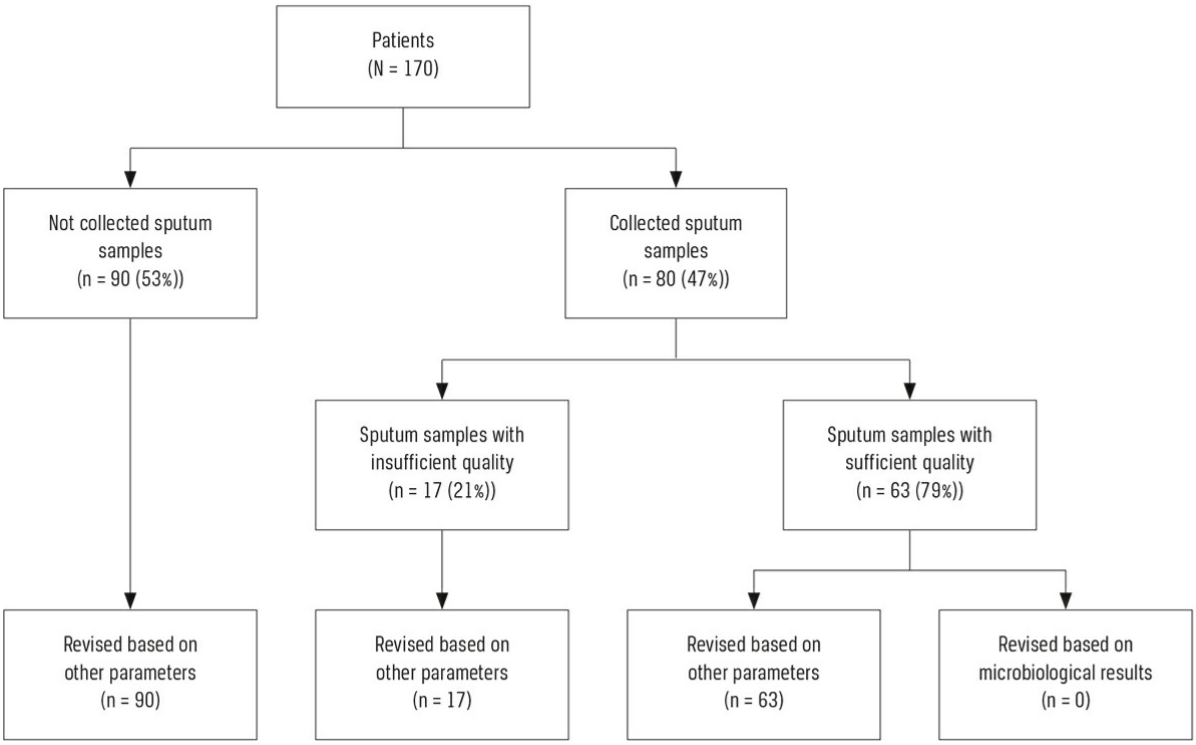
From these 170 medical records, 80 (47%) sputum samples were obtained and submitted for analysis. Among

these 80 collected samples, 63 (79%) had the required quality for cultivation, and 29 samples (46%) identified pathogens: *Haemophilus influenzae* (n = 6), *Streptococcus pneumoniae* (n = 3), *Staphylococcus aureus* (n = 3), *Moraxella catarrhalis* (n = 4), group B streptococcus (n = 1), *Pseudomonas aeruginosa* (n = 2), *Candida* species (n = 7) and coliform bacteria (n = 3). No atypical pathogens were identified.

Adjustment of the antibiotic treatment

Revision of the antibiotic treatment occurred within 48 hours for all patients (**Figure 1**). However, none of the treatments were revised based on microbiological results. All adjustments to treatment were based on other parameters, including clinical status, vital signs, leukocyte count and C-reactive protein.

FIGURE 1 / Distribution of sputum samples.



DISCUSSION

Our study found an 89% adherence to the RSD guidelines for prescription of an empiric antibiotic treatment. Sputum samples had been collected from 47% of the study population, and 79% of these had sufficient quality for cultivation. Among the cultivated samples, 46% identified pathogens. None of the empirical antibiotic treatments were revised based on these results.

Recommendation of sputum samples

The RSD guidelines recommend routine culture of sputum specimens from patients admitted with LRTI to identify optimal antibiotic treatment [1]. In contrast, guidelines from other Antibiotic Stewardship Programmes recommend culture of a sputum sample on a case-by-case basis [7]. Consensus on sputum collection is challenging in relation to its diagnostic yield and reliability [8]. However, sputum culture has the potential to improve clinical decisions, narrowing the antibiotic spectrum and improving identification of resistant pathogens [7]. Consequently, national and international guidelines advocate further research to develop rapid, sensitive diagnostic tests and strategies when making decisions about the optimal antibiotic treatment [1, 7].

Correct prescription of the empiric antibiotic therapy

Some Danish studies report adherence to antibiotic guidelines, but studies from other European countries report frequent non-adherence [9, 10]. One study from the Netherlands reported 61% adherence to overall guidelines and 43% adherence in patients with pneumonia [9]. A six-month Norwegian intervention study using feedback on prescription of appropriate empirical antibiotics reported an increase of adherence from 61.7% to 83.8% [10]. The relatively high adherence to RSD guidelines in this study may be owed to the continuous and individual written feedback provided during the implementation period.

The results and quality of the pre-antibiotic sputum collection

Sputum sample collection is challenging. In a larger study of 1,669 patients on the usefulness of sputum samples in guiding diagnosis of pneumonia, samples were collected from 59% of the patients; only 54% were of good quality and 14.4% of these identified a pathogen [11]. A multidisciplinary study reported that patients' mental status, degree of infection and immune status were related to the quality of sputum collection [12]. Predictors of sputum production failure included weakness, non-compliance, an unproductive cough and an age of > 75 years [13]. The results from the present study complement these findings. The mean age for this study population was 74 years; and frailty, non-compliance and unproductive cough efforts were all reported factors reducing the sample collection. In addition, ED nurses reported that collection of sputum samples was time-consuming, especially when tracheal aspiration was necessary. This occasionally made it impossible to complete the task.

Adjustment of antibiotic treatment based on the microbiological results

A remarkable finding in our study is that even when the microbiological analyses identified pathogens causative for LRTI, none of these patients had their antibiotic treatment revised based on those results. Similarly, other studies have reported a low impact of microbiological results on treatment revision despite recognising the importance of establishing a microbial aetiology for optimising antibiotic therapy [14, 15].

One explanation for the lack of adjustment of antibiotic treatment may be that clinicians assess results from microbiological analysis as irrelevant as a narrow spectrum antibiotic was often chosen as the empirical antibiotic treatment. The majority of patients only needed adjustment from intravenous to oral antibiotics and this decision does not require microbiological support. Another explanation may be that microbiological results rarely show positive results and that about half of the pathogens most likely originate in the upper respiratory tract (*S. aureus*, *P. aeruginosa*, *Candida* species and coliform bacteria).

In a Dutch study, culturing analysis time was reported to be a barrier to adjustment of antibiotic therapy [16]. Correspondingly, in this study, despite every fifth patient having a positive culture, most patients were discharged before cultivation results were available. Therefore, a useful answer was rarely available at the time of antibiotic revision. Aside from organisational barriers to adjustment of antibiotic therapy, the Dutch study revealed that physicians were uncertain about tailoring empirical broad-spectrum to narrow-spectrum antibiotic therapy, and inexperienced clinicians were more likely to accept suggestions from microbiologists concerning the optimal antibiotic for the patient [16].

If sputum specimens are to have any impact on the choice of antibiotic treatment of patients with LRTI in the ED, alternative methods for sputum collection [17] and availability of rapid point-of-care microbiological analysis by multiplex PCR are essential [18]. The availability of these tools may increase awareness of the potential for microbiological diagnostics to achieve optimal antibiotic treatment and facilitate interdisciplinary cooperation between clinicians and microbiologists.

Strength and limitations of the study

A major strength of this study is the written feedback that appears to have a positive impact on clinician adherence to RSDs antibiotic guidelines [19].

A major limitation is the short study period, which increases the risk that adherence to the RSDs antibiotic guidelines may be temporary. In addition, the manual exclusion of patients based on patient history information may have increased the risk of sampling bias.

CONCLUSIONS

The RSDs antibiotic stewardship programme was, in part, successfully implemented into the working routines of doctors in the ED. However, the results of sputum analysis were sparse and, when there, were not taken into account by the clinicians. In this study, we cannot draw conclusions about the benefit of obtaining good quality sputum. Further research is required to investigate whether optimisation of sputum collection and faster microbiological results may support clinical decisions to the benefit of patients admitted with LRTI and in preventing the development of antibiotic resistance.

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