

Guideline adherence for empirical treatment of pneumonia and patient outcome

Treating pneumonia in the Netherlands

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ABSTRACT

Introduction: According to the Dutch guidelines, severity of community acquired pneumonia (CAP) (mild, moderate-severe, severe) should be based on either PSI, CURB65 or a 'pragmatic' classification. In the last mentioned, the type of ward of admission, as decided by the treating physician, is used as classifier: no hospital admission is mild, admission to a general ward is moderate-severe and admission to an intensive care unit (ICU) is severe CAP. Empiric antibiotic recommendations for each severity class are uniform. We investigated, in 23 hospitals, which of the three classification systems empirical treatment of CAP best adhered to, and whether a too narrow spectrum coverage (according to each of the systems) was associated with a poor patient outcome (in-hospital mortality or need for ICU admission).
Patients and methods: Prospective observational study in 23 hospitals.

Results: 271 (26%) of 1047 patients with CAP confirmed by X-ray were categorised in the same severity class with all three classification methods. Proportions of patients receiving guideline-adherent antibiotics were 62.9% (95% CI 60.0-65.8%) for the pragmatic, 43.1% (95% CI 40.1-46.1%) for PSI and 30.5% (95% CI 27.8-33.3%) for CURB65 classification. 'Under-treatment' based on the pragmatic classification was associated with a trend towards poor clinical outcome, but no such trend was apparent for the other two scoring systems.

Conclusions: Concordance between three CAP severity classification systems was low, implying large heterogeneity in antibiotic treatment for CAP patients. Empirical treatment appeared most adherent to the pragmatic classification. Non-adherence to treatment recommendations based on the PSI and CURB65 was not associated with a poor clinical outcome.

KEYWORDS

Antibiotic treatment, antimicrobial treatment, community acquired pneumonia, guideline adherence, patient outcome

INTRODUCTION

Ideally, antibiotic treatment of community acquired pneumonia (CAP) should be directed against the causative pathogen, but history taking, physical examination, clinical symptoms and radiological features are not reliable for predicting aetiology.^{1,3} Moreover, aetiology remains unknown in 25-45% of CAP episodes.⁴⁻⁶ Because of these diagnostic uncertainties it is widely recommended to use the clinical severity of CAP as guidance for empirical therapy; more severe cases should be treated with a broader spectrum of antibiotic coverage. Guideline recommendations for antibiotic treatment, though, must carefully balance between achieving appropriate empirical treatment (especially in severely ill patients) and avoiding inappropriate antibiotic use, as this will augment antibiotic resistance development and adverse events.⁷

The guidelines for the treatment of CAP issued by the Dutch Working Group on Antibiotic Policy distinguish three levels of clinical severity (mild, moderate-severe and severe) with specific recommendations for empirical treatment for each severity class.⁸ For instance, oral therapy with doxycycline (or amoxicillin as alternative) is recommended for patients with mild CAP and one of three options is recommended for patients with severe CAP (table 1). A critical point in using these guidelines is the definition for the different severity classes, especially for severe CAP. The guidelines provide three sets of definitions, without prioritising any: the PSI score;⁹ the CURB65;¹⁰ and a pragmatic score (mild is when the patient is treated as an outpatient, moderate-severe is when hospitalised on non-ICU wards and severe CAP when admitted to the ICU, without criteria to define ICU admission). The classification system used is at the discretion of treating physicians. The aims of this prospective observational study were to

monitor – without treatment dictated by study protocol – current daily clinical practice of empirical antibiotic treatment of patients with CAP in 23 hospitals across the Netherlands, to determine consistency of daily practice with the three systems for severity classification offered by the Dutch guidelines for empirical CAP management and, finally, to determine, for each of the three options, whether non-adherence was associated with clinical outcome.

MATERIALS AND METHODS

Patients

We conducted a prospective, observational, cohort study in 23 Dutch hospitals (four academic hospitals, 15 teaching hospitals and four non-teaching hospitals), between January 2008 and April 2009. Adult patients, 18 years or older, with a clinical suspicion of CAP or lower respiratory tract infection (LRTI) presenting to the emergency department or admitted to one of the participating hospitals were eligible, but only patients with ‘confirmed’ CAP were included in the analysis. A clinical suspicion of CAP or LRTI was defined as the presence of at least two of the following criteria: fever or hypothermia, cough or change in chronic coughing pattern, dyspnoea or tachypnoea or hypoxia, findings with percussion or auscultation consistent with pneumonia, leucocytosis or leukopenia or left shift or an infiltrate on the chest X-ray. Exclusion criteria were recent hospitalisation (<14 days) or residing in a nursing home; known anatomical bronchial obstruction; history of post-obstructive pneumonia, primary lung cancer or another malignancy metastatic to the lungs; AIDS; known or suspected *Pneumocystis jirovecii* pneumonia or tuberculosis; inability to give consent; not being hospitalised. The study was approved by all local Research Ethics Committees and written informed consent was obtained from all participants.

Data collection

All data were collected in standardised case record forms by trained research nurses and/or physicians in every hospital. Antibiotic therapy was not dictated by protocol and choices of empirical antibiotic therapy were made by attending physicians only. Data collected included antibiotic use (last two weeks before admission and empirical treatment), physical examination, biochemical and haematological blood tests, chest X-ray, microbiological test results, ICU admission and/or intubation at any moment during hospital stay and all-cause in-hospital mortality.

Definitions of determinants and outcome

‘Confirmed’ CAP was defined as the presence of an infiltrate on the chest X-ray within 48 hours after admission together with at least two of the following signs

Table 1. Dutch (2005) guidelines for treatment of community acquired pneumonia

Severity of CAP	Treatment Dutch guidelines
Mild	Amoxicillin or doxycycline
Moderate-severe	
• Negative or no Legionella test	β-lactam monotherapy
• Positive Legionella test	Macrolide or quinolone monotherapy
Severe	Moxifloxacin monotherapy OR penicillin & ciprofloxacin OR penicillin & macrolide OR cephalosporin & macrolide

or symptoms: (increased) cough, sputum production, temperature $>38^{\circ}\text{C}$ or $<36.1^{\circ}\text{C}$, auscultatory findings consistent with pneumonia, leucocytosis ($>10.0 \times 10^9$ WBC/l) or leukopenia ($<4.5 \times 10^9$ WBC/l), C reactive protein more than three times the upper limit of normal, hypoxaemia with $\text{pO}_2 < 60$ mmHg while the patient is breathing room air or dyspnoea/ tachypnoea.

For all three severity classification methods (PSI, CURB65 and pragmatic) all subjects were assigned to 'under-treatment', 'compliant treatment' or 'over-treatment' according to the Dutch guidelines.⁸ Treatment compliant to the guidelines is summarised in table 1. In patients categorised as moderate-severe CAP without evidence of *Legionella* infection (negative urinary antigen test or test not performed) β -lactam monotherapy is recommended, which included all penicillins, β -lactam antibiotics with clavulanate, cephalosporins, as well as combinations of two β -lactam antibiotics. Antibiotic therapy was considered to be 'under-treatment' if the regimen covered a narrower spectrum than the Dutch guidelines advised, and therapy was considered to be 'over-treatment' if the spectrum was broader than recommended. ICU admission during hospital stay was determined only for patients who were initially admitted to a general ward.

Data analysis

The SPSS statistical package (version 20.0, SPSS Inc, Chicago, IL, USA) was used for the statistical analysis. Missing data of continuous variables included in the PSI or CURB65 score were imputed by regression methods (age, systolic blood pressure, temperature, pulse frequency, arterial pH, blood urea nitrogen, sodium, glucose, haematocrit and O_2 saturation), for the arterial pH 19.8% of the values had to be imputed and for O_2 saturation 9.1%, all other imputed values had no more than 6.0% missing values. With the imputed data the PSI and CURB65 scores were calculated.

To evaluate associations between guideline compliance and patient outcome, 'under-treatment' was compared with patients with 'over-treatment' or guideline-compliant treatment. Associations between 'in-hospital mortality' and guideline-compliant empirical treatment were evaluated by calculating crude odds ratios (ORs) first, followed by adjusted ORs after including severity of disease (based on PSI score) in a multivariate logistic regression model. PSI was included as a continuous variable in the model to limit the degrees of freedom. Subjects for whom no PSI score was calculated – the subjects in PSI class I – were assumed to have a PSI score of zero. Multivariate analyses were performed for all three classification methods (PSI, CURB65 and pragmatic). The same analyses were repeated for the endpoints ICU admission during hospital stay and the composite endpoint (in-hospital mortality or ICU admission).

RESULTS

Study population

In all, 1758 patients with a clinical suspicion of CAP were included, of whom 557 failed to meet the criteria for CAP (552 had no infiltrate on chest X-ray within 48 hours after admission and five did not meet other criteria) and 69 patients had one or more exclusion criteria. Of the 1132 patients with confirmed CAP, information on antibiotic use was missing from 33 patients and 52 patients were not admitted. So, the study population included 1047 hospitalised patients with confirmed CAP (figure 1). The median age of this population was 70 years (IQR 58-79), 62.8% were male, and 30.2% received antibiotic treatment before admission and 6.6% died during admission.

Empirical antibiotic therapy

Most patients (62.9%) received β -lactam monotherapy as initial treatment and 254 (24.3%) received combination treatment of β -lactams and quinolones (table 2).

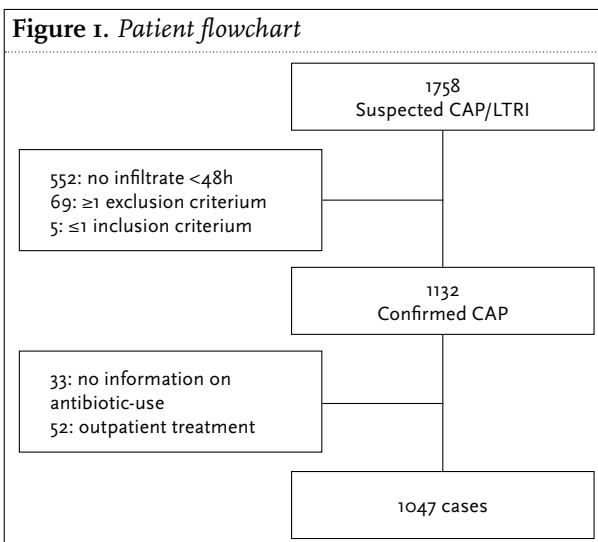


Table 2. Empirical antibiotics in patients with CAP (n=1044)

	β -lactam	Macro- lide	Quino- lone	Tetra- cycline	Other
β -lactam	659 (62.9%)				
Macrolide	27 (2.6%)	14 (1.3%)			
Quinolone	254 (24.3%)	3 (0.3%)	42 (4.0%)		
Tetracycline	1 (0.1%)	-	-	14 (1.3%)	
Other	18 (1.7%)	-	2 (0.2%)	-	10 (1.0%)

Three patients, not included in the table, received a combination of three antibiotics as empirical treatment.

There are marked differences in the numbers of patients assigned to each of the severity classes according to the three classification schemes. For instance, only 33 patients (3%) were considered severe CAP based on the pragmatic classification, as compared with 131 (12.5%) and 226 (21.6%) when using the PSI or CURB65 classification, respectively (table 3). As our analysis was restricted to hospitalised patients, no patients with mild CAP according to the pragmatic classification were included. Only 271 patients (26%) were categorised in the same severity class for all three different classification methods, of which 261 had moderate-severe and ten had severe CAP.

Antibiotic therapy was most compliant to guideline recommendations based on the pragmatic severity classification: 62.9% (95% CI 60.0-65.8%) as compared with 43.1% (95% CI 40.1-46.1%) and 30.5% (95% CI 27.8-33.3%) when based on the PSI and CURB65 classifications, respectively (table 3). 'Under-treatment' occurred most frequently in patients with 'severe' CAP, and was mainly due to β -lactam monotherapy. Proportions of 'under-treatment' were 8.9% (n=92) based on PSI classification, 13.8% (n=144) based on CURB65 classification and 3% (n=31) based on the pragmatic classification. In the PSI and CURB65 classification systems, 90% (n=83) and 93% (n=135) of episodes of 'under-treatment' occurred in patients with severe CAP, as compared with 35% (n=11) of 'under-treatment' episodes in the pragmatic classification system.

Adherence to guidelines and clinical outcome

Data on all-cause in-hospital mortality were available for 1036 subjects, of whom 69 (6.7%) died. Based on the PSI classification the crude OR for in-hospital mortality of 'under-treatment' was 3.70 (95% CI 2.01-6.79), but this

association disappeared when adjusting for the severity of CAP (table 4). A similar result was found for the CURB65 classification. Comparable observations were made for the need for ICU admission and the combined endpoint. When using the pragmatic classification, adjustment for severity of CAP hardly changed ORs. However, no significant association was found.

'Under-treatment' could be misclassified in patients with severe CAP in whom coverage of *Legionella* was omitted because of negative results of the *Legionella* antigen test, known at the time of antibiotic prescription. There were 49, 101 and 18 patients with a negative *Legionella* urine antigen test on the day of admission and with severe CAP according to the PSI, CURB and pragmatic classification, respectively. If all these episodes were counted as 'correct treatment' instead of 'under-treatment' the adjusted OR for the combined endpoint would be 2.68 (95% CI 1.04-6.94) for the pragmatic classification. For the other severity classifications crude and adjusted ORs for outcome remained largely unchanged compared with the ORs (data not shown).

DISCUSSION

This observational study demonstrates that clinical use of three proposed severity classifications for CAP (based on PSI, CURB65 and a pragmatic approach) as currently recommended in the Dutch guidelines results in large heterogeneity in severity classification, with a level of concordance for classifying CAP severity as low as 26%. Adherence to antibiotic recommendations for each of these classifications will lead to markedly different antibiotic usage. The current practice as observed in this multicentre

Table 3. Spectrum of empirical antibiotic treatment according to severity of disease classification systems; compliant treatment is considered adherent to guideline recommendations

Severity of CAP		Antibiotic treatment according to guideline						Total
		Under-treatment	% of class	Compliant treatment	% of class	Over-treatment	% of class	
PSI	Mild	0	0.0	39	13.0	261	87.0	300
	Moderate-severe	9	1.5	389	63.1	218	35.4	616
	Severe	83	63.4	23	17.6	25	19.0	131
	Total	92	8.9	451	43.1	504	48.1	1047
CURB65	Mild	0	0.0	51	10.6	430	89.4	481
	Moderate-severe	9	2.6	230	67.6	101	29.7	340
	Severe	135	59.7	38	16.8	53	23.5	226
	Total	144	13.8	319	30.5	584	55.7	1047
Pragmatic	Mild	-	-	-	-	-	-	-
	Moderate-severe	20	2.0	648	63.9	346	34.1	1014
	Severe	11	33.3	11	33.3	11	33.3	33
	Total	31	3.0	659	62.9	357	34.1	1047

Table 4. Associations between ‘under-treatment’ and patient outcome according to severity classification

Clinical outcome		PSI	CURB65	Pragmatic
Hospital mortality (n=1036, 69 died)				
	N with under-treatment	89	143	31
	Crude OR	3.70 (2.01-6.79)	2.58 (1.47-4.53)	2.14 (0.73-6.31)
	Adjusted* OR	0.77 (0.37-1.61)	1.06 (0.57-1.98)	1.90 (0.59-6.06)
ICU admission (n=1013, 67 ICU)				
	N with under-treatment	88	140	21
	Crude OR	2.50 (1.28-4.87)	1.72 (0.93-3.19)	2.42 (0.69-8.42)
	Adjusted* OR	1.06 (0.49-2.29)	1.02 (0.52-1.97)	2.71 (0.76-9.72)
Combined endpoint (n=1035, 112 endpoints)				
	N with under-treatment	89	143	31
	Crude OR	3.60 (2.15-6.04)	2.21 (1.38-3.55)	2.50 (1.05-5.94)
	Adjusted* OR	1.09 (0.59-2.02)	1.07 (0.64-1.81)	2.38 (0.94-6.03)

OR = odds ratio. *Adjusted for severity of disease, based on PSI score.

study was most adherent to recommendations based on the pragmatic score (62.9% concordance) and least adherent to recommendations based on CURB65 (30.5%). Under-treatment based on the pragmatic classification was associated with a trend to increased risks of either ICU admission or in-hospital mortality (adjusted OR 2.38 (95% CI 0.94-6.03)).

The Dutch guidelines for CAP differ from other guidelines. The Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) guidelines use a pragmatic classification (outpatient, non-ICU inpatient and ICU inpatient) with separate recommendations for outpatients with comorbidities.¹¹ The British Thoracic Society (BTS) guidelines use the CURB65 score in combination with clinical judgement.¹² The Dutch guidelines are a mixture of the IDSA/ATS and BTS guidelines, as any of three classification systems (PSI, CURB65 or pragmatic classification) is recommended, without advising one in particular. Obviously, the three methods for severity classification are not unambiguous. Furthermore, Dutch guidelines still recommend β -lactam monotherapy for patients with moderate-severe CAP, where most other guidelines advise combination therapy in these patients. The clinical effects of these different guideline recommendations have never been prospectively determined.

The existence of three possible classification systems seriously complicates the analysis of guideline adherence and quantification of the clinical effects of using either of these systems if their use is not randomised. In the current study only 271 of 1047 patients (26%) were categorised in the same severity class with all three classification methods. The rationale of using severity of disease classification for choosing empirical treatment is that ‘under-treatment’ reduces clinical outcome, and that ‘over-treatment’ induces unnecessary antibiotic use. In the current

study no such association could be demonstrated between ‘under-treatment’ based on the PSI and CURB65 classification and poor clinical outcome. Yet, for ‘under-treatment’ based on the pragmatic system a strong trend towards poor clinical outcome was apparent. Achieving better adherence to the PSI and CURB65-based algorithms would, therefore, increase the use of broad-spectrum antibiotics, although ‘under-treatment’ had no determinable detrimental effects on patient outcome. Associations between guideline adherence and patient outcome have been studied before, but not in Dutch patient cohorts.¹³⁻²⁴ The results of these studies are inconsistent, which might result from differences in study design and data analysis: in some studies guideline-compliant therapy was compared with non-compliant therapy (defined as either over- or under-treatment), some evaluated compliance to guidelines not available at the time of patient inclusion or to guidelines from another country, and some only performed univariate analyses of associations.^{15,16,22,24} Our findings illustrate the importance of adjustment for disease severity in such analyses.

Naturally, there are limitations to this non-experimental study. During the study period the 2005 Dutch guidelines were used, which were revised recently.²⁵ The major change in the new guidelines is the preference of amoxicillin above doxycycline for patients with mild CAP, which was the other way around before. Applying this change to the current data would not influence the results. Secondly the pragmatic classification might be influenced by subjective assessment, as clinical decisions to admit patients to the ICU may differ per hospital, may depend on availability of ICU beds and may be guided by restrictions in treatment ambitions, and this also applies to ICU admission after treatment failure. This information was not available and could not, therefore, be included in our analysis. Due to logistical reasons, not all

consecutive patients were included. If treatment decisions were influenced by the timing of admission, this could have influenced our findings, but we are not aware of this happening. Furthermore, there were some missing data for which imputation was used, and there were no data on 30-day mortality or causes of death, and, therefore, all-cause in-hospital mortality was used. Obviously, this may lead to misclassification if patients die shortly after hospital discharge. Finally, there were no data collected about reasons to deviate from the guidelines, such as pregnancy, allergies or previous culture results.

The strengths of our study include the large number of patients included, allowing a robust model to determine associations between 'under-treatment' and patient outcome, its multicentre design, which increases the generalisability, its prospective nature, maximising reliable and complete data collection, and, its relatively short study period, excluding changes in guideline recommendations and clinical practice. Our findings demonstrate that currently decisions for empiric antibiotic prescription coincide best with a pragmatic risk assessment. This leads to high proportions of patients who are receiving 'under-treatment' according to the more objective risk classifications based on PSI and CURB65. Yet, this 'under-treatment' according to PSI and CURB65 was not associated with a poor clinical outcome. Only 3% of all patients received 'under-treatment' according to the pragmatic risk assessment, and there was a strong tendency that this was associated with poor outcome. This provides a clear target to improve the outcome of patients hospitalised with CAP, by improving antibiotic prescription in a small proportion of patients.

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