Lower respiratory tract infections in the elderly: Prognostic studies in primary care

Jettie Bont

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Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht.
Thesis, with summary in Dutch
Proefschrift, met samenvatting in het Nederlands

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Lower respiratory tract infections in the elderly: Prognostic studies in primary care

Lage luchtweginfecties bij ouderen:
Prognostische studies in de eerste lijn

(met een samenvatting in het Nederlands)

PROEFSCHRIFT

Ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. J.C. Stoof, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op

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door

Jettie Bont

geboren op 28 februari 1973 te Amsterdam

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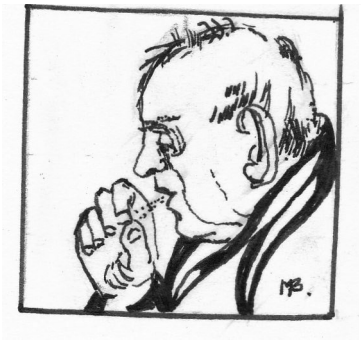
Chapter 1

General introduction

PROGNOSIS OF LOWER RESPIRATORY TRACT INFECTIONS IN ELDERLY



A 78-year-old man visits the general practitioner (GP) because of severe cough. He has a history of high blood pressure and five years ago he suffered from a heart attack. Now he has been feeling sick for the past three days. He produces green sputum and experiences shortness of breath. The GP examines the patient. His temperature is 37.4°C, his pulse 90 beats per minute, and his respiratory rate 22 breaths per minute. Auscultation of the lungs reveals some diffuse wheezes and rhonchi. The GP diagnoses acute bronchitis and considers to prescribe antibiotics. What is the patient's prognosis?

The clinical problem

Lower respiratory tract infections (LRTI), such as acute bronchitis, exacerbations of chronic obstructive pulmonary disease (ECOPD) and pneumonia, are among the most common diseases presented in primary care. Elderly patients with LRTI are of particular importance for several reasons. First, the incidence of LRTI in elderly is three times higher compared to the general population.[1] Second, due to changing demographics the number of elderly will increase dramatically during the next decade, and third, elderly are more prone to develop complications. Obviously, it is important to recognise those patients likely to develop complications, since this will influence patient management. Low risk patients will usually be treated at home as a wait-and-see policy is likely to be safe. For example physicians will be more confident to refrain from prescribing antibiotics to otherwise healthy patients with acute bronchitis. In contrast, high risk patients will require more intensive monitoring and treatment, either at home or in hospital and future preventive measurements, such as new vaccinations, may be of interest. If prognostication is imprecise it may lead to unwanted scenarios. For instance, if too many elderly are considered high risk, antibiotic use will increase and more patients will be referred to hospital, leading to increased antibiotic resistance, unnecessary side-effects and increased costs. Moreover, if patients are wrongly considered to be at low risk and intensive treatment is withheld, patients may suffer unnecessary complications. Management tools, for example prediction rules, may be instrumental to improve prognostication in daily practice.

Antibiotics and lower respiratory tract infections

Acute bronchitis is thought to reflect an inflammatory response to infections of the bronchi. Viruses are usually considered the main cause of acute bronchitis. Still, bacteria, commonly implicated in community acquired pneumonia, have been isolated as well and are more often found in elderly with acute bronchitis. Importantly, discrimination between viral and bacterial aetiology is difficult, if not impossible, with routine diagnostic tests such as history and physical examination. Nevertheless, the natural course is self-limiting and it is unlikely that all bacterial infections need to be treated.[2] In spite of this, the majority of patients is treated with antibiotics (estimates vary around 80%)[3-5] and although antibiotic prescription rates are relatively low in The Netherlands, acute bronchitis is treated with antibiotics as

often as in other countries. Guidelines are one way to tackle this problem. The Dutch guideline on acute cough recommends antibiotics only in patients with suspected pneumonia, in infants and elderly (>75 years old) with fever or in patients with relevant comorbid disease, such as heart failure, COPD and some neurological disorders.[6] However, with a prescription rate of 80% it is questionable whether physicians adhere to these guidelines.[3] As mentioned above, current guidelines advise to take co-morbidity into account in the decision to prescribe antibiotics. Studies assessing whether this is indeed the case in every day practice, are however, scarce. We performed such a study in the primary care setting and the results are presented in Chapter 2.1.

First research question
Is co-morbidity taken into account in the antibiotic management of elderly patients with acute bronchitis and COPD exacerbations?

In case of acute bronchitis most guidelines are clear and recommend withholding antibiotics in *uncomplicated* acute bronchitis. Since prescription rates are high it might be possible that physicians considered most of their elderly patients as having complicated bronchitis. This hypothesis led to our next research question and a study addressing this issue is reported in Chapter 2.2:

Second research question
What are determinants of antibiotic prescribing in elderly patients with acute bronchitis?

Although the first two research questions are important to understand current antibiotic prescription habits in primary care and find ways for improvement, it might be even more important to study clinical determinants that *should* be considered when deciding on the different management options; i.e. to identify patient characteristic that influence prognosis. This directed us to the next part of the manuscript.

Prognostic studies
How can one identify patients with a poor prognosis in clinical practice? Several studies have focussed on this issue, mostly pertaining to adult patients presented in hospital with pneumonia.[7-17] Different risk factors were identified for 30-day mortality. (table 1) Some of the predictors could be useful for primary care and others are of limited value due to lack of easy access or the complexity of the tests, e.g. radiological or laboratory tests. Even though some predictors could be useful, we do not know whether they will predict poor prognosis in a primary care population including only elderly with LRTI instead of adults with pneumonia presented in hospital.
The guidelines of the British Thoracic Society on community acquired pneumonia included a decision model based on the study by Lim et.al.[14;18;19] The model uses only four criteria:

Confusion, high Urea, high Respiratory rate, low Blood pressure and age ≥65 years (CURB65) and predicts 30-day mortality in patients with pneumonia. They recommend this model, without the urea level, for the primary care setting. (figure 1)

Figure 1. Severity assessment by the CRB-65-score used to determine the management of CAP in patients in the community (Lim et al, 2003).[14]

Characteristic	Score assigned
New mental confusion	1
Respiratory rate 30/min or more	1
BP <90 mmHg systolic or £60 mmHg diastolic	1
Age ≥65 years	1

	Risk class I	Risk class II	Risk class III
Sum of scores	0	1 or 2	3 or 4
Risk of 30-day mortality	Low (1.2%)	Intermediate (8.2%)	High (31.3%)
Treatment options	Likely suitable for home treatment	Likely need hospital referral and assessment	Urgent hospital admission

The CRB65 decision model seems easy applicable. It should be validated in an elderly primary care population, before its use can be recommended. This was done in a study reported in Chapter 3.1.

Third research question

Is the CRB65-rule applicable in a primary care population including elderly patients with pneumonia?

Still, the CRB65-rule does not provide us with support when dealing with elderly with different manifestations of LRTI, such as acute bronchitis, ECOPD or pneumonia. This is important, as it is often not possible to differentiate between these, partly because pulmonary radiography is not often used in daily practice. In addition, the CURB65-rule predicts mortality only and this outcome is rare in primary care and less severe outcomes are important too. This dilemma has led to our next research question.

Table 1. Overview of prognostic factors for 30-day mortality in patients with community acquired pneumonia and/ or acute bronchitis

First author of study	Conte[7]	Farr[8]	Fine[10]	García[11]	Houston[12]	Lim[14]	Lim[13]	Mortensen[15]	Riquelme[16]	Seppä[17]
Number of patients included	2,356	245	14,199	343	413	1,068	158	2287	101	950
Mortality in pneumonia	9%	8.2%	10.2%	14.3%	13.2%	9%	*	9%	26%	4.1%
Risk factors										
Demographics										
Increasing age	+		+			+		+		
Male gender			+							
Nursing home residents			+							
History										
Immunocompromised patients								+		
Acute aggravation of coexisting illness										+
Cerebrovascular disease			+							
Congestive heart failure			+							
Dementia								+		
Evidence of aspiration								+	+	
Liver disease			+					+		
Neoplastic disease			+		+			+		
Neurologic disease					+					
Presence of a comorbid condition	+									
Recent use of antibiotics					+					
Renal disease			+							

First author of the study	Conte[7]	Farr[8]	Fine[10]	García[11]	Houston[12]	Lim[14]	Lim[13]	Mortensen[15]	Riquelme[16]	Seppä[17]
Signs and symptoms										
Abnormal vital signs	+	+	+	+		+	+	+	+	+
Altered mental status or confusion			+	+		+	+	+		
Atypical symptoms (poor eating, confusion, lethargy)					+					
Impared motor response	+									
Low temperature or no fever				+			+	+	+	
Temperature <35 or ≥40			+							
Additional tests										
Laboratory or radiographic abnormality	+	+	+	+		+	+	+	+	+

*Case-control study

Fourth research question
What patient characteristics are independently associated with a poor prognosis in elderly patients presented with LRTI in primary care and can they be used to develop a prediction rule?

This question is addressed in Chapter 3.2 en 3.3.

Prognostication in lower respiratory tract infections: prediction rule or physician?
Before a prediction rule can be recommended for use in clinical practice its accuracy should be established in the relevant clinical domain. In fact, some of the available prediction rules in patients with LRTIs have been validated several times. Application of such a rule, however, will undoubtedly be enhanced further, if its prognostic value *compared with* the GP's estimation of the patient's prognosis has been shown to bee higher. Formal comparisons of prognostic rules and the prognosis anticipated by the treating primary care physician are, however, virtually lacking. We performed such a study and its results are presented in Chapter 4.

Fifth research question
What is the value of a rule predicting prognosis in elderly patients with LRTI in primary care patients *compared* to the prognosis as estimated by the GP ?

In the general discussion the clinical consequences of the findings presented in this thesis are discussed and directions for future research are given (Chapter 5). The final chapters of this thesis include an English (Chapter 6.1) and Dutch summary (Chapter 6.2).

Reference List

1. Hak E, Rovers MM, Kuyvenhoven MM, Schellevis FG, Verheij TJ. Incidence of GP-diagnosed respiratory tract infections according to age, gender and high-risk co-morbidity: the Second Dutch National Survey of General Practice. *Fam.Pract.* 2006;23:291-4.
2. Smucny J, Fahey T, Becker L, Glazier R. Antibiotics for acute bronchitis. *Cochrane.Database.Syst.Rev.* 2004;CD000245.
3. Akkerman AE, Kuyvenhoven MM, van der Wouden JC, Verheij TJ. Determinants of antibiotic overprescribing in respiratory tract infections in general practice. *J.Antimicrob.Chemother.* 2005;56:930-6.
4. Bont J, Hak E, Birkhoff CE, Hoes AW, Verheij TJ. Is co-morbidity taken into account in the antibiotic management of elderly patients with acute bronchitis and COPD exacerbations? *Fam.Pract.* 2007;..
5. Fischer T, Fischer S, Kochen MM, Hummers-Pradier E. Influence of patient symptoms and physical findings on general practitioners' treatment of respiratory tract infections: a direct observation study. *BMC.Fam.Pract.* 2005;6:6.
6. Verheij TJ, Salomé Ph.L., Bindels P.J., Chavannes A.W., Ponsioen B.P., Sachs APE *et al.* NHG Standaard: Acuut hoesten. *Huisarts en Wetenschap* 2003;46:496-506.
7. Conte HA, Chen YT, Mehal W, Scinto JD, Quagliarello VJ. A prognostic rule for elderly patients admitted with community-acquired pneumonia. *Am.J.Med.* 1999;106:20-8.
8. Farr BM, Sloman AJ, Fisch MJ. Predicting death in patients hospitalized for community-acquired pneumonia. *Ann.Intern.Med.* 1991;115:428-36.
9. Fine MJ, Orloff JJ, Arisumi D, Fang GD, Arena VC, Hanusa BH *et al.* Prognosis of patients hospitalized with community-acquired pneumonia. *Am.J.Med.* 1990;88:1N-8N.
10. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE *et al.* A prediction rule to identify low-risk patients with community-acquired pneumonia. *N.Engl.J.Med.* 1997;336:243-50.
11. Garcia-Ordonez MA, Garcia-Jimenez JM, Paez F, Alvarez F, Poyato B, Franquelo M *et al.* Clinical aspects and prognostic factors in elderly patients hospitalised for community-acquired pneumonia. *Eur.J.Clin.Microbiol.Infect.Dis.* 2001;20:14-9.
12. Houston MS, Silverstein MD, Suman VJ. Risk factors for 30-day mortality in elderly patients with lower respiratory tract infection. Community-based study. *Arch.Intern.Med.* 1997;157:2190-5.
13. Lim WS,.Macfarlane JT. Defining prognostic factors in the elderly with community acquired pneumonia: a case controlled study of patients aged > or = 75 yrs. *Eur.Respir.J.* 2001;17:200-5.
14. Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI *et al.* Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax* 2003;58:377-82.
15. Mortensen EM, Coley CM, Singer DE, Marrie TJ, Obrosky DS, Kapoor WN *et al.* Causes of death for patients with community-acquired pneumonia: results from the Pneumonia Patient Outcomes Research Team cohort study. *Arch.Intern.Med.* 2002;162:1059-64.
16. Riquelme R, Torres A, El Ebiary M, de la Bellacasa JP, Estruch R, Mensa J *et al.* Community-acquired pneumonia in the elderly: A multivariate analysis of risk and prognostic factors. *Am.J.Respir.Crit Care Med.* 1996;154:1450-5.
17. Seppa Y, Bloigu A, Honkanen PO, Miettinen L, Syrjala H. Severity assessment of lower respiratory tract infection in elderly patients in primary care. *Arch.Intern.Med.* 2001;161:2709-13.
18. BTS Guidelines for the Management of Community Acquired Pneumonia in Adults. *Thorax.* 2001;56 Suppl 4:IV1-64.:IV1-64.
19. Macfarlane JT,.Boldy D. 2004 update of BTS pneumonia guidelines: what's new? *Thorax.* 2004;59:364-6.

Chapter 2.1

Is co-morbidity taken into account in the antibiotic management of elderly patients with acute bronchitis and COPD exacerbations?

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ABSTRACT

Background. Guidelines on acute lower respiratory tract infections recommend restrictive use of antibiotics, however in patients with relevant comorbid conditions treatment with antibiotics should be considered. Presently, it is unknown whether GPs adhere to these guidelines and target antibiotic treatment more often at patients with risk-elevating conditions.

Objectives. We assessed whether in elderly primary care patients with acute bronchitis or exacerbations of chronic pulmonary disease (COPD), antibiotics are more often prescribed to patients with risk elevating comorbid conditions.

Methods. Using the Utrecht general practitioner (GP) research database we analyzed 2,643 episodes in patients of 65 years of age or older with a GP diagnosed acute bronchitis or exacerbation of COPD. Multivariable logistic regression analysis was applied to determine independent determinants of antibiotic use.

Results. Antibiotic prescribing rates were high in both acute bronchitis (84%) and in exacerbations of COPD (53%). In acute bronchitis, only age was an independent determinant of antibiotic use (OR 1.03, 95% CI 1.003-1.048) whereas in exacerbations of COPD antibiotics were more often prescribed to male patients (OR 1.3 95% CI 1.0-1.5), patients with diabetes (OR 1.7, 95% CI 1.1-2.4) and heart failure (OR 1.3, 95% CI 1.0-1.7).

Conclusion. Dutch GPs prescribe antibiotics in the majority of elderly patients with acute bronchitis and in half of the episodes of exacerbations of COPD. Tailoring their antibiotic treatment according to the presence or absence of high-risk co-morbid conditions could help GPs in improving antibiotic use in patients with respiratory tract infections in primary care.

INTRODUCTION

Acute lower respiratory tract infections (LRTIs) are a major cause of morbidity and mortality, and one of the most frequent reasons to seek primary medical care[1;2]. Indications for antimicrobial treatment in patients with LRTI are still debated. Only in patients with a pneumonia diagnosis, studies demonstrated that antibiotics favorably influence prognosis.[3] The effectiveness of antibiotic treatment in acute bronchitis or exacerbations of chronic pulmonary disease (COPD), however, remains controversial.[4-10] In the absence of a sound evidence base, American[11] European[12] and national guidelines[13] on LRTI recommend antibiotics for patients with suspected pneumonia and in patients with acute bronchitis with certain chronic conditions and thus to withhold antibiotics from relatively healthy patients.
Presently, it is unknown whether GPs adhere to these guidelines and target antibiotic treatment more often at patients with risk-elevating conditions. The Utrecht Medical Center GP research database enabled us to address this issue.

METHODS

Design and setting

In this retrospective cohort study we included data from community-dwelling elderly patients with episodes of LRTI, diagnosed in Dutch primary care. The general practices involved were part of the Utrecht GP Research Network. Currently, 35 GPs from this network serve approximately 58,000 noninstitutionalised persons. Participating GPs keep a uniform, structured registration of medical data, using computerized medical records (ELIAS®, Isoft, Nieuwegein). The network has been described in detail elsewhere.[14] Diagnosis and drug prescriptions are registered using the International Classification of Primary Care (ICPC)[15] and Anatomical Therapeutically Classification (ATC) codes,[16] respectively. All data are stored in a computerized central database.

Study population

From January 1997 until October 2003 all patients aged 65 years and older, with a GP-diagnosed acute bronchitis or exacerbations of COPD were included. A diagnosis of acute bronchitis was made when patients met the ICPC-criteria for acute bronchitis (R78), consisting of coughing and fever with diffuse abnormalities on pulmonary examination like wheezing and crepitations.[17] Since fever is often absent in elderly, we allowed for this criterion to be ignored. When an episode of acute bronchitis was diagnosed and the patient had a history of COPD the episode was recoded into an exacerbation of COPD. Since ICPC coding is absent for exacerbations of COPD, we accepted the diagnosis of the GP. We defined exacerbations of COPD according to the Anthonisen criteria in the absence of a GP diagnosis.[4] Criteria were met if two out of three symptoms (increased dyspnoea, sputum volume and sputum purulence) were present in patients with known COPD. When only one of these symptoms occurred, at least one other finding (signs of upper respiratory tract infection such as sore throat and nasal discharge within the past five days, fever without other cause, increased wheezing, increased cough or increase in either respiratory rate or heart rate) had to be present. During the study period, patients could provide more than one episode of LRTI. Patients in secondary or tertiary care at the time of diagnosis, with a

diagnosis of lung cancer, HIV or hematological malignancies, or those who used immunosuppressive medication other than oral glucocorticoids were not included.

Selection of risk factors for a complicated course

For the selection of possible determinants from medical history we included relevant items, such as age, a history of heart failure, severe COPD or neurological disorders, mentioned in the Dutch guideline on acute cough[13] as well as potential risk-elevating co morbid conditions from available prognostic studies not mentioned in the guideline.[18-23] Co-morbidity was defined as the presence of a co-morbid condition in the patient's history recorded according to the International Classification of Primary Care coding system (ICPC). The following relevant variables were included: increasing age, male gender, presence of COPD or, emphysema (R91, R95) or asthma R96), diabetes mellitus (T90), presence of a malignancy, congestive heart failure (K77, K82), cardiovascular diseases (defined as angina pectoris (K74) or myocardial infarction (K75, K76)), stroke (K90), dementia (P70), renal disease (U99) and current use of antibiotics. Severe COPD was indicated by the presence of maintenance therapy with oral glucocorticoids, since severe COPD is not always accurately recorded in medical files. Similarly, the presence of diabetes was indicated by the use of oral diabetic medication or insulin.

Data collection and data analysis

All variables, except for age, were classified as dichotomous variables. Descriptive statistics as proportions, means and odd ratios were calculated using SPSS for Windows (version 12.0.1) in order to define our study population in terms of baseline characteristics.

To assess the associations between antibiotic use and risk-related variables, we excluded all episodes in which the patient was immediately admitted to hospital (n=63), as treatment is often postponed until arrival in hospital. We applied univariable logistic regression to obtain estimates of associations between prescriptions of antibiotics and the presence of potential risk factors for complications given by odds ratios and their corresponding 95% confidence intervals (95% CI). Variables with a p-level of 0.15 or lower were further examined in the multivariable logistic regression analysis, and a p-level of 0.05 was considered to indicate statistical significance. The analysis was repeated including only first episodes for each person to controle for within-person depency.

RESULTS

From January 1997 until October 2003, 2,643 episodes of LRTI were recorded in 1,693 patients, with an average of 1.9 episodes per patient. We recorded 1,120 episodes of acute bronchitis and 1,523 exacerbations of COPD in 1,362 patients. 542 patients were included more than once. 456 exacerbations of COPD were primarily diagnosed as acute bronchitis and were recoded into exacerbations of COPD due to the presence of COPD in the medical history. The populations' mean age was 75 years (standard deviation [SD] 7 years). Co-morbid conditions were common in this population (86%), mostly COPD, emphysema or asthma (47% of episodes) and heart failure was present in 21% and angina pectoris in 17%.

In all, 175 (6.6%) patients were hospitalized or died within 30 days after the diagnosis was made (Table 1).

Table 1. Characteristics of acute bronchitis and exacerbations of chronic obstructive pulmonary disease (COPD)

Characteristic[a]	Acute bronchitis N= 1,120 N(%)[b]	Exacerbations of COPD N=1,523 N (%)[b]	Total N=2,643 N (%)[b]
Demographics			
Mean age (SD and range)	76	75	75
	(7.5 and 65-101)	(6.6 and 65-98)	(7,0 and 65-101)
Male	418 (37)	776 (51)	1194 (45)
Medication use at time of diagnosis			
Oral steroids[c]	13 (1.2)	125 (8.2)	138 (5.2)
Antibiotics[d]	62 (5.5)	98 (6.4)	160 (6.1)
Co-morbidity			
Diabetes type 1 or 2	112 (10)	139 (9.1)	251 (9.5)
Malignancies[e]	158 (14)	203 (13)	361 (14)
Heart failure	137 (12)	425 (28)	562 (21)
Cardiovascular disease	248 (22)	371 (24)	619 (23)
Stroke	68 (6.1)	94 (6.2)	162 (6.1)
Dementia	18 (1.6)	27 (1.8)	45 (1.7)
Renal disease	26 (2.3)	42 (2.8)	68 (2.6)
Course of illness			
30-day hospitalization	33 (2.9)	123 (8.1)	156 (5.9)
30-day death	13 (1.2)	20 (1.3)	33 (1.2)

Legend table 1

[a]See method section for corresponding explanation of the different characteristics.

[b]Patients can have more than one coexisting condition.

[c]Medication had to be used for at least 7 days at the time the diagnosis was made.

[d]The last tablet of a course had to be taken in the preceding month.

[e]Lung cancer and hematological malignancies were not registered, since patients with these malignancies were excluded.

The majority of episodes of LRTI were handled in primary care and 2.4% of cases were referred to hospital within 2 days after first presentation at the GP practice (Table 2). Admission rates were lower for episodes of acute bronchitis (0.4%) than in patients with exacerbations of COPD (4%). In episodes of patients not directly admitted to hospital, GPs prescribed medication in the majority of cases. Acute bronchitis was treated with antibiotics in 84% of cases. Exacerbations of COPD were treated primarily with lung medication (75% of cases), while antibiotics were given in 53% of episodes.

Table 2. General Practitioners medical treatment of acute bronchitis and exacerbations of chronic pulmonary disease (COPD)

Diagnosis made by GP	Acute bronchitis N=1,120 N (%)	Exacerbations of COPD N=1,523 N (%)	In all N=2,643 N(%)
Intervention[a]			
Admission to hospital < 48 hours after diagnosis	5 (0.4)	58 (3.8)	63 (2.4)
Treatment within Primary Care[**]	1115 (100)	1465 (96)	2580 (98)
•No Medication	27 (2)	36 (3)	63 (2.4)
•Antibiotics[b]	931 (84)	777 (53)	1708 (66)
•Lung medication[bc]	377 (34)	1092 (75)	1469 (57)
•Other medication[c]	113 (10)	143 (10)	256 (10)

Legend table 2

[a]Numbers do not sum up as patients could have been prescribed more than one type of medication

[b]Lung medication included bronchodilators, inhalation corticosteroids and oral steroids.

[c]Other medication included for example mucus solvents.

Table 3. Comparison between acute bronchitis treated without - and with antibiotics (N=1,115)

Characteristic	No antibiotics prescribed 184 (17%)	Antibiotics prescribed 931 (84%)	Univariate OR (95% CI)	Multivariate OR (95% CI)	p-value
Mean age (SD)	74.4 (7.0)	75.7 (7.6)	1.03 (1.003-1.05)	1.03 (1.003-1.05)	0.03
Male gender	63 (34)	352 (38)	1.2 (0.8-1.6)	-	NS
Previous use of antibiotics[a]	14 (7.6)	46 (4.9)	0.6 (0.3-1.2)	-	NS
Diabetes Mellitus type 1 or 2	19 (10)	91 (10)	0.9 (0.6-1.6)	-	NS
Malignancy[b]	23 (13)	134 (14)	1.2 (0.7-1.9)	-	NS
Heart failure	21 (11)	116 (13)	1.1 (0.7-1.8)	-	NS
Cardiovascular disease	43 (23)	203 (22)	0.9 (0.6-1.3)	-	NS
Stroke	11 (6.0)	57 (6.1)	1.0 (0.5-2.0)	-	NS
Dementia	1 (0.5)	17 (1.8)	3.4 (0.5-25.7)	-	NS
Kidney disease	3 (1.6)	22 (2.4)	1.5 (0.4-4.9)	-	NS

NS = Not significant (p>0,05)

[a]Last tablet of a course had to be taken in the preceding month.

[b]Lung cancer and hematological malignancies were not registered, since patients with these malignancies were excluded.

In patients with an acute bronchitis we found a weak but significant association between antibiotic prescription and age only (OR 1.03, 95% CI 1.003-1.048) (Table 3).

In patients with exacerbations of COPD antibiotics were more readily prescribed to male patients (OR 1.3 95% CI 1.0-1.5). Furthermore GPs prescribed antibiotics more often in patients with exacerbations of COPD when also diabetes was present (OR 1.7, 95% CI 1.1-2.4) and when there was a history of heart failure (OR 1.3, 95% CI 1.0-1.7). No significant association was observed with other co-morbid conditions (Table 4). These co morbid conditions were independent determinants for antibiotic prescriptions, except for a history of a myocardial infarction. Controlling for within-person depency by re-analysing our data taking only the first episodes into account gave similar estimations of associations between determinants and outcome.

Table 4: Comparison between exacerbations of chronic pulmonary disease treated without - and with antibiotics (N=1,465)

Characteristic	No antibiotics prescribed 688 (47%)	Antibiotics prescribed 777 (53%)	Univariate OR (95% CI)	Multivariate OR (95% CI)	p-value
Mean Age (SD)	74.7 (6.5)	74.9 (6.8)	1.0 (1.0-1.0)	-	NS
Male gender	329 (48)	414 (53)	1.2 (1.0-1.5)	1.3 (1.0-1.5)	0.03
Use of oral glucocorticoids[a]	47 (6.8)	56 (7.2)	1.1 (0.7-1.6)	-	NS
Previous use of antibiotics[b]	45 (6.5)	45 (5.8)	0.9 (0.6-1.3)	-	NS
Diabetes Mellitus type 1 or 2	45 (6.5)	83 (11)	1.7 (1.2-2.5)	1.7 (1.1-2.4)	0.01
Malignancy[c]	88 (13)	110 (14)	1.1 (0.8-1.5)	-	NS
Heart failure	166 (24)	235 (30)	1.4 (1.1-1.7)	1.3 (1.0-1.7)	0.02
Cardiovascular disease	149 (22)	202 (26)	1.3 (1.0-1.6)	-	NS
Stroke	41 (6.0)	49 (6.3)	1.1 (0.7-1.6)	-	NS
Dementia	11 (1.6)	16 (2.1)	1.3 (0.6-2.8)	-	NS
Kidney disease	14 (2.0)	25 (3.2)	1.6 (0.8-3.1)	-	NS

NS = Not significant (p>0,05);

[a] Medication had to be used for at least 7 days at the time the diagnosis was made.

[b] Last tablet of a course had to be taken in the preceding month.

[c] Lung cancer and hematological malignancies were not registered, since patients with these malignancies were excluded.

DISCUSSION

Key findings

This study showed that GPs prescribe antibiotics in the majority of cases of acute bronchitis and exacerbations of COPD. In case of acute bronchitis, we found no association between co-morbid conditions and antibiotic use whereas in exacerbations of COPD antibiotics were more often prescribed to patients with diabetes mellitus and heart failure.

Limitations

Some limitations of our study should be mentioned. We missed valid information on history taking and physical examination, as well as information on smoking behavior. Clinical information could give more insight in prescribing behavior of GPs. For instance, previous studies have shown an association between clinical parameters, e.g. fever, with antibiotic use.[24;25] On the other hand, other studies have shown no relation between antibiotics and clinical parameters.[7;26] Apart from signs and symptoms we however think that co-morbid conditions should be taken into account when deciding on antibiotic treatment, because we saw in a recent study that co-morbidity predicts poor outcome.[27] Prospective studies should however be done to elucidate the effects of antibiotics in patients with different clinical syndromes and different chronic conditions and further improve and specify current guidelines on antibiotic therapy.

Also, the database did not allow us to collect information on the severity of comorbid conditions, possibly leading to an underestimation of associations. For example, patients with severe heart failure or renal disease may have received antibiotics more often whereas we could not demonstrate this. In spite of the retrospective design this study ensured that participating GPs made their decisions concerning treatment and referral independently and shows the presence or absence of relations of prescription of antibiotics with easy obtainable information on co-morbid conditions of the patients. Consequently, the results of this study describe the customary course of events of LRTI in primary care. We have described setting and patients as detailed as possible and international criteria were used to categorise diagnoses and medical treatment. Therefore we think that our results are also of importance for similar primary settings in other countries.

External comparison

The prescription rate of antibiotics in episodes of acute bronchitis found in this study is high. Nevertheless it is largely in accordance with many other studies.[24;26;28] Some studies show somewhat lower prescription rates in acute bronchitis.[7;9;29] We assume that the high prescription rate is caused by the high age of our study population. Secondly, it is often difficult to differentiate between acute bronchitis and pneumonia in the absence of a pulmonary x-ray and therefore antibiotics are often prescribed.

In exacerbations of COPD our prescription rates were higher compared to other studies.[29-31] The main reason for these discrepancies might be again the inclusion of older patients in our study. Only one study had higher rates of antibiotic prescriptions probably because of the hospital setting.[32]

Importantly, our data show that the indications that GPs use in daily practice do not concur with indications mentioned in evidence-based guidelines as far as it concerns the presence

of co morbid conditions. So far, we are aware of only few studies focusing specifically on the association between prescribing antibiotics and the presence of potential risk factors in case of acute bronchitis or exacerbations of COPD.[7;9;24;26;28;33] In contrast to our study, two of these studies did not find high age being a predictive characteristic for prescribing antibiotics. Also gender has not been related to antibiotic management in previous studies and these studies included few elderly.[28;33]

In general, antibiotics are less often prescribed in Dutch primary care compared to other countries.[34] This is most likely explained by strong recommendations in Dutch guidelines to withhold from antibiotics unless the effect is proven. Nevertheless, our study and a previous study from Akkerman et al.[24] show higher antibiotic prescription rates than expected according to guidelines. According to literature and these guidelines we expected that prescriptions rates were higher in patients with risk-related co-morbidity and less in patients without co-morbidity. Our results do not support this reasoning. Also, after taking the number of comorbid conditions into account, we could not find a significant association between comorbid conditions and antibiotic prescribing (data not shown).

Conclusion

Until definite results from future preferably RCT's on this subject are available, GPs should be urged to more use information, in addition to other considerations, about the presence or absence of risk-related co-morbid conditions in their decision to prescribe antibiotics to patients with acute bronchitis or exacerbations of COPD. Tailoring their antibiotic treatment in this way could help GPs to improve antibiotic use in patients with respiratory tract infections in primary care.

Reference List

1. Hak E, Rovers MM, Kuyvenhoven MM, Schellevis FG, Verheij TJ. Incidence of GP-diagnosed respiratory tract infections according to age, gender and high-risk co-morbidity: the Second Dutch National Survey of General Practice. *Fam.Pract.* 2006;23:291-4.
2. Meyer KC. Lung infections and aging. *Ageing Res.Rev.* 2004;3:55-67.
3. BTS Guidelines for the Management of Community Acquired Pneumonia in Adults. *Thorax.* 2001;56 Suppl 4:IV1-64.:IV1-64.
4. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann.Intern.Med.* 1987;106:196-204.
5. Bent S, Saint S, Vittinghoff E, Grady D. Antibiotics in acute bronchitis: a meta-analysis. *Am.J.Med.* 1999;107:62-7.
6. Fahey T, Stocks N, Thomas T. Quantitative systematic review of randomised controlled trials comparing antibiotic with placebo for acute cough in adults. *BMJ* 1998;316:906-10.
7. Holmes WF, Macfarlane JT, Macfarlane RM, Hubbard R. Symptoms, signs, and prescribing for acute lower respiratory tract illness. *Br.J.Gen.Pract.* 2001;51:177-81.
8. Smucny J, Fahey T, Becker L, Glazier R. Antibiotics for acute bronchitis. *Cochrane.Database.Syst.Rev.* 2004;CD000245.
9. Gonzales R, Steiner JF, Sande MA. Antibiotic prescribing for adults with colds, upper respiratory tract infections, and bronchitis by ambulatory care physicians. *JAMA* 1997;278:901-4.

10. Woodhead M. Management of lower respiratory tract infections in out-patients. *Monaldi Arch.Chest Dis.* 1997;52:486-91.
11. Knutson D,.Braun C. Diagnosis and management of acute bronchitis. *Am.Fam.Physician.* 2002;65:2039-44.
12. Woodhead M, Blasi F, Ewig S, Huchon G, Leven M, Ortqvist A *et al.* Guidelines for the management of adult lower respiratory tract infections. *Eur.Respir.J.* 2005;26:1138-80.
13. Verheij TJ, Salomé Ph.L., Bindels P.J., Chavannes A.W., Ponsioen B.P., Sachs APE *et al.* NHG Standaard: Acuut hoesten. *Huisarts en Wetenschap* 2003;46:496-506.
14. Plasschaert AI, Rovers MM, Schilder AG, Verheij TJ, Hak E. Trends in doctor consultations, antibiotic prescription, and specialist referrals for otitis media in children: 1995-2003. *Pediatrics.* 2006;117:1879-86.
15. Classification Committee of the World Organization of Family Doctors (WICC). ICPC-2: International Classification of Primary Care. Oxford: Oxford University Press. 1997.
Ref Type: Report
16. WHO Collaborating Centre for Drug Statistics Methodology (Norway). ATC index with DDDs. WHO Collaborating Centre, Oslo. 1999.
Ref Type: Conference Proceeding
17. Gebel R.S., Okkes I.M., and red.ICPC-2-NL. International Classification of Primary Care, second edition, Dutch version, Utrecht, Amsterdam: Dutch College of General Practitioners, Academic Medical Centre Amsterdam/ University of Amsterdam. 2000.
Ref Type: Generic
18. Conte HA, Chen YT, Mehal W, Scinto JD, Quagliarello VJ. A prognostic rule for elderly patients admitted with community-acquired pneumonia. *Am.J.Med.* 1999;106:20-8.
19. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE *et al.* A prediction rule to identify low-risk patients with community-acquired pneumonia. *N.Engl.J.Med.* 1997;336:243-50.
20. Houston MS, Silverstein MD, Suman VJ. Risk factors for 30-day mortality in elderly patients with lower respiratory tract infection. Community-based study. *Arch.Intern.Med.* 1997;157:2190-5.
21. Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI *et al.* Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax* 2003;58:377-82.
22. Mortensen EM, Coley CM, Singer DE, Marrie TJ, Obrosky DS, Kapoor WN *et al.* Causes of death for patients with community-acquired pneumonia: results from the Pneumonia Patient Outcomes Research Team cohort study. *Arch.Intern.Med.* 2002;162:1059-64.
23. Seppa Y, Bloigu A, Honkanen PO, Miettinen L, Syrjala H. Severity assessment of lower respiratory tract infection in elderly patients in primary care. *Arch.Intern.Med.* 2001;161:2709-13.
24. Akkerman AE, Kuyvenhoven MM, van der Wouden JC, Verheij TJ. Determinants of antibiotic overprescribing in respiratory tract infections in general practice. *J.Antimicrob.Chemother.* 2005;56:930-6.
25. Fischer T, Fischer S, Kochen MM, Hummers-Pradier E. Influence of patient symptoms and physical findings on general practitioners' treatment of respiratory tract infections: a direct observation study. *BMC.Fam.Pract.* 2005;6:6.
26. Steinman MA, Sauaia A, Maselli JH, Houck PM, Gonzales R. Office evaluation and treatment of elderly patients with acute bronchitis. *J.Am.Geriatr.Soc.* 2004;52:875-9.
27. Bont J, Hak E, Hoes AW, Schipper M, Schellevis FG, Verheij TJ. A prediction rule for elder primary care patients with lower respiratory tract infections. *Eur.Respir.J.* 2007;10 (Epub ahead of print).
28. Gonzales R, Barrett PH, Jr., Crane LA, Steiner JF. Factors associated with antibiotic use for acute bronchitis. *J.Gen.Intern.Med.* 1998;13:541-8.
29. Kuyvenhoven MM, Verheij TJ, de Melker RA, van d, V. Antimicrobial agents in lower respiratory tract infections in Dutch general practice. *Br.J.Gen.Pract.* 2000;50:133-4.

30. Cydulka RK, Rowe BH, Clark S, Emerman CL, Camargo CA, Jr. Emergency department management of acute exacerbations of chronic obstructive pulmonary disease in the elderly: the Multicenter Airway Research Collaboration. *J.Am.Geriatr.Soc.* 2003;51:908-16.
31. Akkerman AE, Kuyvenhoven MM, van der Wouden JC, Verheij TJ. Prescribing antibiotics for respiratory tract infections by GPs: management and prescriber characteristics. *Br.J.Gen.Pract.* 2005;55:114-8.
32. Smith JA, Redman P, Woodhead MA. Antibiotic use in patients admitted with acute exacerbations of chronic obstructive pulmonary disease. *Eur.Respir.J.* 1999;13:835-8.
33. Akkerman AE, van der Wouden JC, Kuyvenhoven MM, Dieleman JP, Verheij TJ. Antibiotic prescribing for respiratory tract infections in Dutch primary care in relation to patient age and clinical entities. *J.Antimicrob.Chemother.* 2004;54:1116-21.
34. Goossens H, Ferech M, Vander SR, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet.* 2005;365:579-87.

Chapter 2.2

Antibiotic prescribing in elderly patients with acute bronchitis

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ABSTRACT

Background. As high volume of antibiotic use has been associated with growing resistance, reasons for antibiotic prescribing in acute bronchitis have been the object of several studies. For the group of elderly patients in whom antibiotics are prescribed more frequently due to diagnostic and prognostic uncertainty, such reasons are unclear.
Objectives. This study assessed clinical determinants of antibiotic prescribing in elderly patients diagnosed with acute bronchitis in the community.
Methods. Data including demographics, medical history and signs and symptoms were obtained from a prospective observational study including patients aged ≥65 years visiting a general practitioner with an episode of acute bronchitis between October 2004 and May 2006. Multivariable regression analysis was used to assess independent clinical characteristics associated with antibiotic use.
Results. Antibiotics were prescribed in 249 (82%) of 304 episodes of acute bronchitis. Purulent sputum and an abnormal auscultation with sounds of infection such as localised rales, rhonchi or bronchial breathing sounds were significantly associated with antibiotic use.
Conclusion. Antibiotic prescribing rates appeared high in elderly. Only two determinants were significantly associated with antibiotic prescribing while other important prognostic characteristics were not. More appropriate prescribing may be accomplished by taking determinants such as presence of serious co-morbid disease, high temperature and tachycardia into account.

INTRODUCTION

According to expert recommendations physicians should be restrictive in prescribing antibiotics for uncomplicated acute bronchitis.(1-5) Nevertheless prescription rates are still high, even in The Netherlands where antibiotic prescribing generally is low.(6;7) To support and improve quality assurance programs aiming at a more prudent use of antibiotics, reasons to prescribe antibiotics have been the focus of several studies.(8-18) A systematic review of these studies shows several determinants of antibiotic prescribing. (table 1) Unfortunately, most studies did not include a substantial population of elderly patients. Elderly are important since antibiotic prescribing rates are very high.(19) It is understandable that the treatment-decision is difficult in elderly due to diagnostic and prognostic uncertainty(20;21). On the other hand, recently we have shown that a relevant proportion of elderly have a high risk for poor outcome and that patient characteristics such as co-morbidity have clear prognostic value.(22) Monitoring and intervention, like antimicrobial treatment, should be focused on these high risk patients. These important clinical considerations were not included in studies so far. (table 1) In this prospective observational study therefore we studied antibiotic prescriptions in elderly and the role of important risk factors like co-morbidity in this.

METHODS

Study population and data collection

Between November 2005 and May 2006 191 Dutch GPs prospectively identified patients aged 65 years or older with LRTI, including acute bronchitis, exacerbations of chronic obstructive pulmonary disease (COPD) or pneumonia. For this study we only included episodes of acute bronchitis, which was defined by the International Classification of Primary Care (ICPC)-codes.(23;24) Patients were allowed to have more than one episode. The inclusion criterion for acute bronchitis (ICPC-code: R78) was coughing with diffuse abnormalities on pulmonary examination like wheezing, rhonchi or crepitations. Fever was not obligatory since elderly do not always present themselves with fever. Patients with pre-existent COPD or emphysema were excluded, as were patients with lung cancer, a haematological malignancy, an infection with the Human Immunodeficiency Virus, or patients being hospitalised during the two weeks preceding the diagnosis, using immunosuppressive medication (except oral glucocorticoids) or nursing home residents.

Selection of potential predictors of antibiotic prescribing

During the consultation GPs filled in a structured questionnaire with data on age, smoking history, comorbid conditions, signs and symptoms and treatment. Based on previous studies and guidelines, we hypothesised that physicians are more likely to prescribe antibiotics to patients with a potential poorer prognosis (see also table 1).(2;22;25;26) We therefore included data on age, gender, medical history and signs and symptoms.

Table 1. Overview of literature on determinants of antibiotic prescribing in lower respiratory tract infection (LRTI).

Year of publication and first author	Study design	Type of LRTI (N)	Subgroup-analysis age ≥65 years	Patients with comor-bidities	Data on vital signs	Prescribing rate acute bronchitis (%)	Independent determinants of antibiotic prescribing
2006, Hopstaken(16)	Prosp. cohort	Pneumonia (21) and acute bronchitis (225)	No	Included	Present	79% (including pneumonia)	• Thoracic pain • Diarrhoea and vomiting • Auscultation abnormalities
2005, Akkerman(9)	Prospective cohort	Sinusitis (575), tonsillitis (238), bronchitis (656)	No	Included	Absent	78%	• Age • Wheezing (negative association) • Signs of inflammation • GP's perception of severity of illness and patient expectations
2005, Fischer(12)	Prospective cohort	Upper RTI (203) and bronchitis (70)	No	Not reported	Absent	77%	• Type of RTI • Rales • Fatigue • Wheezing • Fever • Yellow sputum • Pathological findings: tonsils, otoscopy, cervical lymph nodes, sinus palpation
2004, Steinman(18)	Retrospective cohort/ cross-sectional	Uncomplicated acute bronchitis (198)	Yes	Included	Present (17-50% missing!)	83%	• Sex
2003, Mazzaglia(17)	Retrospective cohort/ cross-sectional	Upper and lower RTI (67.761), incl. acute bronchitis (11,083)	No	Included, not reported	Absent	81%	• Area of practice • Number of patients under care No association patient's characteristics & antibiotic use.
2001, Holmes(15)	Prospective cohort	Only LRTI (391)	No	Excluded	Present	71%	• Sex and age • Discoloured sputum • Pulse >90 bpm
2000, Dosh(11)	Prospective cohort	Upper LRTI (167), sinusitis (176), bronchitis (139)	No	Included, not reported	Absent	80%	• Sinus tenderness • Rales/rhonchi • Yellow/green nasal discharge • Postnasal drainage • Clear nasal discharge
1998, Gonzales(14)	Prosp.cohort	Acute bronchitis (151)	No	Excluded	Absent	85%	No significant associations were found
1997, Gonzales(13)	Sample survey	Upper RTI (11,033) & bronchitis (10,235)	No	Included	Absent	66%	• Practice location

Statistical analysis

Multivariable logistic regression analysis was performed to assess independent associations between patient characteristics and antibiotic prescription rates. All characteristics were treated as dichotomous variables (absence or presence). Age was dichotomised into younger or older than 80 years. Variables with a p-level of 0.2 or lower in the univariable regression analysis were further examined in the multivariable logistic regression analysis. Goodness-of-fit of the model was given by the Hosmer-Lemeshow Goodness of fit test. A p-level of 0.05 or lower was considered to indicate statistical significance.

RESULTS

A total of 304 episodes were included in the analysis with seven patients who had two episodes during the study period. The mean age of the patients was 76 years (range 65 to 97) and 66% were female. Co-morbid conditions were common with heart failure being present in 16% and diabetes in 17%.

Patients were mainly treated with antibiotics (82%) and other medication was infrequently prescribed (inhalation medication (18%), oral glucocorticosteroids (5%) and other therapy (4%)). Patients often received more than one type of medication. Only in 9% of the subjects, the physician followed a wait-and-see policy without prescribing any medication. None of the patients were referred to the hospital, thus all were home treated by their GP.

In the multivariable analysis, only purulent sputum and abnormal auscultation with sounds of infection such as rales and rhonchi were significantly associated with antibiotic prescribing. Patients age, co-morbidity, smoking status and symptoms such as dyspnoea or increased sputum volume and signs such as fever, tachycardia, low blood pressure and tachypnoea appeared not to be significantly associated. (table 2.)

Table 2. Characteristics of patients with acute bronchitis and comparison between patients treated without and with antibiotics.

Characteristic	Total N=304 (100%)	Treated without antibiotics N=55 (18%)	Treated with antibiotics N=249 (82%)	Univariate OR (95% CI)	Multivariate OR (95%CI)
Age ≥80 yrs	103 (34)	15 (27)	88 (35)	NS	
Mean age (SD)	76 (7)	76 (7)	76 (8)	NS	
Male gender	104 (34%)	20 (36)	84 (34)	NS	
History					
Heart failure	47 (16)	8 (15)	39 (16)	NS	
Diabetes mellitus	52 (17)	11 (20)	41 (17)	NS	
Stroke	26 (8.6)	3 (5.5)	23 (9.2)	NS	
Malignancy[#]	20 (6.6)	4 (7.3)	16 (6.4)	NS	
Smoking >10 sig/ day	13 (4.3)	1 (1.8)	12 (4.8)	NS	
Antibiotic use in previous month	15 (4.9)	5 (9.1)	10 (4.0)	0.42 (0.1-1.3)	NS
Hospitalisation ≥1 in prior year	38 (13)	8 (15)	30 (12)	NS	
Signs and symptoms					
General malaise	212 (70)	33 (60)	179 (72)	1.7 (0.9-3.1)	NS
Prior signs of URTI	235 (77)	40 (73)	195 (78)	NS	
Dypnoea	193 (64)	31 (56)	87 (65)	NS	
Increased sputum production	230 (76)	41 (75)	189 (76)	NS	
Purulent sputum	110 (36)	10 (18)	100 (40)	3.0 (1.5-6.3)	2.6 (1.3-5.6)
Painful breathing	43 (14)	3 (5.5)	40 (16)	3.3 (1.0-11.1)	
Abnormal orientation in time and person	9 (3.0)	1 (1.8)	8 (3.2)	NS	
Diminished consciousness	3 (1.0)	0	3 (1.2)	NS	
High body temperature (>38)	43 (14)	4 (7.3)	39 (16)	2.4 (0.8-6.9)	NS
Pulse rate > 100	13 (4.3)	2 (3.6)	11 (4.4)	NS	
Low blood pressure[¶]	16 (5.3)	4 (7.3)	12 (4.8)	NS	
Respiratory rate ≥30	16 (5.3)	3 (5.5)	13 (5.2)	NS	
Abnormal auscultation with sounds of infection[+]	235 (77)	29 (53)	206 (83)	4.3 (2.3-8.1)	3.9 (2.1-7.4)

The Hosmer-Lemoshow Goodness of fit test was 0,37; NS= not significant (P>0.05); [#] Patients with a pulmonary malignancy were excluded; [¶] Low blood pressure = diastolic <60 or systolic <90 mmHg; [+] Presence of uni- or bilatereal localised crackles, rhonchi,, bronchial breath sounds, etc. instead of or on top of wheezing or a prolonged expirium

DISCUSSION

This observational study showed that elderly patients with acute bronchitis were mostly treated with antibiotics and all patients were treated in primary care. Only purulent sputum and abnormal auscultation with sounds of infection such as rales and rhonchi were independently associated with antibiotic prescribing. In contrast to our hypothesis, antibiotics were not more often prescribed in patients with additional risk factors for a poor prognosis.

A major strength of this study is the inclusion of many episodes among elderly, since they have not been prospectively studied so far. Also the analysis of vital parameters is important because of their diagnostic and prognostic value.(22;25;26) In most patients no chest X-ray was done and therefore a more definitive differentiation of LRTI was not possible. According to GP practice, diagnostic uncertainty may play an important role in the decision to prescribe antibiotics.(20) We choose however for this design to follow daily GP practice in which radiology is not part of routine daily care.
It should also be noted that some patient characteristics like high pulse rate, tachypnoea and low blood pressure were only present in low numbers of patients. Although our conclusions can therefore not cover these variables, that only occur rarely in primary care, they are valid for important and more frequent risk factors like diabetes and cardiac failure.

In a recent study we have shown that risk factors for a poor prognosis can be identified in elderly patients with lower respiratory tract infections.(22) For example, a patient of 82 years old diagnosed with acute bronchitis, with a medical history of diabetes and heart failure and who has already received antibiotics in the previous month, has a probability of more than 30% of hospitalisation or death within the next 30 days. Although it may seem obvious that patients with such risk factors are at risk, we did not find an association with antibiotic prescribing.

As in some other studies, discoloured sputum was a reason for GPs to prescribe antibiotics in adults.(11;12;15) However, sputum characteristics do not provide sufficient reason to indicate a bacterial infection needing antibiotics.(27;28) On the other hand, abnormal auscultation with signs of infection such as rales and rhonchi was also a clear predictor for antibiotic prescribing. This reasoning is more logical since there is evidence that only in the absence of any vital sign abnormality or any abnormality on chest auscultation, one can safely reject a diagnosis of pneumonia.(26) Still, our study shows that antibiotics are prescribed in 60% of the cases of acute bronchitis without these diagnostic characteristics. (data available)

In conclusion, antibiotics were prescribed to the majority of elderly with acute bronchitis. Except for abnormal auscultation with signs of infection such as rales and rhonchi, other relevant diagnostic and prognostic factors, like diabetes and cardiac failure, were not significantly associated with antibiotic use. Therefore it seems that there are clear possibilities to improve antibiotic prescribing, even in elderly. Such improvement would mean less overprescribing but also less risk for underprescribing in some high risk patients.

Reference List

1. Morice, A. H., McGarvey, L., and Pavord, I. Recommendations for the Management of Cough in Adults. Thorax 2006;61 Suppl 1:i1-24.
2. Verheij, T. J., Salomé Ph.L., Bindels P.J., Chavannes A.W., Ponsioen B.P., Sachs APE, and et al. NHG Standaard: Acuut Hoesten. Huisarts en Wetenschap 2003;46(9):496-506.
3. Woodhead, M., Blasi, F., Ewig, S., Huchon, G., Ieven, M., Ortqvist, A., Schaberg, T., Torres, A., van der, Heijden G., and Verheij, T. J. Guidelines for the Management of Adult Lower Respiratory Tract Infections. Eur.Respir.J. 2005;26(6):1138-80.
4. Snow, V., Mottur-Pilson, C., and Gonzales, R. Principles of Appropriate Antibiotic Use for Treatment of Acute Bronchitis in Adults. Ann.Intern.Med. 20-3-2001;134(6):518-20.
5. Wong, D. M., Blumberg, D. A., and Lowe, L. G. Guidelines for the Use of Antibiotics in Acute Upper Respiratory Tract Infections. Am.Fam.Physician 15-9-2006;74(6):956-66.
6. Cars, O., Molstad, S., and Melander, A. Variation in Antibiotic Use in the European Union. Lancet 9-6-2001;357(9271):1851-3.
7. Goossens, H., Ferech, M., Vander, Stichele R., and Elseviers, M. Outpatient Antibiotic Use in Europe and Association With Resistance: a Cross-National Database Study. Lancet. 12-2-2005;365(9459):579-87.
8. Akkerman, A. E., van der Wouden, J. C., Kuyvenhoven, M. M., Dieleman, J. P., and Verheij, T. J. Antibiotic Prescribing for Respiratory Tract Infections in Dutch Primary Care in Relation to Patient Age and Clinical Entities. J.Antimicrob.Chemother. 2004;54(6):1116-21.
9. Akkerman, A. E., Kuyvenhoven, M. M., van der Wouden, J. C., and Verheij, T. J. Determinants of Antibiotic Overprescribing in Respiratory Tract Infections in General Practice. J.Antimicrob.Chemother. 2005;56(5):930-6.
10. Akkerman, A. E., Kuyvenhoven, M. M., van der Wouden, J. C., and Verheij, T. J. Prescribing Antibiotics for Respiratory Tract Infections by GPs: Management and Prescriber Characteristics. Br.J.Gen.Pract. 2005;55(511):114-8.
11. Dosh, S. A., Hickner, J. M., Mainous, A. G., III, and Ebell, M. H. Predictors of Antibiotic Prescribing for Nonspecific Upper Respiratory Infections, Acute Bronchitis, and Acute Sinusitis. An UPRNet Study. Upper Peninsula Research Network. J.Fam.Pract. 2000;49(5):407-14.
12. Fischer, T., Fischer, S., Kochen, M. M., and Hummers-Pradier, E. Influence of Patient Symptoms and Physical Findings on General Practitioners' Treatment of Respiratory Tract Infections: a Direct Observation Study. BMC.Fam.Pract. 7-2-2005;6(1):6.
13. Gonzales, R., Steiner, J. F., and Sande, M. A. Antibiotic Prescribing for Adults With Colds, Upper Respiratory Tract Infections, and Bronchitis by Ambulatory Care Physicians. JAMA 17-9-1997;278(11):901-4.
14. Gonzales, R., Barrett, P. H., Jr., Crane, L. A., and Steiner, J. F. Factors Associated With Antibiotic Use for Acute Bronchitis. J.Gen.Intern.Med. 1998;13(8):541-8.
15. Holmes, W. F., Macfarlane, J. T., Macfarlane, R. M., and Hubbard, R. Symptoms, Signs, and Prescribing for Acute Lower Respiratory Tract Illness. Br.J.Gen.Pract. 2001;51(464):177-81.
16. Hopstaken, R. M., Butler, C. C., Muris, J. W., Knottnerus, J. A., Kester, A. D., Rinkens, P. E., and Dinant, G. J. Do Clinical Findings in Lower Respiratory Tract Infection Help General Practitioners Prescribe Antibiotics Appropriately? An Observational Cohort Study in General Practice. Fam.Pract. 2006;23(2):180-7.
17. Mazzaglia, G., Caputi, A. P., Rossi, A., Bettoncelli, G., Stefanini, G., Ventriglia, G., Nardi, R., Brignoli, O., and Cricelli, C. Exploring Patient- and Doctor-Related Variables Associated With Antibiotic Prescribing for Respiratory Infections in Primary Care. Eur.J.Clin.Pharmacol. 2003;59(8-9):651-7.
18. Steinman, M. A., Sauaia, A., Maselli, J. H., Houck, P. M., and Gonzales, R. Office Evaluation and Treatment of Elderly Patients With Acute Bronchitis. J.Am.Geriatr.Soc. 2004;52(6):875-9.

19. Bont, J., Hak, E., Birkhoff, C. E., Hoes, A. W., and Verheij, T. J. Is Co-Morbidity Taken into Account in the Antibiotic Management of Elderly Patients With Acute Bronchitis and COPD Exacerbations? Fam.Pract. 29-6-2007;.
20. Coenen, S., Van Royen, P., Vermeire, E., Hermann, I., and Denekens, J. Antibiotics for Coughing in General Practice: a Qualitative Decision Analysis. Fam.Pract. 2000;17(5):380-5.
21. Macfarlane, J., Holmes, W., Gard, P., Macfarlane, R., Rose, D., Weston, V., Leinonen, M., Saikku, P., and Myint, S. Prospective Study of the Incidence, Aetiology and Outcome of Adult Lower Respiratory Tract Illness in the Community. Thorax 2001;56(2):109-14.
22. Bont, J., Hak, E., Hoes, A. W., Schipper, M., Schellevis, F. G., and Verheij, T. J. A Prediction Rule for Elderly Primary-Care Patients With Lower Respiratory Tract Infections. Eur.Respir.J. 2007;29(5):969-75.
23. . Classification Committee of the World Organization of Family Doctors (WICC). ICPC-2: International Classification of Primary Care. Oxford: Oxford University Press. 1997.
24. Gebel R.S.; Okkes I.M.; red.ICPC-2-NL. International Classification of Primary Care, second edition, Dutch version, Utrecht, Amsterdam: Dutch College of General Practitioners, Academic Medical Centre Amsterdam/ University of Amsterdam. 2000.
Ref Type: Generic
25. Lim, W. S., van der Eerden, M. M., Laing, R., Boersma, W. G., Karalus, N., Town, G. I., Lewis, S. A., and Macfarlane, J. T. Defining Community Acquired Pneumonia Severity on Presentation to Hospital: an International Derivation and Validation Study. Thorax 2003;58(5):377-82.
26. Metlay, J. P., Kapoor, W. N., and Fine, M. J. Does This Patient Have Community-Acquired Pneumonia? Diagnosing Pneumonia by History and Physical Examination. JAMA 5-11-1997;278(17):1440-5.
27. Chodosh, S. Acute Bacterial Exacerbations in Bronchitis and Asthma. Am.J.Med. 27-4-1987;82(4A):154-63.
28. Stockley, R. A., O'Brien, C., Pye, A., and Hill, S. L. Relationship of Sputum Color to Nature and Outpatient Management of Acute Exacerbations of COPD. Chest 2000;117(6):1638-45.

Chapter 3.1

Predicting death in elderly patients with pneumonia in the community; a prospective validation study re-evaluating the CRB-65 severity assessment tool

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ABSTRACT

Background: The CRB-65 severity score (**C**onfusion, high **R**espiratory rate, low **B**lood pressure and Age **65** years or over; score ranging 0-4) has been recommended as a management tool for community acquired pneumonia (CAP) in the community. Although the CRB-65 score has not been validated in the community, it recommends hospital referral for a score ≥1 and thus all patients aged 65 years or older with CAP. We assessed the validity of the CRB-65 score in a primary health care setting including only elderly patients.
Methods: A prospective cohort study was performed in patients aged 65 years or older consulting their primary care physician with CAP. Clinical features at presentation were used to validate the CRB-65 score. Predictive values were calculated for 30-day mortality.
Results: 314 patients with CAP were included with a mortality rate of 3.5%. Patients with 1, 2 or ≥3 points had a mortality-rate of 0.9%, 8.2% and 17.4%, respectively. Choosing a cut-off of ≥2, the positive and negative predictive values, sensitivity and specificity of the CRB-65 score were respectively 11%, 99%, 82% and 75%. These values are comparable to the original study. The discriminative value of the CRB-65 score was good (AUC=0.79, 95% CI 0.65-0.92).
Conclusions: The CRB-65 score adequately predicts mortality in an unselected elderly primary care population with CAP. However, since the a-priori probability is much lower in this subgroup than in hospitalised patients, distinction between low and high risk patients should be made using a cut-off level of 2 instead of 1.

INTRODUCTION

Severity scores are helpful in predicting mortality in patients presenting with community acquired pneumonia (CAP). They enable physicians to decide their management strategies and site of care according to the expected mortality risk. In Europe most cases of lower respiratory tract infections (LRTIs) and CAP are managed in primary care by general practitioners (GPs). However, most severity scores have been derived and validated in a hospital setting.

The best accepted tools to discriminate patients with CAP into high- or low risk are the CURB-65 score (**C**onfusion, **U**rea > 7 mmol/L, **R**espiratory rate ≥ 30/min., low **B**lood pressure and **A**ge ≥ 65 yrs) and the Pneumonia Severity Index (PSI).[1;2] The CURB-65 score consists of five easily accessible data, while the PSI includes many tests that are not accessible in primary care. This latter score is therefore not useful for the GP. Recently several studies evaluated the CURB-65 score and confirmed its validity, but validation was not yet done in an unselected primary care population.[3-9]

A modification of the CURB-65 score, the CRB-65 score, is recommended in the community by GPs where blood urea measurements are often not available. It is expected to support GP judgement in stratifying patients into different management groups, ranging from home treatment to urgent hospital admission[1] (figure 1). This management model seems unlikely to be practical in a primary care population as it recommends hospital referral for a score of ≥1 and thus for all patients aged over 65. (figure 1) We therefore conducted a study to evaluate the validity of the CRB-65 score in primary care.

Figure 1. Severity assessment by the CRB-65-score used to determine the management of CAP in patients in the community (Lim et al, 2003).[1]

Characteristic	Score assigned
New mental confusion	1
Respiratory rate 30/min or more	1
BP <90 mmHg systolic or £60 mmHg diastolic	1
Age ≥65 years	1

	Risk class I	Risk class II	Risk class III
Sum of scores	0	1 or 2	3 or 4
Risk of 30-day mortality	Low (1.2%)	Intermediate (8.2%)	High (31.3%)
Treatment options	Likely suitable for home treatment	Likely need hospital referral and assessment	Urgent hospital admission

METHODS

Study population

Between November 2005 and May 2006 Dutch GPs prospectively included patients aged 65 years or older consulting with CAP. CAP was diagnosed by the presence of one or more features, including new localising signs present on chest examination, new infiltrates on a chest X-ray or when the GP had a strong suspicion of CAP due to severe dyspnoea in a very ill patient, even in the absence of chest signs. This third criterion for CAP was chosen, because it equates to usual practice in daily primary care, thus ensuring generalisibility of study results.
Patients were not included in the study if they were known to have lung cancer, a haematological malignancy or an infection with the Human Immunodeficiency Virus, used immunosuppressive medication (except prednisone), had been hospitalised during the two weeks preceding the diagnosis or were nursing home residents.

Data, including all CRB items and age, were collected prospectively at the same time as the index consultation, when diagnosis and management was decided. The CRB-65 rule is scored on the presence of: Confusion, Respiratory rate ≥30 per minute, low Blood pressure (systolic blood pressure <90 or diastolic pressure ≤60 mm Hg) and age ≥65. The outcome was 30-day mortality.

Statistical aspects

Descriptive statistics included frequencies, percentages and means. We examined the accuracy of the CRB-65 rule in episodes of CAP using SPSS Version 12.1 for Windows, Chicago, USA, with 30 day mortality as the outcome. Positive predictive value (PPV), negative predictive value (NPV), sensitivity, specificity and the area under the receiver operating curve (AUC) with corresponding 95% confidence intervals (CI) were calculated and compared with the original study of Lim et al.[1] Next, the mortality for different CRB-65 scores was determined. We also calculated the correlation between the individual CRB-65 scores and referral patterns.

RESULTS

Patients' characteristics

The study population consisted of 315 elderly patients (mean age 77.3 years) who lived at home and were diagnosed with CAP. Of these, 17 patients were diagnosed only on the basis of a strong suspicion of having pneumonia (third diagnostic criterion). In 119 episodes a chest X-ray was present, with 50 showing infiltrates. One patient was lost to follow up and excluded from the analysis. Forty seven (15%) patients were hospitalised and 11 (3.5%) died within 30 days. (table 1) Mortality was 4% in patients with a chest X-ray. 89% were treated initially by the GP with antibiotics, 7% were referred to hospital immediately, and 4% did not get antimicrobial treatment nor were referred immediately (none of these 14 patients died within 30 days).

Table 1. Demographic -, co-morbid and clinical characteristics of the derivation cohort (Lim et al.)[1] and the validation cohort of primary care patients with CAP (current study)

Characteristic	Derivation cohort Hospital setting N=821	Validation cohort Primary care setting N=314
Male* (%)	550 (51)	145 (46)
Mean age* (years)	64.1	77.3
Age ≥ 65 years (%)	475 (58)	314 (100)
Age ≥ 75 years (%)	296 (36)	187 (60)
Comorbid illnesses		
Chronic lung disease* (%)	375 (35)	123 (39)
IHD/ Heart failure*# (%)	197 (18)	65 (21)
CVD*† (%)	91 (9)	27 (9)
Diabetes mellitus* (%)	107 (10)	61 (19)
Signs and symptoms		
Dyspnoea	‡	221 (70)
Cough	‡	300 (96)
Sputum	‡	233 (48)
Painful breathing	‡	75 (24)
Confusion (%)	125 (15)	10 (3)
Respiratory rate ≥30/ min (%)	277 (34)	50 (16)
Pulse rate ≥125/ minute	87 (11)	7 (2)
BP <90 mmHg systolic or ≤60 mmHg diastolic (%)	199 (24)	41 (13)
Auscultatory abnormalities	‡	290 (92)
X-ray confirmed CAP	821 (100)	50 (16%)$
Outcome		
30-day mortality	89 (8)	11 (4)
30-day hospitalisation	‡	47 (15)

IHD, ischaemic heart disease; CVD, cerebrovascular disease; BP, blood pressure.
* Lim et al only presented numbers for the total cohort that included 1,068 patients.
# the current study recorded only heart failure.
† the current study recorded only stroke.
‡ Data were not presented by Lim et al.
$ In 119 patients (38%) chest X-rays were performed, either by the general practitioner or in hospital.

Accuracy of the CRB-65 score

By comparison with the original study by Lim et al., a similar trend was found in the association between the CRB-65 score and 30-day mortality, though none of our patients had zero score (as they were all aged 65 or over) or a high score of 4. (table 2)

Table 2. Association between number of prognostic features of the CRB-65 score and risk of 30-day mortality. Comparison between the original study by Lim et al. and the current study.

	Original dataset by Lim et al N=932		**Current study N=314**	
Score	**Total N (%)**	**Mortality N (%)**	**Total N (%)**	**Mortality N (%)**
0*	212 (22.7)	2 (0.9)	-	
1	344 (36.9)	18 (5.2)	230 (73.2)	2 (0.9)
2	251 (26.9)	30 (11.8)	61 (19.4)	5 (8.2)
3	111 (11.9)	36 (32.4)	23 (7.3)	4 (17.4)
4*	14 (1.5)	3 (21.4)	-	

CRB-65, **C**onfusion, **R**espiratory rate ≥30/min, low **B**lood pressure (<90 mmHg systolic or ≤60 mmHg diastolic), age ≥**65** years

* All patients in the current study were 65 years or older. Therefore there were no patients with a CRB-65 score of 0. Also no patients had a score of ≥4

The test-characteristics of the CRB-65 score in our study taking a cut-off of ≥2 were very much similar to that of the original cohort. (table 3) Also the discriminative value was good (AUC=0.79, 95% CI 0.65-0.92).

Table 3. Comparison of the test-characteristics of CRB-65 ≥ 2 between the original dataset of Lim et al and the current study taking 30 day mortality as the endpoint.

	Original dataset by Lim et al	**Current study**
	Derivation set N=932	**Validation set N=314**
Sensitivity (%)	77.5	82.2
Specificity (%)	63.6	75.2
PPV (%)	18.4	10.7
NPV (%)	96.4	99.1

CRB-65, **C**onfusion, **R**espiratory rate ≥30/min, low **B**lood pressure (<90 mmHg systolic or ≤60 mmHg diastolic), Age ≥**65** years; PPV=positive predictive value; NPV=negative predictive value

Management of CAP

Patients with a score of 1 (73%) had a low mortality rate of 0.9%, suggesting they may be suitable for usual home management. A score of 2 or higher was associated with a much higher mortality rate (11%) suggesting they required either close monitoring at home or hospital referral. (table 2) This is not in agreement with the site of care decision recommended in the BTS Guidelines and the Lim study. (figure 1)

In our study cohort, only 23 (7.3%) patients with pneumonia were referred to the hospital. Of the 230 patients with a score of 1, only 9 were referred to hospital and the remainder were treated at home. Two patients (0.9%) died, both in the home managed group. Only 7 patients with a CRB-65 score of 3 were referred to hospital and of the other 16 patients treated at home, 2 (13%) died. (table 4)

Table 4. GP referral pattern of elderly patients with pneumonia in relation to the CRB-65 score (N=314)

	Low risk CRB-65 score=1 N=230 (73%)	**Medium risk CRB-65 score=2 N=62 (20%)**	**High risk CRB-65 score=3 N=23 (7%)**
Patients directly referred to hospital	9 (4%)	7 (12%)	7 (30%)
30-day mortality	0	2 (29%)	1 (14%)
Patients not directly referred to hospital	221 (96%)	54 (89%)	16 (70%)
30-day mortality	2 (0.9%)	3 (6%)	2 (13%)

DISCUSSION

When using a score of 2 or more to indicate high-risk, our study showed that the CRB65-score has similar accuracy in predicting 30-day mortality in elderly primary care patients compared to the original study of Lim et al. including patients of all ages in a hospital setting.[1] Thus, our study shows that in an elderly primary care population the cut-off for considering hospital referral can be increased to a score of 2 or more. This does not imply that all such patients should be referred to hospital. Referral also depends on other adverse prognostic features, social circumstances and wishes of the patient, as well as the availability of close health monitoring at home. Whether referral to hospital will decrease mortality rates in high risk patients with CAP is even not entirely clear. In our study, most patients with an elevated risk were not referred. Whether the mortality rate would be lower if they would have been sent to hospital is unknown.

The results from this study differ somewhat from other validation studies. In particular, the a priori probability of 30-day mortality was lower than in previous validation studies; 3.5% versus 4.3-14%.[1;3-6;8;10] In these earlier studies however, mixed groups of referred and non-referred patients were studied with probably a higher risk for complications. Another possible explanation for the low mortality could be that bacterial resistance rates are low in the Netherlands. However, overall Dutch mortality rates for CAP are not lower compared to those in countries with higher resistance rates.[11]

Discrimination between different kinds of LRTI is difficult in primary care since pulmonary radiography and laboratory tests are not routinely carried out. We chose to include CAP without radiographic evidence to follow daily GP practice more accurately. Although it seems that differentiation between CAP and acute bronchitis is more difficult without radiography, the prognosis of these two forms of LRTI was very different in our whole study with a mortality rate of 3.5% in patients with CAP and 0.2% for acute bronchitis (data available). Since death in acute bronchitis was very infrequent, using the CRB65-score as a predictor of 30 day mortality in acute bronchitis was not useful. New studies should focus predicting other unfavourable outcomes, apart from death, in a broader range of LRTI.

In conclusion, the simple CRB-65 severity assessment tool accurately identifies low risk patients in an elderly primary care population and suggests that age alone is not a sufficient reason to classify patients as high risk. Patients with a score of 2 or higher have an increased risk and should be intensively monitored, for example by re-consultation within 24-48 hours or should be referred to secondary care. Since mortality rates are low in primary care, new studies should focus on less severe outcomes.

Reference List

1. Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI *et al*. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax* 2003;**58**:377-82.
2. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE *et al*. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N.Engl.J.Med.* 1997;**336**:243-50.
3. Aujesky D, Auble TE, Yealy DM, Stone RA, Obrosky DS, Meehan TP *et al*. Prospective comparison of three validated prediction rules for prognosis in community-acquired pneumonia. *Am.J.Med.* 2005;**118**:384-92.
4. Bauer TT, Ewig S, Marre R, Suttorp N, Welte T. CRB-65 predicts death from community-acquired pneumonia. *J.Intern.Med.* 2006;**260**:93-101.
5. Buising KL, Thursky KA, Black JF, MacGregor L, Street AC, Kennedy MP *et al*. A prospective comparison of severity scores for identifying patients with severe community acquired pneumonia: reconsidering what is meant by severe pneumonia. *Thorax* 2006;**61**:419-24.
6. Capelastegui A, Espana PP, Quintana JM, Areitio I, Gorordo I, Egurrola M *et al*. Validation of a predictive rule for the management of community-acquired pneumonia. *Eur.Respir.J.* 2006;**27**:151-7.
7. Myint PK, Kamath AV, Vowler SL, Maisey DN, Harrison BD. The CURB (confusion, urea, respiratory rate and blood pressure) criteria in community-acquired pneumonia (CAP) in hospitalised elderly patients aged 65 years and over: a prospective observational cohort study. *Age Ageing* 2005;**34**:75-7.
8. Myint PK, Kamath AV, Vowler SL, Maisey DN, Harrison BD. Severity assessment criteria recommended by the British Thoracic Society (BTS) for community-acquired pneumonia (CAP) and older patients. Should SOAR (systolic blood pressure, oxygenation, age and respiratory rate) criteria be used in older people? A compilation study of two prospective cohorts. *Age Ageing* 2006;**35**:286-91.
9. Yan MS, Lee N, Ip M, Antonio GE, Chau SS, Mak P *et al*. Prospective comparison of three predictive rules for assessing severity of community-acquired pneumonia in Hong Kong. *Thorax.* 2007;**62**:348-53.
10. Ewig S, Ruiz M, Mensa J, Marcos MA, Martinez JA, Arancibia F *et al*. Severe community-acquired pneumonia. Assessment of severity criteria. *Am.J.Respir.Crit Care Med.* 1998;**158**:1102-8.
11. International comparisons (Website VTV 2006: www.rivm.nl/vtv/). 2006.
Ref Type: Internet Communication

Chapter 3.2

A prediction rule for elder primary care patients with lower respiratory tract infections

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ABSTRACT

Objectives. Prognostic scores for lower respiratory tract infections (LRTI) have been mainly derived in a hospital setting. We developed and validated a prediction rule for the prognosis of acute LRTI in elderly primary care patients.

Methods. Data, including demographics, medication use, health care use and comorbid conditions, from 3,166 episodes of patients aged ≥ 65 years visiting the general practitioner (GP) with LRTI were collected. Multiple logistic regression analysis was used to construct a predictive model. The main outcome measure was 30-day hospitalisation or death. The Second Dutch Survey of GPs was used for validation.

Results. The following were independent predictors of 30-day hospitalisation or death: increasing age; previous hospitalisation; heart failure; diabetes; use of oral glucocorticoids; previous use of antibiotics; a diagnosis of pneumonia; and exacerbation of Chronic Obstructive Pulmonary Disease. A prediction rule based on these variables showed that the outcome increased directly with increasing scores: 3, 10 and 31% for scores of <2 points, 3-6 and ≥7 points, respectively. Corresponding figures for the validation cohort were 3, 11, 26%, respectively.

Conclusion. This simple prediction rule can help the primary care physician to differentiate between high- and low-risk patients. As a possible consequence, low-risk patients may be suitable for home-treatment whereas high risk patients might be monitored more closely in a homecare or hospital setting. Further studies should assess whether information on signs and symptoms can further improve this prediction rule.

INTRODUCTION

Acute lower respiratory tract infections (LRTI) such as pneumonia and acute bronchitis are among the most common reasons to attend a general practitioner (GP), notably among elderly persons.[1] In The Netherlands, the annual incidence of pneumonia and acute bronchitis per 1,000 patients aged 65 to 74 years is 12 and 32, respectively, and this is even much higher in the very old.[2] Elderly persons are of particular concern to GPs, since they are more likely to develop complications from LRTI compared to younger patients. Correctly classifying these patients into high- or low-risk may reduce unnecessary (antibiotic) treatment in low-risk patients and improve tailoring of more intensive interventions in high-risk patients.

Severity scores are important in predicting outcome. Many guidelines use these scores to tailor management decisions.[3-6] However, the usefulness of the available studies from which scores are derived is limited for primary care physicians. First, the majority of studies included hospitalised patients[7-18] or a selected group of patients with community-acquired pneumonia (CAP) only.[7-13;15-20] While mortality is the most commonly used outcome and of importance, other more frequent complications leading to hospitalisation are relevant from a patients and physicians perspective as well. Also, most studies included only a small number of elderly. Finally, the data-analysis of some studies included the development of a prediction rule, but few validated such rule in an elderly primary care population with LRTI[7-9;12-14;16;20]. To be able to target management decisions in elderly with LRTI more efficiently, we aimed to develop a prediction rule with the use of easily obtainable data to estimate the absolute risk of elderly primary care patients with LRTI to be admitted to hospital or die within 30 days after diagnosis, and validated the rule in a large nationally representative cohort.

METHODS

Setting and study population

We retrospectively analysed medical data from two large cohorts of elderly patients with physician-attended LRTI. The first cohort was used to identify characteristics that were predictive of 30-day hospitalisation or death and to develop a prediction rule. The second cohort served to validate the predictive model.

The derivation cohort originates from patient-data stored in the database of the Utrecht GP research network (Utrecht patient cohort). In this network a structured and uniform morbidity registration system has been in use since the early nineties. Currently, thirty-five GPs of this network serve approximately 58,000 non-institutionalised persons. The patient population is representative for the Dutch population with regard to age and gender.[21] All patient data are registered in the patient record using the International Classification of Primary Care (ICPC)-codes for diagnoses. Using the computerized medical records of all elderly persons from the Utrecht patient cohort, we collected data on eligible LRTI episodes from January 1997 to February 2003 in elderly patients aged 65 years or older. During the study period, the participating physicians made their decisions concerning their treatment and possible referral of patients according to usual care.

Data on the *validation cohort* were obtained from data of patients from the Second Dutch National Survey of General Practice (National patient cohort), conducted by the Netherlands Institute for Health Services Research (NIVEL) in 2001. The study included 359,625 patients from 163 GPs in 85 practices.[22] All GPs participated in a training programme aimed at uniform registration of diagnosis and prescriptions. Data were collected over a 12-month period in 2000/2001.

Definition of LRTI

LRTIs consisted of episodes of pneumonia, acute bronchitis and exacerbations of chronic obstructive pulmonary disease (COPD). Patients were allowed to have more than one episode of LRTI with at least three weeks and a symptom free interval in between each episode. ICPC-codes were used to select the episodes. The ICPC-criterion for pneumonia (R81) is evidence of pulmonary consolidation based on either physical examination or chest X-ray. The ICPC-criteria for acute bronchitis (R78) are coughing and fever with diffuse abnormalities on pulmonary examination like wheezing and crepitations. Since fever is often absent in elderly, we allowed for this criterion to be ignored. An exacerbation of COPD (R91, R95) was defined according to the Anthonisen criteria.[23] Criteria were met if 2 out of 3 of the following symptoms occurred: increased dyspnoea, sputum volume or sputum purulence. If 1 out of 3 symptoms was found, at least one of the following findings had to be present: upper respiratory infection (sore throat, nasal discharge) within the past 5 days, fever without other cause, increased wheezing, increased cough, or increase in respiratory rate or heart rate.[23]

Episodes from patients who were treated with antibiotics within the previous 3 weeks for another respiratory problem were excluded. Also episodes were excluded if at the moment of presentation the patient was known to have lung cancer, a haematological malignancy or an infection with the Human Immunodeficiency virus, used immunosuppressive medication (except oral glucocorticoids), or was hospitalised during the two weeks preceding the diagnosis.

The validation cohort included patients with episodes of acute bronchitis and pneumonia only. Unfortunately the database did not allow us to use the same inclusion criteria for selecting episodes of COPD exacerbations. Therefore we choose not to use these episodes for the external validation.

Selection of potential predictor variables

The selection of potential predictive variables routinely available in the GP medical records, was based on a review based on relevant literature pertaining to the prognosis of community-acquired LRTI.[7-16;18;20;24-26] We collected demographic data including age and gender, present use of medication, pre-existing potentially risk-elevating co-morbidity and health care use in the 12 months prior to consultation including previous hospitalisation and number of GP visits. Present use of medication was described as medication used at the day of the diagnosis and at least one week prior to this day, including oral glucocorticoids and benzodiazepines or antidepressants. Prior antibiotic use was present if the last tablet of a course was taken within the month prior to diagnosis. Co-morbidity was defined as the

presence of a co-morbid condition in the patient's history recorded according to the International Classification of Primary Care coding system. We recorded the presence of COPD or emphysema (R91, R95) or asthma (R96), malignancies (besides haematological malignancies and lung cancer, as they belong to the exclusion criteria), congestive heart failure (K77, K82), myocardial infarction (K75, K76), angina pectoris (K74), stroke (K90), dementia (P70), neurological diseases (N86, N87, N99), diseases of the kidney (U99) and liver (D72, D97) and diabetes (T90). The latter was indicated as present when oral diabetic medication or insulin was used.

Endpoint

The combined endpoint was defined as the occurrence of hospitalisation or death irrespective of the primary cause within 30 days after the day of diagnosis. This information was obtained from the patients' medical file. We repeated our analysis with the separate endpoint all-cause death to be able to compare our results with those of others.

Model development

Derivation of the prediction rule in the Utrecht patient cohort. All variables, except hospitalisation in the year preceding diagnosis, were classified as dichotomous variables. Hospitalisation was classified into three groups consisting of no hospitalisation, hospitalised once or more than once in the preceding year. Descriptive statistics as proportions and means (SD) using SPSS for Windows, version 12.1 (SPSS inc., Chicago, Illinois, USA) were calculated in those with or without the outcome. The absence of a characteristic in the medical database was assumed to indicate no presence of the characteristic under study for the presence of characteristics is assumed to be accurately documented in the Utrecht GP network.[27] In case of a missing numeric variable the median value based on non-missing episodes was entered. This method was applied in cases in which the number of hospital visits (n=12), general practitioner visits (n=6) or the history of diagnoses of pneumonia (n=6) in the previous year was missing on the research registration forms.

We used all episodes in the development phase of the model. Since most patients had more than one episode and within-person dependency could be present, data were analysed by means of multilevel logistic regression in MlwiN (Center for Multilevel Modelling, Bristol). The variables associated with the outcome in the multilevel univariable analysis at a p-level of 0.2 or lower were included in a multilevel multivariable logistic regression model. Factors that were associated at a p-level lower than 0.05 were included in the final model. Odds ratios [OR] and their corresponding 95% confidence intervals [95% CI] were calculated for each of the prognostic factors.

Internal validity. We internally cross-validated our model twice by a split-sampling model using 2/3 of the total derivation set. Factors were removed from the final model when the p-level was higher than 0.05 in the multivariable model of both split samples. The calibration of the final multivariable logistic regression model was determined by the Hosmer-Lemeshow goodness-of-fit statistic. The area under the receiver-operating curve (ROC) was used to assess the model's discriminative ability. The ROC gives the probability that high-risk patients can be distinguished from low-risk patients when the prediction rule is applied. An

area under the curve (AUC) estimate of 0.5 indicates no discrimination whereas an estimate of 1.0 indicates perfect discrimination.

In the final stage the regression coefficients of the derived multivariable model were used to construct the prediction rule. The predicted probability of outcome equals $1/1+e^{-LP}$ where the linear predictor is computed on the basis of the coefficients of the predictors. For practical interpretation we choose to divide all regression coefficients by the lowest (beta [heart failure]=0.364) and rounded them. We defined risk classes on the basis of the score into low-, medium- and high-risk groups.

External validation of the prediction rule in the National patient cohort. The National patient cohort was used to validate the prediction rule. The AUC of the model in this cohort was compared with the ROC of the model in the derivation cohort. Next, the National cohort was also divided into low-, medium- and high risk groups on the basis of the score and the incidence of outcomes and compared to the results of the derivation cohort.

RESULTS

In the derivation cohort we recorded 3,177 episodes of LRTIs in 1,698 elderly patients. We excluded episodes in which the diagnosis was set in hospital (n=4) or was missing on the registration form (n=1). We also excluded episodes of pleuritis (n=6). Thus we analysed 3,166 episodes of LRTIs in 1,693 elderly. Acute bronchitis was diagnosed in 1,120 episodes, 1,523 episodes were diagnosed as an exacerbation of COPD and pneumonia was diagnosed in 523 episodes. 30-day hospitalisation or death occurred in 274 (8.7%) of all episodes and 76 (2.4%) were fatal. In 72% of episodes the reason for hospitalisation or death was primarily LRTI-related and in 20% the cause was cardiovascular. In the remaining 8% there were other reasons, like gastroenteritis, for hospitalisation or death.
The mean age of the derivation cohort was 75.5 years and 45% had the male gender. One or more of the comorbid conditions were present in 85% and COPD, diabetes, heart failure and neurological disease were present in respectively 49%, 14%, 21% and 16%.

The validation cohort consisted of 2,465 episodes of LRTI, including 1,736 episodes of acute bronchitis and 729 of pneumonia. The combined endpoint occurred in 178 episodes (7.5%) and 59 (2.4%) patients died within 30 days.

Derivation of the prediction rule.
The following of the 20 potential predictors examined for an association with the endpoint were independently associated with hospitalisation or death in the multivariate analysis: increasing age, hospitalisation in 12 month prior to diagnosis, heart failure, use of insulin, use of oral glucocorticoids, use of antibiotics in the month prior to diagnosis, and type of diagnosis (table 1).

Table 1. Univariable and/or multivariable multilevel associations between characteristics and the endpoint 'hospitalisation or death within 30 days' in the total derivation set (n=3,166).

Characteristic	No hospitalisation or death (N=2,892)	Hospitalisation or death (N=274)	Univariable OR (95%CI)	Multivariable OR (95%CI)
Demographics				
Age ≥ 80 years	751 (26%)	109 (40%)	2.0 (1.5-2.8)	1.8 (1.3-2.4)
Male gender	1,287(45%)	147 (54%)	1.4 (1.0-1.9)	NS
Health care use[#]				
GP visit for pneumonia ≥1	114 (3.9)	26 (9.5)	1.7 (0.9-2.9)	NS
Hospitalisation ≥1	422 (15)	106 (39)	2.3 (1.6-3.2)	2.0 (1.4-2.8)
Hospitalisation ≥2	97 (3.4)	48 (18)	4.4 (2.7-7.0)	3.5 (2.1-5.7)
Co-morbidity				
COPD/emphysema/ asthma	1379 (48)	157 (57)	1.3 (1.0-1.8)	NS
Malignancies	399 (14)	43 (16)	1.2 (0.8-1.8)	NS
Diabetes[¶]	263 (9.1)	56 (20)	2.3 (1.5-3.4)	1.9 (1.3-2.8)
Congestive heart failure	572 (20)	102 (37)	2.3 (1.6-3.1)	1.4 (1.0-2.0)
Myocardial infarction	319 (11)	30 (11)	1.0 (0.6-1.6)	NS
Angina Pectoris	481 (17)	62 (23)	1.3 (0.9-1.9)	NS
Stroke	185 (6.4)	22 (8.0)	1.2 (0.7-2.1)	NS
Dementia	55 (1.9)	9 (3.3)	2.1 (0.9-4.7)	NS
Neurological disease	166 (5.7)	19 (6.9)	1.5 (0.9-4.7)	NS
Renal disease	74 (2.6)	12 (4.4)	1.7 (0.7-3.8)	NS
Liver disease	29 (1.0)	4 (1.5)	1.5 (0.4-5.2)	NS
Medication use[+]				
Oral glucocorticoids	109 (3.8)	46 (17)	3.7 (2.2-6.1)	2.6 (1.6-4.3)
Benzodiazepines or antidepressants	717 (25)	85 (31)	1.3 (0.9-1.7)	NS
Antibiotics < 1 month[§]	161 (5.6)	36 (13)	2.3 (1.4-3.5)	1.8 (1.2-2.9)
Diagnosis				
Acute bronchitis	1,079 (37)	41 (15)	reference	
Exacerbation COPD	1,389 (48)	134 (49)	2.4 (1.6-3.5)	1.9 (1.3-2.8)
Pneumonia	424 (15)	99 (36)	5.6 (3.7-8.4)	5.0 (3.3-7.5)

OR= odds ratio. CI= confidence interval. GP= general practitioner. COPD= chronic obstructive pulmonary disease. NS= NS not statistically significant (P>0.05). **#** Health care use was measured over the year preceding the diagnosis. **¶** Diabetes was registered as present if the patient used diabetic medication. **+** Maintenance medication had to be used for at least a week at the start of the episode. **§** In case of antibiotics, the last tablet had to be taken within the previous month.

A split-sample procedure with 2/3 of the total population showed the same results, except for the variable male gender. Male gender was not a significant predictor (p>0.05) in both split

samples and was therefore removed from the final model. All other variables showed similar results. A score was assigned to each predictor variable resulting in the final prediction model (table 2).

Table 2. Prediction rule for estimating the probability of 30-day hospitalisation or death from LRTI in elderly.

Characteristic	Regression coefficient (B)	Score
Diagnosis		
Acute bronchitis	0	
Exacerbation of COPD	0.643	2
Pneumonia	1.608	4
Age category		
65-79	0	
≥80	0.575	2
Congestive heart failure	0.364	1
Diabetes	0.629	2
Using oral glucocorticoids	0.966	3
Hospitalisation in prior year		
0	0	
1	0.676	2
≥2	1.239	3
Using antibiotics in previous month	0.615	2

The calibration of the model was good (Hosmer-Lemeshow goodness-of-fit test p=0.73) and the area under the receiver-operating curve (AUC) was 0.75 (95% confidence interval 0.72 to 0.78) indicating acceptable discriminating properties. When mortality was taken as the sole endpoint, the prediction rule had somewhat better discriminative power (AUC 0.76 with a 95% confidence interval of 0.74 to 0.83). Finally, patients were divided into risk classes according to their score. In the total group of patients with LRTI the risk of complications markedly increased with a higher score. Importantly, similar increases in risks with increasing scores were observed for the separate diagnostic categories of acute bronchitis, exacerbations of COPD and pneumonia. Patients designated to the low-risk class (score of 2 or lower) had a 97% chance of an uncomplicated course (sensitivity and specificity for a cut-off ≥3 points respectively 0.82 and 0.52). Patients with a score 3-6 had an average risk for complications of 9.2%; patients with a score of ≥7 had a strongly elevated risk of 31% for complications leading to hospitalisation or death (sensitivity 0.35, specificity 0.92). (table 3)

Table 3. 30-day hospitalisation or death for different risk classes in the derivation cohort for the total population and for the different diagnoses.

	Total derivation cohort N=3,166		**Acute bronchitis** N=1,120		**Exacerbation of COPD** N=1,523		**Pneumonia** N=523	
RISK CLASS	N	Hospital. or death %	N	Hospital. or death %	N	Hospital. or death %	N	Hospital. or death %
In all	**3,166**	**8.7**	**1,120**	**3.7**	**1,523**	**8.8**	**523**	**18.9**
Group 1 (score ≤2)	1,564	3.2	925	2.6	639	4.1	#	
Group 2 (score 3-6)	1,288	9.9	187	7.5	722	9.6	379	11.6
Group 3 (score ≥7)	314	30.9	8	37.5	162	24.1	144	38.2

A diagnosis of pneumonia gives 4 points, therefore there is no low risk-class.

External validation of the prediction rule

The National patient cohort in which the prediction rule was validated consisted of episodes of acute bronchitis and pneumonia only. The prediction rule showed acceptable discriminative performance in this cohort (AUC 0.74 with a 95% confidence interval (CI) of 0.71 to 0.78). The negative predictive value for a cut off score of 2 points or less was similar (97% in the National cohort and in the derivation cohort). The positive predictive value for a cut off score of 7 points or higher was still high, but somewhat less than observed in the derivation cohort (26% versus 31%). (table 4.)

Table 4. 30-day hospitalisation or death in different risk classes in the derivation- and validation-cohort.

	Derivation cohort N=3,166					Validation cohort N=2,465				
RISK CLASS*	N	Hosp. or death %	Mortality %	Sensi-tivity	Speci-ficity	N	Hosp. or death %	Mortality %	Sensi-tivity	Speci-ficity
In all	3,166	8.7	2.4			2,465	7.3	2.4		
Low risk	1,564	3.2	0.5	0.82#	0.52#	1,953	5.3	1.6	0.42#	0.81#
Medium risk	1,288	9.9	2.8			462	14.5	5.4		
High risk	314	30.9	10.5	0.35¶	0.92¶	50	22.0	6.0	0.06¶	0.98¶

Low risk = score ≤2; medium risk = score 3-6; high risk = score≥7. # Sensitivity and specificity were calculated for a cut-off of ≥3; ¶ Sensitivity and specificity were calculated for a cut-off of ≥7

DISCUSSION

We derived a prediction rule incorporating eight easily applicable items to estimate the probability of 30-day hospitalisation or death in elderly primary care patients with LRTI.

Strength and shortcomings

This study has several strengths. The prediction rule was not only developed but also validated in a large representative cohort and accuracy appeared good in both cohorts. Second, the prediction rule consists of only few variables that can be directly derived from the medical patient file without delay or costly examinations. Also, data for this study were derived from databases of high quality. The GPs participating in the networks have been using the *ICPC*-coding system for diagnoses for several years and received continuing medical education in applying the ICPC- and ATC-coding systems. Finally, statistical power is always an issue to precisely estimate the predictive value of potential risk factors. We included several thousands of episodes with 274 patients experiencing an outcome and according to the rule of thumb (1 predictor for 10 outcomes) we had adequate power.

A potential limitation of our study is the lack of radiographic evidence for pneumonia. Thus differentiation between pneumonia and acute bronchitis or an exacerbation of COPD is difficult. Therefore, it is possible that pneumonia is overestimated and, on the other hand, some cases of pneumonia might have been diagnosed as an acute bronchitis or an exacerbation of COPD. However, to ensure that our results would be applicable to GPs we decided to follow the same procedure as in routine primary care in which diagnostic tests are much less often applied and diagnosis is made in the majority of cases on the basis of medical history and physical examination only. The same diagnostic uncertainty is present regarding the diagnosis COPD. Although the general practitioners participating in this study were trained to diagnose COPD according to our guidelines in which spirometric results are necessary, it is unknown in what percentage of cases the diagnosis was made in concordance with the guidelines. Again we thought that it was essential to include patients in

which the diagnosis COPD was made according to daily routine so results could be generalised to the primary care setting.
Further, the retrospective design did not allow for the inclusion of data based on clinical examination and symptoms stated by patients. For instance guidelines for the management of pneumonia in the community of The British Thoracic Society are based on confusion, high respiratory rate, low blood pressure and high age (CRB-65 score).[3;28] These predictive variables are derived from a study where patients were included in a hospitalised setting.[16] In a primary care setting future prospective studies should look at possible improvement of our predictive model with such clinical data. Until then, we think that the results of our study can support the primary care physician in assessing severity of LRTI in elderly.
Some issues should be mentioned about the validation process. Data of the validation cohort were also retrospectively collected. Although a prospective cohort might have been better, this cohort was comparable in the methods of registration of diagnoses, treatment and outcome. Also, the derivation and validation cohort differed in some respects. The latter did not include COPD exacerbations for we were unable to apply the same criteria in selecting these episodes as in the derivation cohort. This resulted in fewer patients using oral glucocorticoids and fewer patients with heart failure in the validation cohort. Nevertheless the sample size was adequate to show an almost similar discriminative ability of the prediction rule.

Comparison with other studies
Some of the predictor variables were confirmed by other studies. Age is a well-known risk factor,[7;12;14;16;25;29;30] although there are several studies claiming differently.[9;13;15;18;20;24;26] The age-related waning of immunological functions and the presence of co-morbidities due to age-associated diseases largely explain complications in the very old.[31] Therefore, if all co-morbid conditions were taken into account, age would most probable show a less strong association with a poor outcome. Another reason for not finding age as a predictor in other studies is the low number of elderly included in most other studies.

In accordance with Fine et al.[12] and comparable to our previous study,[25] we found an association between a complicated course and heart failure. Although it is sometimes difficult to differentiate between heart failure and LRTI, it is likely that both illnesses can influence each other. For example, it is known that respiratory tract infections can cause aggravation of heart failure leading to hospitalisation or death.[32] Also studies have shown a preventive effect of influenza vaccination for heart failure indicating the interaction between LRTI and heart failure.[33;34]

It was already shown that diabetes is related to an increased risk for getting infections.[35] We have shown, similar to other studies,[36;37] that having diabetes also worsens the prognosis of a LRTI.

The use of oral glucocorticoids was indicative for the outcome as well. Oral glucocorticoids can mask symptoms of infection and can cause deterioration of an infection and therefore increase the risk on a complicated course. On the other hand patients with severe COPD

most likely will already use oral glucocorticoids in advance. Consequently, use of oral glucocorticoids most likely acts as a marker for severe COPD and naturally patients with severe COPD have a worse prognosis.
Antibiotics used in the previous month also appeared predictive for poor outcome. This predictor has been found before by Houston et al[26] and is probably indicative for a pre-existent poor health status, like previous hospitalisation

In conclusion, this prediction rule can help GPs to distinguish elderly patients with LRTI with high and low risk of severe complications leading to hospitalisation or death. A more accurate prediction of the expected course of infection can help the general practitioner to better target preventive and therapeutic management.

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Reference List

1. M.W.van der Linden, G.P.Westert, D.H.de Bakker, and F.G.Schellevis. Second Dutch national survey. 2004. Utrecht/Bilthoven, NIVEL/RIVM, 2004.
Ref Type: Generic
2. Hak E, Rovers MM, Kuyvenhoven, M. M., Schellevis FG, and Verheij ThJM. Incidence of GP-diagnosed respiratory tract infections according to age, gender and high-risk co-morbidity: the Second Dutch National Survey of General Practice. Fam.Pract. 2006.
Ref Type: In Press
3. BTS Guidelines for the Management of Community Acquired Pneumonia in Adults. *Thorax.* 2001;56 Suppl 4:IV1-64.:IV1-64.
4. Mandell LA, Bartlett JG, Dowell SF, File TM, Jr., Musher DM, Whitney C. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. *Clin.Infect.Dis.* 2003;37:1405-33.
5. Niederman MS, Mandell LA, Anzueto A, Bass JB, Broughton WA, Campbell GD *et al.* Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. *Am.J.Respir.Crit Care Med.* 2001;163:1730-54.
6. Woodhead M, Blasi F, Ewig S, Huchon G, Ieven M, Ortqvist A *et al.* Guidelines for the management of adult lower respiratory tract infections. *Eur.Respir.J.* 2005;26:1138-80.
7. Conte HA, Chen YT, Mehal W, Scinto JD, Quagliarello VJ. A prognostic rule for elderly patients admitted with community-acquired pneumonia. *Am.J.Med.* 1999;106:20-8.
8. Ewig S, Bauer T, Hasper E, Pizzulli L, Kubini R, Luderitz B. Prognostic analysis and predictive rule for outcome of hospital-treated community-acquired pneumonia. *Eur.Respir.J.* 1995;8:392-7.
9. Farr BM, Sloman AJ, Fisch MJ. Predicting death in patients hospitalized for community-acquired pneumonia. *Ann.Intern.Med.* 1991;115:428-36.
10. Farr BM, Bartlett CL, Wadsworth J, Miller DL. Risk factors for community-acquired pneumonia diagnosed upon hospital admission. British Thoracic Society Pneumonia Study Group. *Respir.Med.* 2000;94:954-63.

11. Fine MJ, Orloff JJ, Arisumi D, Fang GD, Arena VC, Hanusa BH *et al.* Prognosis of patients hospitalized with community-acquired pneumonia. *Am.J.Med.* 1990;88:1N-8N.
12. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE *et al.* A prediction rule to identify low-risk patients with community-acquired pneumonia. *N.Engl.J.Med.* 1997;336:243-50.
13. Garcia-Ordonez MA, Garcia-Jimenez JM, Paez F, Alvarez F, Poyato B, Franquelo M *et al.* Clinical aspects and prognostic factors in elderly patients hospitalised for community-acquired pneumonia. *Eur.J.Clin.Microbiol.Infect.Dis.* 2001;20:14-9.
14. Hak E, Wei F, Nordin J, Mullooly J, Poblete S, Nichol KL. Development and validation of a clinical prediction rule for hospitalization due to pneumonia or influenza or death during influenza epidemics among community-dwelling elderly persons. *J.Infect.Dis.* 2004;189:450-8.
15. Lim WS,.Macfarlane JT. Defining prognostic factors in the elderly with community acquired pneumonia: a case controlled study of patients aged > or = 75 yrs. *Eur.Respir.J.* 2001;17:200-5.
16. Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI *et al.* Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax* 2003;58:377-82.
17. Myint PK, Kamath AV, Vowler SL, Maisey DN, Harrison BD. The CURB (confusion, urea, respiratory rate and blood pressure) criteria in community-acquired pneumonia (CAP) in hospitalised elderly patients aged 65 years and over: a prospective observational cohort study. *Age Ageing* 2005;34:75-7.
18. Riquelme R, Torres A, El Ebiary M, de la Bellacasa JP, Estruch R, Mensa J *et al.* Community-acquired pneumonia in the elderly: A multivariate analysis of risk and prognostic factors. *Am.J.Respir.Crit Care Med.* 1996;154:1450-5.
19. Farr BM, Woodhead MA, Macfarlane JT, Bartlett CL, McCraken JS, Wadsworth J *et al.* Risk factors for community-acquired pneumonia diagnosed by general practitioners in the community. *Respir.Med.* 2000;94:422-7.
20. Seppa Y, Bloigu A, Honkanen PO, Miettinen L, Syrjala H. Severity assessment of lower respiratory tract infection in elderly patients in primary care. *Arch.Intern.Med.* 2001;161:2709-13.
21. Westert GP, Schellevis FG, de Bakker DH, Groenewegen PP, Bensing JM, van der ZJ. Monitoring health inequalities through general practice: the Second Dutch National Survey of General Practice. *Eur.J.Public Health* 2005;15:59-65.
22. Westert GP, Schellevis FG, de Bakker DH, Groenewegen PP, Bensing JM, van der ZJ. Monitoring health inequalities through general practice: the Second Dutch National Survey of General Practice. *Eur.J.Public Health* 2005;15:59-65.
23. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann.Intern.Med.* 1987;106:196-204.
24. Dewan NA, Rafique S, Kanwar B, Satpathy H, Ryschon K, Tillotson GS *et al.* Acute exacerbation of COPD: factors associated with poor treatment outcome. *Chest* 2000;117:662-71.
25. Hak E, Bont J, Hoes AW, Verheij TJ. Prognostic factors for serious morbidity and mortality from community-acquired lower respiratory tract infections among the elderly in primary care. *Fam.Pract.* 2005;22:375-80.
26. Houston MS, Silverstein MD, Suman VJ. Risk factors for 30-day mortality in elderly patients with lower respiratory tract infection. Community-based study. *Arch.Intern.Med.* 1997;157:2190-5.
27. Hak E, Hoes AW, Grobbee DE, Lammers JW, van Essen GA, van Loon AM *et al.* Conventional influenza vaccination is not associated with complications in working-age patients with asthma or chronic obstructive pulmonary disease. *Am.J.Epidemiol.* 2003;157:692-700.
28. Macfarlane JT,.Boldy D. 2004 update of BTS pneumonia guidelines: what's new? *Thorax.* 2004;59:364-6.
29. Koivula I, Sten M, Makela PH. Risk factors for pneumonia in the elderly. *Am.J.Med.* 1994;96:313-20.
30. Mortensen EM, Coley CM, Singer DE, Marrie TJ, Obrosky DS, Kapoor WN *et al.* Causes of death for patients with community-acquired pneumonia: results from the Pneumonia Patient Outcomes Research Team cohort study. *Arch.Intern.Med.* 2002;162:1059-64.

31. Janssens JP,.Krause KH. Pneumonia in the very old. *Lancet Infect.Dis.* 2004;4:112-24.
32. Khand AU, Gemmell I, Rankin AC, Cleland JG. Clinical events leading to the progression of heart failure: insights from a national database of hospital discharges. *Eur.Heart J.* 2001;22:153-64.
33. Andrawes WF, Bussy C, Belmin J. Prevention of cardiovascular events in elderly people. *Drugs Aging* 2005;22:859-76.
34. Hak E, Buskens E, van Essen GA, de Bakker DH, Grobbee DE, Tacken MA *et al*. Clinical effectiveness of influenza vaccination in persons younger than 65 years with high-risk medical conditions: the PRISMA study. *Arch.Intern.Med.* 2005;165:274-80.
35. Muller LM, Gorter KJ, Hak E, Goudzwaard WL, Schellevis FG, Hoepelman AI *et al*. Increased risk of common infections in patients with type 1 and type 2 diabetes mellitus. *Clin.Infect.Dis.* 2005;41:281-8.
36. Falguera M, Pifarre R, Martin A, Sheikh A, Moreno A. Etiology and outcome of community-acquired pneumonia in patients with diabetes mellitus. *Chest* 2005;128:3233-9.
37. Tierney EF, Geiss LS, Engelgau MM, Thompson TJ, Schaubert D, Shireley LA *et al*. Population-based estimates of mortality associated with diabetes: use of a death certificate check box in North Dakota. *Am.J.Public Health* 2001;91:84-92.

Chapter 3.3

Prognosis of LRTI in elderly primary care patients; prospective validation and optimisation of a prediction rule.

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Submitted.

ABSTRACT

Objectives. Most available prognostic models for lower respiratory tract infections (LRTI) are derived in hospital settings and restricted to patients with pneumonia. We set out to validate and optimise a simple prediction rule for hospitalisation or death in elderly with acute LRTI in the community.
Design. Prospective cohort study in which a retrospectively derived prediction rule based on demographics and medical history was validated and optimised with data on signs and symptoms by means of multivariable regression analysis.
Setting. 142 general practices in The Netherlands.
Participants. 1,158 episodes in 1,099 patients aged 65 years or older visiting the general practitioner with LRTI.
Main outcome measures. 30-day hospitalisation or death.
Results. 110 patients (9.5%) had the combined outcome and 14 patients (1.2%) died. The discriminative value of the retrospective prediction rule was 0.73 (95% CI 0.69 to 0.78). Addition of signs and symptoms including general malaise, absence of increasing cough, absence of signs of upper respiratory tract infection, diminished consciousness, temperature of ≥38° Celsius and a pulse rate of ≥100 bpm further improved the discriminative capacity (AUC 0.81, 95% CI 0.77-0.85). The clinical prediction rule identified 55% of the total population as low-risk (rate of 30-day hospitalisation or death <3%) compared to 38% with the retrospective rule. Both rules selected a similar proportion of high-risk patients (13 and 16%, respectively), yet the positive predictive value was higher with the clinical prediction rule (33% versus 22%).
Conclusions. A clinical prediction rule including signs and symptoms can help the physician to accurately estimate the prognosis in elderly patients with LRTI in the community.

INTRODUCTION

Lower Respiratory Tract Infections (LRTI) in elderly are a major concern in terms of burden of illness and high costs. In elderly the incidence is high and more patients have a complicated course. Estimating prognosis is crucial in the assessment and management of these patients; guiding therapeutic decisions such as antibiotic use, direct need for hospitalisation or a wait-and-see policy. As a result many prognostic models have been developed and validated in adults with LRTI, but their usefulness for elderly patients in primary care is limited. The majority was derived and validated in hospitalised populations, include only a small proportion of elderly and focus solely on community acquired pneumonia (CAP). Moreover, the outcome was restricted to mortality, while also other outcomes, such as hospitalisations are of interest.[1-9] Two well-known severity assessment tools that estimate mortality risk in patients with CAP are the Pneumonia Severity Index (PSI) and the CRB-65 prediction rule.[7;9] Since pulmonary radiography is not routinely performed in primary care and differential diagnosis of LRTI and CAP may not be accurate, these rules are of limited use. In an earlier study, we therefore derived and validated a prediction rule with data readily available to the primary care physician to estimate the risk of 30-day hospitalisation or death in patients with LRTI.[10] (Figure 1) The aim of the current study was to optimise this retrospective rule with the inclusion of clinical information on signs and symptoms.

METHODS

Setting and patient selection

Between November 2005 and May 2006 191 Dutch GPs prospectively identified patients with LRTI aged 65 years or older, including acute bronchitis, exacerbations of chronic obstructive pulmonary disease (ECOPD) or CAP. The inclusion criterion for acute bronchitis, defined by the International Classification of Primary Care (ICPC)-codes[11;12] (R78), was coughing with diffuse abnormalities on pulmonary examination, like wheezing and crackles. Fever was not obligatory since elderly do not always present themselves with fever. In absence of ICPC-criteria, ECOPD was defined according to the Anthonisen-criteria[13]. Patients known with pre-existent COPD were included if 2 out of 3 of the following symptoms occurred: increased dyspnoea, sputum volume or – purulence. If only one of these symptoms was present, the patient had to have one of the following signs or symptoms: prior signs of an upper respiratory tract infection (sore throat or nasal discharge), fever, new or increased wheezing or cough or increased respiratory - or heart rate. CAP (ICPC code: R81) was diagnosed when localising signs were present on chest examination, and/or new infiltrates on a chest X-ray or when the GP had a strong suspicion of CAP due to severe dyspnoea in a very ill patient, even in the absence of chest signs. This third criterion was chosen, because it equates to usual practice in daily primary care, thus ensuring generalisibility of study results.

Patients were not included in the study if they were known to have lung cancer, a haematological malignancy or an infection with the Human Immunodeficiency Virus, used immunosuppressive medication (except oral glucocorticoids), had been hospitalised during the two weeks preceding the diagnosis or were nursing home residents.

Figure 1. Retrospective prediction rule for estimating the probability of 30-day hospitalisation or death from Lower Respiratory Tract Infections in elderly primary care patients, based on a previous study by Bont et al, 2006. (N=3,166)[10]

Characteristic	Score assigned
Diagnosis	
Exacerbation of COPD	2
Pneumonia	4
Age (years)	
≥80	2
Medical history	
Heart failure	1
Diabetes	2
Hospitalisation: once	2
twice or more	3
Medication	
Taking oral glucocorticoids at time of diagnosis	3
Taking antibiotics in previous month	2

	Low risk	Medium risk	High risk
Sum of scores	≤2	3-6	≥7
Patients within risk class N (%)	1,564 (49)	1,288 (41)	314 (10)
Risk of 30-day hospitalisation or death %	3%	10%	31%
Risk of 30-day mortality	0.5%	3%	11%
Treatment options	Likely suitable for home treatment	Need for close monitoring either at home or in hospital	

Data collection

The participating GPs collected data on patient's history, medication use, signs and symptoms during the consultancy using a standard questionnaire. Data on all items included in the retrospective prediction rule (figure 1) were collected. For the optimisation process the GPs were asked to document as set of predefined signs and symptoms (table 1). The primary endpoint was defined as hospitalisation or death from all causes within 30 days. If the endpoint occurred, the GP recorded date and cause of hospitalisation or death. We used 30-day mortality alone as the secondary outcome to compare our results with other studies.

Statistical aspects

Validation of the retrospective prediction rule. The formula of the retrospective prediction rule (PR_retrospective) was the following:

PR_ retrospective = 2[ECOPD] + 4*[CAP] + 2*[age≥80yrs] + 1*[congestive heart failure] + 2*[diabetes] + 3*[oral glucocorticoids maintenance therapy] + 2*[antibiotics in previous month] + 2*[hospitalised once in previous year] + 3*[hospitalised more than once in previous year]*

Positive (PPV) and negative predictive values (NPV), sensitivity and specificity of the retrospective prediction rule were calculated for relevant cut-off scores in the new dataset. Next, the area under the receiver-operating curve (AUC) was calculated for the combined outcome 30-day hospitalisation or mortality, as a measure for the model's discriminative ability. The AUC gives the probability that high-risk patients can be distinguished from low-risk patients when the prediction rule is applied. An AUC estimate of 0.5 indicates no discrimination whereas an estimate of 1.0 indicates perfect discrimination. The AUC was also calculated for 30-day mortality alone. In the final step of validation, the combined outcome was determined for different risk score cut-off point, in accordance with the derivation study.

Optimisation of the retrospective prediction rule. According to the rule of thumb one variable per ten outcomes should be included to have adequate statistical power to fit the model.[14;15] A priori we aimed to analyse eleven variables in addition to the retrospective prediction rule and therefore 110 to 120 outcomes were needed. A simple updating method was chosen in which the regression coefficients of the retrospective prediction rule were maintained to prevent over fitting of the model.[16;17] The retrospective prediction rule score (PR_ retrospective) was used as a single continuous variable. With a stepwise forward regression analysis signs & symptom items with a p-value lower than 0.05 were entered into the model resulting in a new formula of the clinical prediction rule (PR_clinical):

$PR\_clinical = B_{PR\_retrospective} * PR\_clinical + B_1 * X_1 + B_2 * X_2 + B_3 * X_3 + B_4 * X_4 + B_5 * X_5$ *, in which X is a new variable and B the corresponding regression coefficient.*

Next, the linear predictor of PR_clinical ($B_{PR\_retrospective}$) was used to shrink the betas of the predictors of the retrospective prediction rule. In the final stage we choose to divide all regression coefficients by the lowest and rounded them. Again, the AUC was calculated for the combined outcome and 30-day mortality alone. Cut-off scores were determined based on the same risk classification used in the retrospective derivation study, that is a probability of 30-day hospitalisation or death of <3% for the low-risk group and >30% for the high-risk group. (figure 1). Finally, PPV, NPV, sensitivity and specificity were calculated for cut-off scores. All analyses were performed with the use of SPSS Version 12.1 for Windows, Chicago, USA.

RESULTS

Patients' characteristics

The study population consisted of 1,159 episodes of LRTI in 1,099 elderly patients (mean age 76.3 years). Acute bronchitis occurred in 36%, ECOPD in 37% and CAP in 27%. One patient, seen during the out-of-hours service, was lost to follow up and further excluded from the analysis. In 110 of 1,158 episodes (9.5%) the patient was hospitalised or died within 30 days after the initial diagnosis. Table 1 shows the characteristics of the derivation and validation cohort. In the validation cohort slightly more patients had co-morbid conditions (73% versus 68%) and the incidence of CAP was higher (27% versus 17%). The occurrence of the combined outcome was similar in both cohorts.

Accuracy of the retrospective prediction rule

The AUC of the retrospective rule for the combined outcome was 0.73 (95% CI 0.69 to 0.78) in the validation cohort, while the AUC in the derivation cohort was 0.75 (95% CI 0.72 to 0.78). For mortality as the single outcome measure the discriminative values were higher: AUC of 0.82 (95% CI 0.70 to 0.94) and 0.79 (95% CI 0.74 to 0.83), respectively.

The predictive values of the retrospective prediction rule for cut-off scores of ≤2 and ≥7 in the validation and derivation cohort are shown in table 2. The sensitivity for detecting the outcome with a cut-off of >3 was 88% in the validation and 82% in the derivation cohort, while the corresponding specificities for detecting those without the outcome were 41% and 54%, respectively. For a cut-off of ≥7 the sensitivity was also slightly higher in the validation cohort (36% and 34%, respectively) and the specificity was lower (86% and 92%, respectively). The positive predictive value of this cut-off was lower in the validation cohort (22% versus 31%).

Table 1. Demographic and clinical characteristics of the patients in the derivation and validation cohort.

Characteristic	Derivation cohort N=3,166 N (%)	Validation cohort N=1,158 N (%)
Demographic factor		
Mean age (SD)	75.5 (7.3)	76.3 (7.3)
Male sex	1434 (45)	502 (43)
Coexisting conditions		
Any of the following high risk comorbid conditions	2137 (68)	843 (73)
COPD, asthma or emphysema	1536 (49)	641 (55)
Congestive heart failure	674 (21)	237 (21)
Diabetes Mellitus	319 (10)	198 (17)
Stroke	207 (7)	98 (8)
Neoplastic Disease	442 (14)	100 (9)
Medication use		
Oral corticosteroid maintenance therapy	155 (5)	86 (7)
Antibiotic use in previous month	197 (6)	100 (9)
Hospitalisation in previous year		
Once	528 (17)	187 (16)
Twice or more	145 (5)	48 (4)
Smoking behaviour*		
Smoking > 10 cigarettes per day	-	104 (9)
Signs*		
General malaise	-	841 (73)
Absence of prior signs of URTI	-	337 (29)
Absence of new or increasing cough	-	38 (3)
New or increasing sputum production	-	904 (78)
New or increasing purulence of sputum	-	506 (44)
Physical examination*		
Diminished level of consciousness	-	15 (1)
Disorientation in time and space	-	34 (3)
Temperature > 38° Celsius	-	186 (16)
Pulse ≥100 per minute	-	117 (10)
Systolic <90 or diastolic blood pressure <60 mm Hg	-	97 (8)
Respiratory rate ≥30 per minute	-	128 (11)
Initial diagnosis		
Acute bronchitis	1,120 (35)	415 (36)
Exacerbation of COPD	1,523 (48)	429 (37)
Pneumonia	523 (17)	314 (27)
Antibiotic treatment	2171 (69%)	890 (77%)
Outcome		
Hospitalisation or death ≤ 30 days	274 (9)	110 (9)
Mortality ≤ 30 days	76 (2)	14 (1)

The shaded data were used in the logistic regression analysis of the clinical prediction rule
*Data on smoking behaviour, signs and symptoms were not available in the derivation cohort.

Table 2. Measures of performance of the retrospective prediction rule and the clinical prediction rule in predicting 30-day hospitalisation or death in the derivation and validation cohort.

Retrospective prediction rule	**Proportion of the population N (%)**	**Sensitivity (score≥3) %**	**Specificity (score≥3) %**	**PPV (score≥3) %**	**NPV (score≥3) %**
Low risk (score ≤2)					
Retrospective derivation cohort (N=3,166)	1,564 (49)	82	54	14	97
Prospective validation cohort (N= 1,158)	441 (38)	88	41	14	97
		Sensitivity %	**Specificity %**	**PPV %**	**NPV %**
High risk (score ≥7)					
Retrospective derivation cohort (N= 3,166)	314 (10)	34	92	31	94
Prospective validation cohort (N= 1,158)	186 (16)	36	86	22	93
Clinical prediction rule	**Proportion of the population N (%)**	**Sensitivity (score ≥9) %**	**Specificity (score ≥9) %**	**PPV (score ≥9) %**	**NPV (score ≥9) %**
Low risk (score ≤8)					
Prospective derivation cohort (N= 1,158)	631 (54)	86	59	18	98
		Sensitivity %	**Specificity %**	**PPV %**	**NPV %**
High risk (score ≥14)					
Prospective derivation cohort (N= 1,158)	155 (13)	46	90	33	94

In both study cohorts a similar trend was found in the associations under study, that is a low score (calculated with the retrospective rule) was associated with a low risk and a higher score with a higher risk. (table 3) In the validation cohort 38% of the population had a score of ≤2 and could be considered as low risk patients, while in the derivation cohort 49% was identified as low risk. For high-risk patients (score ≥7) these percentages were 16% and 10%, respectively.

Table 3. Probability of '30-day hospitalisation or death' and '30-day mortality' according to the retrospective prediction rule in the derivation – and validation cohort.

		Overall risk N (%)	**Low risk (score ≤2) N (%)**	**Medium risk (score 3-6) N (%)**	**High risk (score ≥7) N (%)**
Derivation cohort N= 3,166	No. of episodes N (%)	3,166 (100)	1,564 (49)	1,288 (41)	314 (10)
	Combined outcome N (%)	274 (9)	50 (3)	127 (10)	97 (31)
	Mortality N (%)	76 (2)	8 (0.5)	36 (3)	32 (10)
Validation cohort N=1,158	No. of episodes N (%)	1,158 (100)	441 (38)	531 (46)	186 (16)
	Combined outcome N (%)	110 (9)	13 (3)	57 (11)	40 (22)
	Mortality N (%)	14 (1)	1 (0.2)	6 (1)	7 (4)

Score = based on retrospective prediction rule (figure 1); Combined outcome = 30-day hospitalisation or death

Optimisation of the prediction rule

In the clinical prediction rule the following variables were independently and statistically significantly associated with the outcome in addition to the retrospective prediction rule: general malaise, absence of increasing cough, absence of signs of upper respiratory tract infection, diminished consciousness, temperature of ≥38° Celsius and a pulse rate of ≥100 bpm. (table 4)

Table 4. Association between clinical characteristics and 30-day hospitalisation or death in addition to the retrospective prediction rule.

Characteristic	With outcome* N=110 (%)	Without outcome* N=1,048 (%)	Multivariate OR (95% CI)
Original prediction rule (mean score)**	5.9	3.7	2.0 (1.6-2.4)
Signs			
General malaise	97 (88)	744 (71)	2.4 (1.3-4.5)
Absence of signs of URTI in past two weeks	56 (51)	281 (27)	2.2 (1.4-3.4)
Absence of new or increasing cough	10 (9)	28 (3)	3.0 (1.3-6.7)
New or increasing sputum production	80 (73)	824 (79)	NS
New or increasing purulence of sputum	49 (45)	457 (44)	NS
Physical examination			
Disorientation in time and space	12 (11)	22 (2)	NS
Diminished level of consciousness	9 (8)	6 (0.6)	6.9 (2.0-23.8)
Temperature >38 °Celsius	36 (33)	150 (14)	1.7 (1.03-2.8)
Pulse rate ≥100 bpm	28 (26)	89 (8)	2.1 (1.2-3.7)
Systolic <90 or diastolic blood pressure ≤60 mm Hg	19 (17)	78 (7)	NS
Respiratory rate ≥30 per minute	30 (27)	98 (9)	NS

*Outcome= 30 day hospitalisation or death;
**The retrospective prediction rule is explained in the method section;
OR= odds ratio; CI= confidence interval; NA= not assessed; NS= not significant (p>0.05); bpm= beats per minute;

A low score (≤8) was assigned to 55% of the patients and the outcome occurred in 2%. 13% of the patients had a high score (≥14) with the outcome occurring in 33%.

The most important differences with the retrospective prediction rule were seen in the larger proportion of patients selected as low-risk (55% vs 38%) and the increase in observed outcomes in the high-risk class (33% vs 22%). Also the discriminative value of the clinical prediction rule was higher for the combined outcome (AUC 0.81 [95% CI 0.77-0.85] versus 0.73 [95% CI 0.69-0.78]) and for 30-day mortality alone (AUC 0.87 [95% CI 0.76-0.99] versus 0.82 [95% CI 0.70-0.94]). The optimised clinical prediction rule is presented in figure 2.

Figure 2. Clinical prediction rule for estimating the probability of 30-day hospitalisation or death from Lower Respiratory Tract Infections in elderly primary care patients.

Characteristic	Score assigned
Variables of the retrospective prediction rule	
Diagnosis	
Exacerbation of COPD	2
Pneumonia	4
Age (years)	
≥80	2
Medical history	
Heart failure	1
Diabetes	2
Hospitalisation: once	2
twice or more	3
Medication	
Taking oral glucocorticoids at time of diagnosis	3
Taking antibiotics in previous month	2
Additional variables used in the clinical prediction rule	
Signs	
General malaise	4
Absence of prior signs of upper respiratory tract infection	3
Absence of new or increasing cough	4
Physical examination	
Diminished level of consciousness	8
Temperature >38 °Celsius	2
Pulse rate ≥100 beats per minute	3

	Low risk	Medium risk	High risk
Sum of scores	≤8	9-13	≥14
Patients within risk class N (%)	631 (55)	372 (32)	155 (13)
Patients with 30-day hospitalisation or death N (%)	15 (2)	44 (12)	51 (33)
Patients with 30-day mortality N (%)	1 (0.2)	3 (0.8)	10 (6.5)
Treatment options	Likely suitable for home treatment	Need for close monitoring either at home or in hospital	

DISCUSSION

Instead of predicting mortality in patients with CAP as most studies have focussed on so far,[1-9] we validated and optimised a severity assessment tool to predict 30-day hospitalisation or death in patients with LRTI, namely acute bronchitis, ECOPD and CAP, in the community, therefore being more applicable to a primary care population. The original retrospective prediction rule (targeted at the same patient domain) was based on demographics and medical history[10] only. Prospective validation revealed moderate discriminative capacity. Optimisation of the retrospective prediction rule with the inclusion of a limited set of signs and symptoms clearly improved the accuracy of the rule. The most important differences with the retrospective prediction rule were seen in the selection of a larger proportion of low risk patients without losing precision and an increase in observed outcomes in the high-risk class.

Strengths and weaknesses of the study

A major strength of the current study is the validation of the retrospective prediction rule in a prospective design. Although there were differences in the presence of co-morbid conditions and the proportion of patients with acute bronchitis and pneumonia between the derivation and validation cohort, the performance of the retrospective prediction rule was comparable. We can therefore assume that the retrospective prediction rule is stable and will also be applicable to other elderly patients in the community.

A simple method was chosen to optimise the retrospective prediction rule. In the optimisation process the regression coefficients of the variables of the retrospective prediction rule were left unchanged and new variables were analysed in addition to the retrospective prediction rule. This method of optimisation, instead of developing a completely new prediction rule, will lead to more stability with less overfitting.[16;17] In spite of this, the clinical prediction rule was more accurate in selecting low- and high-risk patients and over fitment should be considered, as new variables were analysed in a new cohort. However, a more probable reason for improvement is the higher prognostic value of the clinical data added to the model. For example, tachycardia and fever are strong predictors for a poor prognosis as has been demonstrated before by different studies.[7;18] Although the clinical prediction rule is likely to be stable and generalisable to other populations, external validation of the clinical prediction rule will be needed.

One might argue that a lack of radiographic evidence for CAP makes it impossible to compare our data with those from other studies. However, we believe that our findings are more useful to the general practitioner as it follows routine GP practice.

Antibiotic treatment was not included in the regression analysis as a decision whether or not to prescribe will be taken *after* the prognosis has been estimated. Even so, the performance of the rule appeared similar in antibiotics treated and non-treated patients (data on file).

Using hospitalisation as an outcome could be seen as a shortcoming. After all , the physician decides whether or not the patient should be referred based on the available data.

Therefore, even when referral is not necessary an association might be found between the data and the outcome. To deal with this, only hospitalisation was regarded as an outcome if hospital stay was at least one night. More importantly, in an additional analysis mortality was used as the only outcome to deal with this possible bias. This resulted in better discrimination between low- and high-risk patients.

Comparison with other studies

The BTS-guidelines use the CRB-65 score (confusion, high respiratory rate, low blood pressure and age ≥65 years),[9;19;20] to predict mortality in patients with CAP. Recently, we have shown that the prediction rule is reliable in predicting mortality in a primary care population.[manuscript submitted and available on request] However, mortality is rare in primary care patients and knowing the probability of non-fatal severe outcomes is important in taking management decisions. Unfortunately, validation of the CRB-65 score showed less discriminative power in predicting the combined outcome, 30-day hospitalisation or death, in both patients with CAP and in the total cohort of LRTI (AUC's 0.65 and 0.63 respectively, data available on request). In fact in this prospective cohort, CRB-65 features were not independently associated with the outcome. Moreover, other variables such as diminished level of consciousness, fever and tachycardia seemed of more importance. Although our clinical prediction rule discriminated better for mortality than the CRB-65 score, results should be taken with some consideration for mortality is rare and the prediction rule has not been validated in another primary care population. On the other hand, our study is not the first showing that confusion,[5;21;22] low blood pressure,[21;22] and high respiratory rate are not independent prognostic features.[5;23] Also, we found general malaise, absence of cough and prior signs of upper respiratory tract infection to be independent prognostic features. The characteristics could well be related to viral infections. We found no other studies that assessed the prognostic value of these characteristics.

Applicability and reliability of the prediction rules

The retrospective prediction rule consists of 7 easily obtainable variables all known by the physician at the time the patient is seen, thus facilitating its applicability in daily practice. Although sensitivity of a high score (high risk) and specificity of a low score (low risk) are not very high, the retrospective prediction is still useful in selecting low risk patients. It safely selects low risk patients with in fact only 3% events occurring. This prediction rule, being validated twice in an external cohort, is reliable and could therefore be used in daily practice. As it only contains data that are available on forehand, it could be used by, for example, practice assistants who carry out the first triage of a patient. On the other hand, the clinical prediction rule seems to perform more accurate. More variables are necessary (14), but the treating physician knows them all as they are part of routine examinations. This clinical rule is able to select a higher proportion of low risk patients with fewer events occurring (2%) and the high-risk group contains less false positives. Also a physician is more inclined to work with the clinical rule as it contains signs and symptoms that instinctively will always be used as part of the process of estimating diagnosis and prognosis. Therefore the clinical rule is superior, yet naturally has to be validated as well.

In conclusion, elderly patients with LRTI in the community can be easily stratified into different risk groups with the use of simple prediction rules. Triaging staff could use the retrospective prediction rule to select low risk patients and physicians could use the clinical prediction rule that includes also signs and symptoms. Low-risk patients may be managed in primary care as usual while higher risk patients should be monitored more closely and timely referred to hospital. Future studies should demonstrate whether these implications will lead to fewer complications and lower costs.

Reference List

1. Aujesky D, Auble TE, Yealy DM, Stone RA, Obrosky DS, Meehan TP *et al.* Prospective comparison of three validated prediction rules for prognosis in community-acquired pneumonia. *Am.J.Med.* 2005;118:384-92.
2. Bauer TT, Ewig S, Marre R, Suttorp N, Welte T. CRB-65 predicts death from community-acquired pneumonia. *J.Intern.Med.* 2006;260:93-101.
3. Buising KL, Thursky KA, Black JF, MacGregor L, Street AC, Kennedy MP *et al.* A prospective comparison of severity scores for identifying patients with severe community acquired pneumonia: reconsidering what is meant by severe pneumonia. *Thorax* 2006;61:419-24.
4. Capelastegui A, Espana PP, Quintana JM, Areitio I, Gorordo I, Egurrola M *et al.* Validation of a predictive rule for the management of community-acquired pneumonia. *Eur.Respir.J.* 2006;27:151-7.
5. Conte HA, Chen YT, Mehal W, Scinto JD, Quagliarello VJ. A prognostic rule for elderly patients admitted with community-acquired pneumonia. *Am.J.Med.* 1999;106:20-8.
6. Ewig S, de Roux A, Bauer T, Garcia E, Mensa J, Niederman M *et al.* Validation of predictive rules and indices of severity for community acquired pneumonia. *Thorax.* 2004;59:421-7.
7. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE *et al.* A prediction rule to identify low-risk patients with community-acquired pneumonia. *N.Engl.J.Med.* 1997;336:243-50.
8. Houston MS, Silverstein MD, Suman VJ. Risk factors for 30-day mortality in elderly patients with lower respiratory tract infection. Community-based study. *Arch.Intern.Med.* 1997;157:2190-5.
9. Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI *et al.* Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax* 2003;58:377-82.
10. Bont J, Hak E, Hoes AW, Schipper M, Schellevis FG, Verheij TJ. A prediction rule for elderly primary-care patients with lower respiratory tract infections. *Eur.Respir.J.* 2007;29:969-75.
11. Classification Committee of the World Organization of Family Doctors (WICC). ICPC-2: International Classification of Primary Care. Oxford: Oxford University Press. 1997.
Ref Type: Report
12. Gebel R.S., Okkes I.M., and red.ICPC-2-NL. International Classification of Primary Care, second edition, Dutch version, Utrecht, Amsterdam: Dutch College of General Practitioners, Academic Medical Centre Amsterdam/ University of Amsterdam. 2000.
Ref Type: Generic
13. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann.Intern.Med.* 1987;106:196-204.
14. Concato J, Peduzzi P, Holford TR, Feinstein AR. Importance of events per independent variable in proportional hazards analysis. I. Background, goals, and general strategy. *J.Clin.Epidemiol.* 1995;48:1495-501.
15. Peduzzi P, Concato J, Feinstein AR, Holford TR. Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. *J.Clin.Epidemiol.* 1995;48:1503-10.

16. Steyerberg EW, Borsboom GJ, van Houwelingen HC, Eijkemans MJ, Habbema JD. Validation and updating of predictive logistic regression models: a study on sample size and shrinkage. *Stat.Med.* 2004;23:2567-86.
17. van Houwelingen HC. Validation, calibration, revision and combination of prognostic survival models. *Stat.Med.* 2000;19:3401-15.
18. Lim WS,.Macfarlane JT. Defining prognostic factors in the elderly with community acquired pneumonia: a case controlled study of patients aged > or = 75 yrs. *Eur.Respir.J.* 2001;17:200-5.
19. Macfarlane JT,.Boldy D. 2004 update of BTS pneumonia guidelines: what's new? *Thorax*. 2004;59:364-6.
20. BTS Guidelines for the Management of Community Acquired Pneumonia in Adults. *Thorax.* 2001;56 Suppl 4:IV1-64.:IV1-64.
21. Riquelme R, Torres A, El Ebiary M, de la Bellacasa JP, Estruch R, Mensa J *et al.* Community-acquired pneumonia in the elderly: A multivariate analysis of risk and prognostic factors. *Am.J.Respir.Crit Care Med.* 1996;154:1450-5.
22. Seppa Y, Bloigu A, Honkanen PO, Miettinen L, Syrjala H. Severity assessment of lower respiratory tract infection in elderly patients in primary care. *Arch.Intern.Med.* 2001;161:2709-13.
23. Mortensen EM, Coley CM, Singer DE, Marrie TJ, Obrosky DS, Kapoor WN *et al.* Causes of death for patients with community-acquired pneumonia: results from the Pneumonia Patient Outcomes Research Team cohort study. *Arch.Intern.Med.* 2002;162:1059-64.

Chapter 4

Predicting prognosis in lower respiratory tract infections: physician or prediction rule?

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Submitted.

ABSTRACT

Background. Prediction rules (PR) estimating prognosis in patients with lower respiratory tract infections (LRTI) have been developed and used to tailor management decisions. However, the additional value of such rules as compared to the GP's estimation has not been demonstrated yet.

Objectives. To compare two PRs with the prognosis estimated by general practitioners (GP), in an elderly population with LRTI in the community.

Methods. Patients aged ≥ 65 years (N=1,158) visiting the GP with LRTI were enrolled between October 2004 and May 2006 in a prospective observational study. GPs were asked to estimate the probability of 30 day-hospitalisation or death (range from 0 and 100%). We compared the GP's estimation with two available prediction rules: the LRTI-rule developed by our group and the CRB-65 rule developed by Lim et al by use of area under the receiver operating curve (AUC) analysis.

Results. 110 patients (9.5%) had the combined outcome and 14 (1.2%) died. The accuracy of the CRB-65 rule was inferior as compared to the LRTI-rule and the GP (AUC 0.63 compared to 0.81 for both the LRTI-rule and the GP's estimation). GPs correctly recognised 16% of the total population as having a low risk (incidence of 30-day hospitalisation or death <3%). The LRTI-rule identified 55% of the population with a low risk, while the CRB-65 rule was unable to accurately identify low-risk patients (average actual incidence of the outcome 7%). Both prediction rules and the GP recognised high-risk patients, who had a incidence of 30-day hospitalisation or death of more than 30%.

Conclusions: GPs are very capable at identifying high-risk patients and the LRTI and CRB-65 rules do not seem of additional value for this group. Since the LRTI-rule is able to identify many more episodes with a low risk, we recommend applying the LRTI-rule in all elderly patients with LRTI who according to the GP are at a low- or intermediate risk of hospitalisation or death.

INTRODUCTION

Lower respiratory tract infections (LRTI) are among the most frequently occurring diseases in the elderly and because complications, such as hospital admissions and death, are not uncommon, timely identification of high risk patients is important to guide patient management. The Fine-score for example, a rather comprehensive model, is used in the United States for patients presented in hospital with community acquired pneumonia (CAP).[1] A British guideline makes use of a more simple model, the CURB65-score which is based on the items **C**onfusion, high **U**rea, high **R**espiratory rate, low **B**lood pressure and age ≥**65** years old.[2;3] Without the urea parameter the model is also recommended for community care. (figure 1) Recently we have shown that this prediction rule may also be useful to predict mortality in an elderly primary care population with pneumonia.[4] However, mortality is rare in primary care patients and distinction between CAP and other LRTI is often difficult. Consequently, we developed a new clinical prediction rule to predict hospital admission or mortality in elderly patients with LRTI in the primary care setting.[5] (figure 2) Dissemination of such a rule will be enhanced if practicing physicians are convinced that the prediction rule has additional value compared to their own risk estimations, but formal comparisons of the rule's and treating physicians' risk stratifications are very rare. We compared both our primary care LRTI prediction rule and the CRB65-score with the prognosis estimated by the primary care physician in an elderly population with LRTI in the community.

Figure 1. Severity assessment by the CRB-65-score used to determine the management of CAP in patients in the community (Lim et al, 2003).[1]

Characteristic	Score assigned
New mental confusion	1
Respiratory rate 30/min or more	1
BP <90 mmHg systolic or £60 mmHg diastolic	1
Age ≥65 years	1

	Low risk	Medium risk	High risk
Sum of scores	0	1 or 2	3 or 4
Risk of 30-day mortality	Low (1.2%)	Intermediate (8.2%)	High (31.3%)
Treatment options	Likely suitable for home treatment	Likely need hospital referral and assessment	Urgent hospital admission

Figure 2. Clinical prediction rule for estimating the probability of 30-day hospitalisation or death from Lower Respiratory Tract Infections in elderly primary care patients.

Characteristic	Score assigned
Variables of the retrospective prediction rule	
Diagnosis	
Exacerbation of COPD	2
Pneumonia	4
Age (years)	
≥80	2
Medical history	
Heart failure	1
Diabetes	2
Hospitalisation: once	2
twice or more	3
Medication	
Taking oral glucocorticoids at time of diagnosis	3
Taking antibiotics in previous month	2
Additional variables used in the clinical prediction rule	
Signs	
General malaise	4
Absence of prior signs of upper respiratory tract infection	3
Absence of new or increasing cough	4
Physical examination	
Diminished level of consciousness	8
Temperature >38 °Celsius	2
Pulse rate ≥100 beats per minute	3

	Low risk	Medium risk	High risk
Sum of scores	≤8	9-13	≥14
Patients within risk class N (%)	631 (55)	372 (32)	155 (13)
Patients with 30-day hospitalisation or death N (%)	15 (2)	44 (12)	51 (33)
Patients with 30-day mortality N (%)	1 (0.2)	3 (0.8)	10 (6.5)
Treatment options	Likely suitable for home treatment	Need for close monitoring either at home or in hospital	

METHODS

Setting, patient and data selection

Between November 2005 and May 2006, 191 Dutch General Practitioners (GP) prospectively identified patients with LRTI aged 65 years or older, including acute bronchitis, exacerbations of chronic obstructive pulmonary disease (ECOPD) or CAP. The in- and exclusion criteria have been described in more detail elsewhere.[5] The participating GPs collected data on patient's history, medication use and signs and symptoms during the consultation, using a standard questionnaire. With a multivariate regression analysis these data were used to develop a clinical prediction rule, the LRTI-rule, to estimate the probability of 30-day hospitalisation or death.[5] The items of the CRB65-rule were also collected. In addition, the GP was asked to answer the following question at the end of the first consultation: "What is the probability (between 0 and 100%) that this patient will be hospitalised or die within the next 30 days?"

Statistical aspects

The area under the receiver operating curve (AUC) was calculated for the combined outcome '30-day hospitalisation or death', as a measure for the discriminative ability of both prediction rules and the physician. The AUC gives the probability that high-risk patients can be distinguished from low-risk patients. An AUC estimate of 0.5 indicates no discrimination, whereas an estimate of 1.0 indicates perfect discrimination. Next, we divided the population into low -, medium - and high risk groups according to the expected probability of the combined outcome by both prediction rules and the GP. Finally, we analysed the concordance between the prediction rules and the GP for low -, medium - and high risk groups in order to study the possible additional value of the LRTI-rule or the CRB65-rule for the GP in daily care. All analysis were repeated for mortality alone as the outcome variable and performed with the use of SPSS Version 12.1 for Windows, Chicago, USA.

RESULTS

Patients' characteristics

In total, 1,159 episodes of LRTI in 1,099 elderly patients (mean age 76.3 years) were included. Acute bronchitis occurred in 36%, ECOPD in 37% and CAP in 27% of the episodes. One patient, seen during the out-of-hours service, was lost to follow up and further excluded from the analysis. In 110 of 1,158 episodes (9.5%) the patient was hospitalised or died within 30 days after the initial diagnosis. In 1.2% of the LRTI episodes the patient died (Table 1).

Table 1. Demographic and clinical characteristics of the patients of the primary care prospective cohort.

Characteristic	**(N=1,158)**
	N (%)
Demographics	
Mean age (SD)	76.3 (7.3)
Male sex	502 (43)
Coexisting conditions	
Any of the following high risk comorbid conditions	843 (73)
Chronic Obstructive Pulmonary Disease, asthma or emphysema	641 (55)
Congestive heart failure	237 (21)
Diabetes Mellitus	198 (17)
Stroke	98 (8)
Neoplastic Disease	100 (9)
Smoking behaviour	
Smoking > 10 cigarettes per day	104 (9)
Signs	
General malaise	841 (73)
Absence of prior signs of URTI	337 (29)
Absence of new or increasing cough	38 (3)
New or increasing sputum production	904 (78)
New or increasing purulence of sputum	506 (44)
Physical examination	
Diminished level of consciousness	15 (1)
Disorientation in time and space	34 (3)
Temperature > 38° Celsius	186 (16)
Pulse ≥100 per minute	117 (10)
Systolic <90 or diastolic blood pressure <60 mm Hg	97 (8)
Respiratory rate ≥30 per minute	128 (11)
Initial diagnosis	
Acute bronchitis	415 (36)
Exacerbation of COPD	429 (37)
Pneumonia	314 (27)
Outcome	
Hospitalisation or death ≤ 30 days	110 (9)
Mortality ≤ 30 days	14 (1)

Accuracy of the LRTI-rule, CRB65-rule and the general practitioners' prognostication
The AUC of CRB65 for the combined outcome was significantly lower than those of the LRTI-rule and the GP's estimation. For mortality alone, the AUCs did not differ appreciably. (table 2)

Table 2. Discriminative value with 95% confidence intervals for the LRTI-rule[5], the CRB65-rule[6] and the general practitioner's estimation in elderly patients with Lower Respiratory Tract Infections.

	LRTI-rule	CRB65-rule	GP
30-day hospitalisation or death	0.81 (0.77-0.85)	0.63 (0.57-0.69)	0.81 (0.76-0.86)
30-day mortality	0.87 (0.76-0.99)	0.82 (0.69-0.94)	0.91 (0.84-0.99)

The proportion of episodes estimated as low, medium or high risk as well as the proportion of these episodes leading to hospitalisation or death within 30 days are shown in table 3. The CRB65-rule identified 81% episodes as low risk compared to 55 and 16% according to, respectively, our LRTI-rule and the GP's risk stratification. The proportion of patients with the combined outcome in the "low risk" group identified by the CRB65-rule was only slightly lower (7%) compared to the apriori probability (9.5%), while this proportion was much lower in those episodes designated as low risk by the LRTI-rule and the GP (both 2%). Thus, the LRTI-rule and the GP seem better at correctly identifying low risk patients. However, the LRTI-rule was able to select a much larger low risk population than the GP (55 versus 16%). High-risk patients identified as such by the three approaches indeed had a relatively high incidence of hospitalisation or death. The CRB65, however, only identified 3% of the episodes as high risk, compared to 13% with the LRTI-rule and 16% by the GP.
The medium risk category according to the CRB65 included 16% of the total population, compared to 32 and 68% according to, respectively, our LRTI rule and the GP's risk stratification. The proportion of patients with the combined outcome was 17% in episodes identified as medium risk with the CRB65 and this was much higher than the apriori probability of 9.5%. The proportion of patients with the combined outcome was closer to the apriori probability when identified by our LRTI-rule and the GP, respectively 12 and 6%. When mortality was chosen as the outcome, almost all deaths were seen in the high-risk group, if the LRTI-rule or the GP estimated the risk (respectively 10 (6.5%) and 11 (6.0%) deaths out of 11 deaths). When the CRB65 was applied, 3 deaths were observed in the low risk group (0.3%), 7 deaths in the medium risk group (3.8%) and 4 in the high-risk group (11%). (Table 3)

Table 3. Estimation of the probability of 30-day hospitalisation or death from Lower Respiratory Tract Infections in elderly primary care patients according to the LRTI-rule[5], the CRB65-rule[6] and the general practitioner (GP).

	Proportion of episodes estimated as low, medium or high risk (%)			Proportion of episodes with hospitalisation or death ≤ 30 days (%)			Proportion of episodes with 30-day mortality (%)		
	LRTI-rule	**CRB65**	**GP**	**LRTI-rule**	**CRB65**	**GP**	**LRTI-rule**	**CRB65**	**GP**
Low risk *	55	81	16	2	7	2	0	0	0
Medium risk *	32	16	68	12	17	6	1	4	0
High risk *	13	3	16	33	41	34	7	11	6.0

*See method section for the definitions of low-, medium and high risk.

Concordance between the prediction rules and the GP

The LRTI-rule and the GP identified the same low-, medium- and high-risk patients in 471 (41%) episodes. (table 4) In episodes with a high risk according to the GP and a low- or medium risk according to the LRTI-rule, the estimation of the GP was more accurate. In total, 45 episodes estimated as low risk by the GP were considered medium or high risk according to the LRTI rule. In those the proportion of patients with the combined outcome was indeed higher (7%).

In only 306 (26%) episodes there was concordance between CRB65 and the GP's estimation. (table 5) Discordance was especially obvious in 162 patients identified as high risk by the GP but as low- or intermediate by CRB65. In reality these patients were high-risk as 30% of those episodes resulted in hospitalisation or death.

Table 4. Concordance between the estimations of the general practitioner (GP) and the LRTI-rule[5]*.

		Prognosis by GP							
		Low risk <3%	**Observed outcome**	**Intermediate risk 4-29%**	**Observed outcome**	**High risk >30%**	**Observed outcome**	**Total**	**Total Observed outcome**
Prognosis by LRTI-rule	**Low risk Score ≤8**	137	1 (0.7%)	464	11 (2.4%)	28	3 (11%)	631 (55%)	15 (2.4%)
	Intermediate risk Score 9-13	40	2 (5%)	255	22 (8.6%)	76	20 (26%)	372 (32%)	44 (11.8%)
	High risk Score ≥14	5	1 (20%)	71	11 (15.5%)	79	39 (49%)	155 (13%)	51 (32.9%)
	Total*	182 (16%)	4 (2.2%)	790 (68%)	44 (5.6%)	183 (16%)	62 (33.9%)	1,158 (100%)	110 (9.5%)

*LRTI-rule= clinical prediction rule based on demographics, medical history, signs and symptoms

NB. In the assessment of the GP 3 episodes were missing. No outcome occurred in these patients.

Table 5. Concordance between the estimations of the general practitioner (GP) and the CRB65 rule[6]*.

		Prognosis by GP							
		Low risk <3%	**Observed outcome**	**Intermediate risk 4-29%**	**Observed outcome**	**High risk >30%**	**Observed outcome**	**Total**	**Total Observed outcome**
Prognosis by LRTI-rule	**Low risk Score ≤1**	166	4 (2.4%)	655	28 (4.3%)	112	32 (28.6%)	936 (81%)	64 (7%)
	Intermediate risk Score 2	16	0	119	14 (11.8%)	50	17 (34%)	185 (16%)	31 (17%)
	High risk Score ≥3	0	0	16	2 (12.5%)	21	13 (62%)	37 (3.2)	15 (41%)
	Total*	182 (16%)	4 (2.2%)	790 (68%)	44 (5.6%)	183 (16%)	62 (33.9%)	1,158 (100%)	110 (9.5%)

*CRB65-rule= clinical prediction rule based on Confusion, high Respiratory rate, low Blood pressure and age ≥65 years.[6]

NB. In the assessment of the GP 3 episodes were missing. No outcome occurred in these patients.

DISCUSSION

Our comparison of the prognostic accuracy of two prediction rules for LRTI episodes, the CRB65- and the LRTI-rule developed by our own group, with the risk stratification of the general practitioner, showed that only the LRTI-rule, including patient's history, signs and symptoms, was superior to the GP's estimation in that it identified more episodes as low risk (55% versus 16%), while 30-day hospitalisation or death was equally low (2%).

Some strengths and limitations of our study deserve further discussion. This is, to our knowledge, the first study comparing prognostic prediction rules with the estimation of the treating physician and another strength of our study is that it mimics daily care in elderly patients with lower respiratory tract infections consulting the GP. A limitation of our study is the lack of validation in new populations so far. Another possible limitation is the fact that both the final derivation of the LRTI-rule and the estimation of the GPs were performed in the same study. This could explain part of the concordance between the LRTI-rule and the GP's estimations. On the other hand, there was a clear difference between the performance of the LRTI-rule and the GP in the low- and intermediate risk groups. Especially in these patients the LRTI-rule seems of additional value.

In an earlier study we showed that CRB65 can be used to predict mortality in an elderly primary care population with CAP[4]. This outcome, however, is rare in a primary care population with LRTI, even among elderly. This study shows that CRB65 is not useful in identifying patients with low or high risk for 30-day mortality as the majority of deaths were observed during episodes designated as low or medium risk by the CRB65-rule. Also for the less severe outcome '30-day hospitalisation or death' the CRB65 performed inadequately. Several phenomena may account for this result. The CRB65 rule was derived in a hospital setting, included a minority of elderly and involved patients with a radiographic proven CAP; a population clearly distinct from elderly primary care patients with LRTI.[6] In addition mortality was chosen as the primary outcome, while our study focuses on 30-day hospitalisation or death. Despite the fact that CRB65 was not derived in a primary care population, the British guidelines recommend using it for patients with CAP in the community. Another drawback of CRB65 is the necessity of a pulmonary X-ray to diagnose CAP as it was derived in patients with an X-ray confirmed CAP. In primary care, chest X-rays are only performed in a small minority of patients and therefore it is difficult to differentiate between CAP and acute bronchitis or ECOPD. In a previous study we have shown that predictors other than those included in CRB65 are more important[5;7]. Other studies have shown a higher age cutoff.[8;9] Thus, we recommend not to use the CRB65 score in elderly primary care patients with LRTI.

Based on the findings of our study we propose to apply our LRTI-rule as follows in daily primary care: the physician diagnoses an LRTI and estimates the risk of severe complications. If the GP anticipates a high-risk the patient should be monitored extensively, either at home or in hospital and the prediction rule seems unnecessary. When a low- or intermediate-risk is estimated by the GP, the LRTI score-chart should be used; this will primarily result in many more episodes designated as low-risk. Patients with an estimated

low risk for severe complications could be treated at home. Management of patients with an intermediate estimated risk remains difficult and will depend on other medical and social factors. Fortunately this group will be small (12%) following the application of the LRTI rule. In case of acute bronchitis the physician might be more encouraged to prescribe antibiotics, although this study does not provide evidence for doing so. However, we believe that more appropriate prescribing may be accomplished by explicitly taking prognostic factors into account.[10-12]

In conclusion, GPs are very capable of selecting high-risk patients and the LRTI- and CRB65-rule do not seem of additional value. Since the LRTI-rule is able to identify many more episodes with a low risk, we recommend applying the LRTI-rule in all elderly patients with LRTI who according to the GP are at a low- or intermediate risk of hospitalisation or death. Future studies should focus on whether the use op prediction rules will indeed lead to more appropriate treatment and improved prognosis.

Reference List

1. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE *et al*. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N.Engl.J.Med.* 1997;336:243-50.
2. BTS Guidelines for the Management of Community Acquired Pneumonia in Adults. *Thorax*. 2001;56 Suppl 4:IV1-64.:IV1-64.
3. Macfarlane JT,.Boldy D. 2004 update of BTS pneumonia guidelines: what's new? *Thorax.* 2004;59:364-6.
4. Bont J, Hak E, Hoes AW, Macrfarlane, and Verheij TJM. Predicting death in elderly patients with pneumonia in the community; a prospective validation study re-evaluating the CRB-65 severity assessment tool. 2007.
Ref Type: Unpublished Work
5. Bont J, Hak E, Verheij TJM, and Hoes AW. Prognosis of lower respiratory tract infections in elderly patients in the community- a clinical prediction rule. 2007.
Ref Type: Unpublished Work
6. Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI *et al*. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax* 2003;58:377-82.
7. Bont J, Hak E, Hoes AW, Schipper M, Schellevis FG, Verheij TJ. A prediction rule for elderly primary-care patients with lower respiratory tract infections. *Eur.Respir.J.* 2007;29:969-75.
8. Conte HA, Chen YT, Mehal W, Scinto JD, Quagliarello VJ. A prognostic rule for elderly patients admitted with community-acquired pneumonia. *Am.J.Med.* 1999;106:20-8.
9. Espana PP, Capelastegui A, Gorordo I, Esteban C, Oribe M, Ortega M *et al*. Development and Validation of a Clinical Prediction Rule for Severe Community-acquired Pneumonia. *Am.J.Respir.Crit Care Med.* 2006.
10. Akkerman AE, Kuyvenhoven MM, van der Wouden JC, Verheij TJ. Determinants of antibiotic overprescribing in respiratory tract infections in general practice. *J.Antimicrob.Chemother.* 2005;56:930-6.

11. Rautakorpi UM, Huikko S, Honkanen P, Klaukka T, Makela M, Palva E *et al*. The Antimicrobial Treatment Strategies (MIKSTRA) program: a 5-year follow-up of infection-specific antibiotic use in primary health care and the effect of implementation of treatment guidelines. *Clin.Infect.Dis.* 2006;42:1221-30.
12. Steinman MA, Sauaia A, Maselli JH, Houck PM, Gonzales R. Office evaluation and treatment of elderly patients with acute bronchitis. *J.Am.Geriatr.Soc.* 2004;52:875-9.

Chapter 5

General discussion

GENERAL DISCUSSION

This thesis focused on determinants of antibiotic therapy in lower respiratory tract infections (LRTI), and, first and foremost, on the prognosis of LRTI among the subgroup of elderly patients in primary care. This subgroup was targeted for several reasons: First, the incidence of LRTI among this group is considerably higher than in other age groups and LRTIs are a major reason consulting a primary care physician.[1] Second, the problem is growing since in the next decades a vast increase in the number of elderly persons is expected worldwide.[2;3] Third, elderly persons are prone to a more complicated course, which is partly attributable to co-morbidity and immunosenescence.[4] For these reasons, it is of utmost importance for primary care physicians to adequately identify those at a low risk of complications (e.g. hospitalisations or death) as well as high-risk patients in order to efficiently target appropriate preventive and therapeutic measures. Physicians should not only be able to recognize those patients in need of intensive treatment and follow up, but at the same time minimize prescription for antibiotics in low risk patients to prevent side effects, costs and bacterial resistance. In addition, referral to hospital should be restricted to those who need it.

This thesis dealt with three issues closely related to the prognosis of LRTI in elderly. First, we studied the determinants of antibiotic therapy in acute bronchitis and exacerbations of chronic obstructive pulmonary disease (COPD). Second, we determined prognostic factors for a complicated course of LRTI and developed a practical prediction rule. Third, the prediction rule was compared to the prognosis as estimated by the general practitioner (GP). This finally resulted in recommendations how to apply the prediction rule in daily practice. In this chapter we put the results of these three issues into perspective by comparing the data with existing studies in this field and by further elaborating on some methodological problems we encountered. In addition, possible future studies that may solve the remaining issues are discussed.

Determinants of antibiotic therapy

Among elderly persons, antibiotic prescribing rates in acute bronchitis and exacerbations of COPD are high, even in The Netherlands— the country with the lowest antibiotic prescribing rates in Europe.[5] For acute bronchitis our group found prescribing rates over 80%.[6;7] These high rates were also observed in other studies,[8-10] but some reported lower rates.[11-13]

In a retrospective and a prospective cohort study, we assessed determinants of antibiotic therapy. In the retrospective study, advanced age was associated with antibiotic therapy in episodes of acute bronchitis, whereas in the prospective study abnormalities on auscultation and purulent sputum were the strongest determinants of antibiotic use. Purulent sputum has often been assumed to be indicative of a bacterial cause of infection.[14] However, evidence to support this assumption is controversial [15-18] and there is no convincing proof that antibiotics are of more benefit in patients with acute bronchitis and purulent sputum.[19]

In our cohort, abnormal vital signs, such as fever, tachycardia or tachypnoea were not

clearly associated with antibiotic use. We believe that among elderly persons this might actually indicate good clinical practice as pneumonia in these persons is often characterized by an absence of distinctive signs and symptoms.[20] Metlay et al. demonstrated that absence of any abnormality in vital signs or on auscultation makes a diagnosis of pneumonia highly unlikely, but one has to realize that the majority of studies included in that review were restricted to young adults.[21]

It is possible that other factors than those we analysed were taken into account by the physicians in the decision to prescribe antibiotics. In the retrospective study we were not able to systematically collect data on signs and symptoms using computerized medical records. In the prospective study, the subgroup of patients with acute bronchitis was relatively small (n=304) and the power was further reduced because only a small minority (18%) of patients did not receive antibiotics. Therefore we believe that these results should be interpreted with caution and it might be that a larger study will result in other findings.

Antibiotic therapy in patients suffering from an exacerbation of their COPD should be considered separately. Prescribing rates are lower (53%) and there is more evidence than in patients with uncomplicated acute bronchitis, that antibiotics are beneficial in a subgroup of high risk patients with an exacerbation of COPD. The finding in our retrospective study that patients with diabetes or heart failure are more likely to receive antibiotics for COPD exacerbations was, therefore, not surprising.[7] Unfortunately, because of the retrospective design, signs and symptoms could not be studied as they were often missing in the patient's medical file. Also data on COPD severity and smoking status were lacking, while these could have been taken into account by the physician in the decision to prescribe an antibiotic.

Several other factors that were not available in our study might be important determinants of antibiotic use. For example, studies have shown that patients' expectations play an important role in the decision to prescribe antibiotics.[8] However, it has also been demonstrated that GPs often assume patients expect antibiotics, while in fact adequate information and reassurance is all they want. [22] Unfortunately, we could not verify patients' and doctors' expectations. Another possible explanation of high antibiotic prescription rates can be sought in diagnostic labelling in two ways. Acute bronchitis is defined by the International Classification of Primary Care (ICPC)-codes[23;24] (R78) and criteria include coughing with diffuse abnormalities on pulmonary examination, like wheezing and crackles. Fever is not obligatory since elderly do not always present themselves with fever. It may have occurred that GPs suspected pneumonia in their patients, but since this diagnosis might worry the patient much more than acute bronchitis, they labelled their findings as acute bronchitis, especially in case of considerable diagnostic uncertainty. On the other hand, some patients with cough expect antibiotics, while in fact they have no strong signs of a LRTI. In order to 'justify' antibiotic prescription in these patients, GPs may label the symptoms as acute bronchitis instead of acute cough, even though they are aware that in both antibiotics are not indicated.

What is best practice in the treatment of acute bronchitis among elderly persons? Should GPs focus on the diagnosis or prognosis in order to target their antibiotic treatment options?

Given the diagnostic uncertainty in these patients we advocate to classify patients with respiratory symptoms into those with a primary focus of the upper respiratory tract and those with lower respiratory tract symptoms, and then focus on prognostic factors to guide treatment decisions (e.g. antibiotic prescriptions) instead of aiming for a more specific diagnosis (such as pneumonia, acute bronchitis or exacerbations of COPD). In addition, physicians should also take other causes of acute cough into account (such as bronchial hyper responsiveness and gastric reflux), as well as consider treating risk-elevating co-morbidity, such as heart failure, COPD or diabetes mellitus . During infections these disorders tend to exacerbate and increase the patient's risk for complications. In addition non-infectious exacerbations of chronic lung disorders cause signs and symptoms that are similar to those caused by respiratory infections.

Development of prediction rules in LRTI among elderly

A well known and easily applicable prediction rule is the CRB-65 severity score (**C**onfusion, high **R**espiratory rate, low **B**lood pressure and age **65** years or over; score ranging from 0 to 4) which has become part of the British guidelines on community acquired pneumonia (CAP).[25-27] In our study the CBR-65 prediction rule was validated in a prospective cohort including elderly primary care patients with CAP only—other LRTI were excluded. As far as we know, this was the first study validating this important tool in a primary care population. In our cohort, the CRB-65 score predicted 30-day mortality accurately. However, mortality in pneumonia patients in primary care is rare and therefore the precision of the discriminative value estimate (AUC) was low. Nevertheless, low-, medium- and high-risk groups could be identified without too many false positives and negatives. A possible limitation of our cohort study was the lack of urea nitrogen that was included in the original score (C**U**RB65). In our primary care population inclusion of urea was not feasible as this parameter is not routinely determined in daily practice. Besides, also the BTS-guidelines recommends using the score without urea nitrogen.[25;27] In addition, discriminating CAP from acute bronchitis in primary care is difficult without routine chest X-ray's. Therefore, it is not inconceivable that among the patients included in the subgroup analysis on CAP some patients actually suffered from acute bronchitis.

Again, the choice for a pragmatic study prevailed to generate results that are applicable to primary care physicians that do not have routine access to X-rays.

As mortality is a rare outcome even in elderly persons and because of diagnostic uncertainties regarding the differential diagnosis of LRTI we developed a new prediction rule for this group that also included hospitalisation as an outcome. We performed both a retrospective and a prospective study in elderly patients with LRTI in primary care. A systematic literature review showed that so far many studies aimed at establishing prognostic factors for a complicated course of LRTI. However, the majority of the studies were performed in the hospital setting[26;28-37], only few included elderly patients and the focus was on community acquired pneumonia (CAP)[26;28-39] instead of all LRTI. To mimic daily primary care practice, we also included acute bronchitis and exacerbations of COPD to develop a clinical prediction rule to be applied in "LRTI patients".

First, we conducted a large retrospective cohort study. We performed multivariable multi-level logistic regression analysis to identify independent prognostic determinants and applied multi-level analyses to adjust for potential within-patient dependency among those who had more than one LRTI episode during the 5-year study period. The internal validity of the final regression equation was enhanced by the use of conventional split-level analyses. The prediction rule derived from the regression coefficients of the predictor variables from the retrospective cohort study was then prospectively validated in another primary care cohort of elderly patients with acute bronchitis or pneumonia. Further, we optimised the retrospectively derived simple prediction rule by including additional data from medical history and signs and symptoms from the prospective cohort study. In the process of optimisation the original regression coefficients were maintained, i.e. the relative weight of each predictor of the retrospective rule remained the same. This prevented over-fitting of the model. We found six signs or symptoms that were predictive of hospitalisation or death in addition to the variables from the retrospective prediction rule. This resulted in the final model: a clinical prediction rule consisting of 15 variables known to the GP at the first consultation.

Some possible limitations should be mentioned. The most important one is the retrospective design of the derivation study. Therefore signs and symptoms could initially not be included. We used the complete retrospective prediction rule in the prospective optimisation study after validation had twice showed a reasonable discriminative value and confirmed that low and high risk groups could be adequately identified. However, some risk factors appeared less predictive when signs and symptoms were added. This meant that some variables of the retrospective prediction rule provide the same information as some signs and symptoms. Nevertheless, we choose to keep all data in the prediction rule to prevent over-fitting. The down-side of this approach is that our rule contains 15 variables that could hamper implementation. (see also below)

Obviously, this improved clinical prediction rule should also be validated in an external population to further assess its validity. In addition, it would be interesting to study the validity of the prediction rule in an international patient cohort as all predictors are derived in Dutch primary care practices. For example, previous antibiotic use is one of the prognostic determinants. Possibly, this characteristic is not predictive in a country were antibiotics are more easily prescribed.

We did not have a “golden” standard available to accurately classify the LRTI episodes, since chest X-rays were not routinely performed. In addition, spirometric measurements were not often available. Therefore, no definitive distinction between patients with and without chronic lung disorders could be made. However, because diagnoses in daily practice are also often without the use of additional tests, our approach enhanced the applicability of our findings in primary care.

Also the choice of our primary outcome, ’30-day hospitalisation or death’, warrants further discussion. Referral to hospital is an important management option for primary care physicians and may have been influenced by the determinants. In other words, as the physician also registered the patient’s characteristics, it is possible that certain items that he

or she considered a risk factor for complications determined the inclination to referral. We tried to quantify this potential bias by adding separate analyses taking mortality as the single outcome. Interestingly, the accuracy of the rule even improved, illustrating that this type of bias is unlikely.

An additional important and undervalued issue that arises from the development of prediction rules is its applicability in medical care. Many prediction rules are seldom used in clinical practice. As Redelmeier et al reported 'the most immediate problem with prognostic indices relates to limitations of human memory'.[40] Even when a prediction model consists of 6 items only, it is hard to remember them without a score-chart. Our clinical prediction rule contains 15 items and can only be applied if a score-chart is available. And even so it may not be used as physicians are not used to apply such methods or they might have problems in believing that the rule will be superior to their own clinical prognostic skills. As a matter a fact, it is typically unknown whether such rules should be used instead of - or in addition to the physician's assessment or only when the physician is uncertain about the expected prognosis. We therefore compared the prognostic ability of the clinical prediction rule and the CRB-65 score one the one hand with the prognostic skills of the Dutch primary care physicians on the other. The results of this study showed that physicians were at least as accurate in recognizing patients at high risk for the combined outcome. Therefore, there seems to be no need for a prediction model to recognize high risk patients. GPs were also correct when they considered a patient as having a low risk. However, they only designated a small proportion of patients (16%) as low-risk, while they identified a large proportion of patients as having a medium risk (68% of the population). We showed that our clinical prediction rule was able to classify more than half of these medium-risk patients as being at low risk. Thus, GPs seem reluctant to classify episodes as low risk when in doubt about the risk for complications. This is understandable: to miss high risk patients is evidently much worse than to misclassify a low risk patient as being at medium risk. However, we have shown that our clinical prediction rule can safely be used as in fact very few low risk patients as identified by our rule had a complicated course (<3%).

Although we recommend using the clinical prediction rule in patients with a low or medium risk according to the treating primary care, future studies should determine whether this will lead to a higher quality of care and lower costs. Thus, future studies should focus on quantifying the effect of the prognostic rule on for instance antibiotic use, quality of life and hospitalisation- or death rates. Also, incorporation of our prediction rule may improve the GPs' skills in estimating prognosis, limiting the added value of our rule. Until this had been achieved and convincingly shown, however, application of our rule is may be an important first step in optimising prognostication and subsequent management of elderly patients with LRTI in primary care.

Reference List

1. Westert GP, Schellevis FG, de Bakker DH, Groenewegen PP, Bensing JM, van der ZJ. Monitoring health inequalities through general practice: the Second Dutch National Survey of General Practice. *Eur.J.Public Health* 2005;15:59-65.
2. Jozan P. The epidemiological future. *Health Policy.* 1991;19:19-32.
3. Yoshikawa TT. Epidemiology and unique aspects of aging and infectious diseases. *Clin.Infect.Dis.* 2000;30:931-3.
4. Hakim FT,.Gress RE. Immunosenescence: deficits in adaptive immunity in the elderly. *Tissue Antigens.* 2007;70:179-89.
5. Goossens H, Ferech M, Vander SR, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet.* 2005;365:579-87.
6. Bont J, Hak E, oes AW, and Verheij TJ. Antibiotic prescribing in elderly patients with acute bronchitis. 2007.
Ref Type: Thesis/Dissertation
7. Bont J, Hak E, Birkhoff CE, Hoes AW, Verheij TJ. Is co-morbidity taken into account in the antibiotic management of elderly patients with acute bronchitis and COPD exacerbations? *Fam.Pract.* 2007;..
8. Akkerman AE, Kuyvenhoven MM, van der Wouden JC, Verheij TJ. Determinants of antibiotic overprescribing in respiratory tract infections in general practice. *J.Antimicrob.Chemother.* 2005;56:930-6.
9. Gonzales R, Barrett PH, Jr., Crane LA, Steiner JF. Factors associated with antibiotic use for acute bronchitis. *J.Gen.Intern.Med.* 1998;13:541-8.
10. Steinman MA, Sauaia A, Maselli JH, Houck PM, Gonzales R. Office evaluation and treatment of elderly patients with acute bronchitis. *J.Am.Geriatr.Soc.* 2004;52:875-9.
11. Gonzales R, Steiner JF, Sande MA. Antibiotic prescribing for adults with colds, upper respiratory tract infections, and bronchitis by ambulatory care physicians. *JAMA* 1997;278:901-4.
12. Holmes WF, Macfarlane JT, Macfarlane RM, Hubbard R. Symptoms, signs, and prescribing for acute lower respiratory tract illness. *Br.J.Gen.Pract.* 2001;51:177-81.
13. Kuyvenhoven MM, Verheij TJ, de Melker RA, van d, V. Antimicrobial agents in lower respiratory tract infections in Dutch general practice. *Br.J.Gen.Pract.* 2000;50:133-4.
14. Fischer T, Fischer S, Kochen MM, Hummers-Pradier E. Influence of patient symptoms and physical findings on general practitioners' treatment of respiratory tract infections: a direct observation study. *BMC.Fam.Pract.* 2005;6:6.
15. Allegra L, Blasi F, Diano P, Cosentini R, Tarsia P, Confalonieri M *et al.* Sputum color as a marker of acute bacterial exacerbations of chronic obstructive pulmonary disease. *Respir.Med.* 2005;99:742-7.
16. Hopstaken RM, Stobberingh EE, Knottnerus JA, Muris JW, Nelemans P, Rinkens PE *et al.* Clinical items not helpful in differentiating viral from bacterial lower respiratory tract infections in general practice. *J.Clin.Epidemiol.* 2005;58:175-83.
17. Soler N, Agusti C, Angrill J, Puig DIB, Torres A. Bronchoscopic validation of the significance of sputum purulence in severe exacerbations of chronic obstructive pulmonary disease. *Thorax.* 2007;62:29-35.
18. Macfarlane J, Holmes W, Gard P, Macfarlane R, Rose D, Weston V *et al.* Prospective study of the incidence, aetiology and outcome of adult lower respiratory tract illness in the community. *Thorax* 2001;56:109-14.
19. Smucny J, Fahey T, Becker L, Glazier R. Antibiotics for acute bronchitis. *Cochrane.Database.Syst.Rev.* 2004;CD000245.
20. Metlay JP, Schulz R, Li YH, Singer DE, Marrie TJ, Coley CM *et al.* Influence of age on symptoms at presentation in patients with community-acquired pneumonia. *Arch.Intern.Med.* 1997;157:1453-9.

21. Metlay JP, Kapoor WN, Fine MJ. Does this patient have community-acquired pneumonia? Diagnosing pneumonia by history and physical examination. *JAMA* 1997;278:1440-5.
22. Welschen I, Kuyvenhoven M, Hoes A, Verheij T. Antibiotics for acute respiratory tract symptoms: patients' expectations, GPs' management and patient satisfaction. *Fam.Pract.* 2004;21:234-7.
23. Classification Committee of the World Organization of Family Doctors (WICC). ICPC-2: International Classification of Primary Care. Oxford: Oxford University Press. 1997.
Ref Type: Report
24. Gebel R.S., Okkes I.M., and red.ICPC-2-NL. International Classification of Primary Care, second edition, Dutch version, Utrecht, Amsterdam: Dutch College of General Practitioners, Academic Medical Centre Amsterdam/ University of Amsterdam. 2000.
Ref Type: Generic
25. BTS Guidelines for the Management of Community Acquired Pneumonia in Adults. *Thorax.* 2001;56 Suppl 4:IV1-64.:IV1-64.
26. Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI *et al*. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax* 2003;58:377-82.
27. Macfarlane JT,.Boldy D. 2004 update of BTS pneumonia guidelines: what's new? *Thorax.* 2004;59:364-6.
28. Conte HA, Chen YT, Mehal W, Scinto JD, Quagliarello VJ. A prognostic rule for elderly patients admitted with community-acquired pneumonia. *Am.J.Med.* 1999;106:20-8.
29. Ewig S, Bauer T, Hasper E, Pizzulli L, Kubini R, Luderitz B. Prognostic analysis and predictive rule for outcome of hospital-treated community-acquired pneumonia. *Eur.Respir.J.* 1995;8:392-7.
30. Farr BM, Sloman AJ, Fisch MJ. Predicting death in patients hospitalized for community-acquired pneumonia. *Ann.Intern.Med.* 1991;115:428-36.
31. Farr BM, Bartlett CL, Wadsworth J, Miller DL. Risk factors for community-acquired pneumonia diagnosed upon hospital admission. British Thoracic Society Pneumonia Study Group. *Respir.Med.* 2000;94:954-63.
32. Fine MJ, Orloff JJ, Arisumi D, Fang GD, Arena VC, Hanusa BH *et al*. Prognosis of patients hospitalized with community-acquired pneumonia. *Am.J.Med.* 1990;88:1N-8N.
33. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE *et al*. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N.Engl.J.Med.* 1997;336:243-50.
34. Garcia-Ordonez MA, Garcia-Jimenez JM, Paez F, Alvarez F, Poyato B, Franquelo M *et al*. Clinical aspects and prognostic factors in elderly patients hospitalised for community-acquired pneumonia. *Eur.J.Clin.Microbiol.Infect.Dis.* 2001;20:14-9.
35. Lim WS,.Macfarlane JT. Defining prognostic factors in the elderly with community acquired pneumonia: a case controlled study of patients aged > or = 75 yrs. *Eur.Respir.J.* 2001;17:200-5.
36. Myint PK, Kamath AV, Vowler SL, Maisey DN, Harrison BD. The CURB (confusion, urea, respiratory rate and blood pressure) criteria in community-acquired pneumonia (CAP) in hospitalised elderly patients aged 65 years and over: a prospective observational cohort study. *Age Ageing* 2005;34:75-7.
37. Riquelme R, Torres A, El Ebiary M, de la Bellacasa JP, Estruch R, Mensa J *et al*. Community-acquired pneumonia in the elderly: A multivariate analysis of risk and prognostic factors. *Am.J.Respir.Crit Care Med.* 1996;154:1450-5.
38. Farr BM, Woodhead MA, Macfarlane JT, Bartlett CL, McCraken JS, Wadsworth J *et al*. Risk factors for community-acquired pneumonia diagnosed by general practitioners in the community. *Respir.Med.* 2000;94:422-7.
39. Seppa Y, Bloigu A, Honkanen PO, Miettinen L, Syrjala H. Severity assessment of lower respiratory tract infection in elderly patients in primary care. *Arch.Intern.Med.* 2001;161:2709-13.
40. Redelmeier DA,.Lustig AJ. Prognostic indices in clinical practice. *JAMA.* 2001;%20;285:3024-5.

Chapter 6.1

Summary

Lower respiratory tract infection (LRTI), such as acute bronchitis, exacerbations of chronic obstructive pulmonary disease (COPD) and pneumonia, are among the most common diseases presented in primary care. When the general practitioner (GP) diagnoses an LRTI he or she is confronted with important clinical dilemmas. Does the patient have a low- or high-risk to be hospitalised or die? Should the patient be treated with antibiotics or would a wait-and-see approach be better? Who is at risk of a poor prognosis and therefore in need of intensive treatment at home or in hospital?

Especially in elderly these questions are of importance, as the incidence of LRTI is three times higher compared to the general population (**Chapter 1**) and elderly are more prone to develop complications. In addition, the number of elderly will increase dramatically during the next decade. It is of high importance to recognise those patients at risk of a complicated course on time. Consequently over – and under treatment with antibiotics could be reduced resulting in less bacterial resistance, side effects and probably also fewer complications. Furthermore, unnecessary referrals to hospital may well be reduced while patients in need will be hospitalised.

Antibiotic prescribing

Antibiotic treatment is one of the major treatment options in LRTI. In principle all patients with pneumonia will be treated with antibiotics as bacteria often cause pneumonia and there is sufficient evidence for the effectiveness of this medication. In contrast, treatment of acute bronchitis with antibiotics is controversial while there is not enough evidence for its effectiveness. The same accounts for patients with mild COPD facing an exacerbation. The Dutch GP-guidelines on acute cough and COPD recommend antibiotics only in certain patients with an increased risk due to for example high age, comorbid conditions or poor lung function. Nevertheless most patients with acute bronchitis and many patients with COPD exacerbations are treated with antibiotics anyway. To improve antibiotic prescribing it is important to study why GPs prescribe antibiotics to certain patients, but not to others. This study is described in chapter 2.

In **chapter 2.1**, we retrospectively analysed the data of elderly patients visiting the GP with acute bronchitis or COPD exacerbations. We assessed whether antibiotics were more often prescribed to patients with risk elevating comorbid conditions. Antibiotics were often prescribed to patients with acute bronchitis (84%), but also to patients with a COPD exacerbation (53%). In acute bronchitis, high age was the only determinant, while in COPD exacerbations antibiotics were more often prescribed to male patients and to patients with diabetes or heart failure. Although we showed that especially in acute bronchitis comorbid conditions are not taken into account in the decision to prescribe antibiotics, the study is limited by the lack of clinical information, such as data on signs and symptoms and their influence on prescribing antibiotics, due to the retrospective design of the study.

In **chapter 2.2** a prospective study on determinants of antibiotic prescribing in elderly patients with acute bronchitis, including data on signs and symptoms, is presented. In 82% of the episodes an antibiotic was prescribed. Purulent sputum and abnormal auscultation with sounds of infection were the only determinants significantly associated with antibiotic use. Some other characteristics also showed an association, however due to a low number of episodes a definite conclusion on possible other determinants is not possible.
According to these two studies presented in chapter 2, we concluded that more appropriate prescribing might be accomplished by taking risk-elevating determinants such as presence of comorbid disease, high temperature or tachycardia more often into account.

Prognostic studies

Identification of patients with LRTI with a poor prognosis is important as a guiding tool for management strategies. Several previous studies have focussed on this issue. However, most studies on LRTI are performed in hospital populations and the results may therefore not be merely applicable to general practice. One of those studies resulted in the well-known CRB-65 severity score (**C**onfusion, high **R**espiratory rate, low **B**lood pressure and Age **65** years or over; score ranging 0-4) to predict 30-day mortality. The model is used in the British guidelines on pneumonia. It has been recommended also as a management tool for pneumonia in the community, yet it has not been validated in primary care. The guideline recommends hospital referral for a CRB-65 score of ≥1. That means *all* patients aged 65 years or older with pneumonia should be referred to hospital. Evidently this would not be practical or desirable in daily care.

In a prospective study of elderly primary care patients with pneumonia, we validated CRB-65. (**Chapter 3.1**) The mortality rate in the total cohort was low (3.5%). Patients with 1, 2 or ≥3 points had a mortality-rate of 0.9%, 8.2% and 17.4%, respectively. Test characteristics were comparable to the original study when a score of ≥2 (and not the recommended score of ≥1) was used. Also the discriminative value of the CRB-65 score was good. We concluded that the CRB-65 score adequately predicts mortality in an unselected elderly primary care population with pneumonia. However, since the a-priori probability of mortality in general practice is much lower than in hospitalised patients, distinction between low- and high-risk patients should be based on a cut-off level of 2 instead of 1.

The CRB-65 score could be used to predict mortality in patients with pneumonia. Still this outcome is rare in primary care and therefore it will be interesting to have a tool that predicts less severe (non-fatal) outcomes as well. Also the tool cannot be used for patients with other LRTI than pneumonia, such as acute bronchitis and COPD exacerbations. This is important, as in primary care it is more difficult to differentiate into the different LRTIs, since laboratory tests and pulmonary X-rays are less easily performed. Therefore we studied prognostic factors for poor outcome in elderly patients visiting the GP with acute bronchitis, COPD exacerbations or pneumonia. Based on these prognostic factors we aimed to develop a prediction model that adequately predicts hospitalisation or death. In **chapter 3.2** this

retrospective cohort study is described. The retrospectively derived prediction rule included the following variables: age ≥80 years, heart failure, diabetes, hospitalisation in the previous year, use of prednisone, recent use of antibiotics and type of LRTI. The rule predicts the probability that patients are hospitalised or die within the next 30 days. It was validated in The Second Dutch Survey of GPs. Patients with a low score (≤2) had a probability of 3% on hospitalisation or death and patients with a high score (≥7) had a probability of 31%. We found a comparable discriminative value of the prediction rule in the validation cohort.

Although this retrospective prediction rule is simple and can help the primary care physician to differentiate between high- and low-risk patients, it does not include potential useful characteristics from history and physical examination. For that reason the retrospective prediction rule was prospectively validated once more and optimised with data on signs and symptoms in a new study with elderly patients with LRTI in general practice. (**Chapter 3.3**) Prospective validation demonstrated that the retrospective prediction rule differentiates well between low- and high-risk patients. In the procedure of optimisation, the original regression coefficients of the retrospective prediction rule were used. This prevented the prediction rule from matching too much with the cohort in which it was derived (overfitting). The final clinical prediction rule that also included data on signs and symptoms was better capable of selecting low- and high-risk patients. Low-risk patients (score ≤8) had a probability of 2% on hospitalisation or death and in high-risk patients (score ≥14) this probability was 33%. The clinical prediction rule could be useful as a management tool; low-risk patients may be suitable for home-treatment whereas high-risk patients might be monitored more closely in a homecare or hospital setting.

GP or prediction rule?

Application of a clinical prediction rule will undoubtedly be enhanced further, if its surplus value compared with the GP's estimation without the use of the prediction rule, is demonstrated. Still there are hardly any studies comparing the prognosis estimated by a prediction rule with the prognosis estimated by the treating physician. In **chapter 4** two prediction rules (the CRB-65 and the clinical prediction as developed by the researchers) were compared in patients with LRTI, with the prognosis estimated by the GP. CRB-65 more often incorrectly classified patients as low- and high-risk then when the clinical prediction rule would have been applied. On the whole GPs were very well capable estimating the probability of individual patients if they were within the extreme groups (low- and high-risk). However, the additional value of the clinical prediction rule was observed in an improved classification of patients in who the GP estimated the risk as medium. This group was large; in 68% of the total population the GP estimated a medium risk. The clinical prediction rule classified more than half of them (59%) as low-risk and it turned out that indeed these patients had a low-risk. It seems that GPs are too defensive if they have to identify low-risk patients. Comparable numbers of high-risk patients were identified by GPs and the clinical prediction rule (16% and 13% respectively). CRB-65 only identified a small proportion of high-risk patients (3%). Our study demonstrates that GPs are very well capable of identifying

high-risk patients. In these patients both CRB-65 and the clinical prediction rule do not have an additional value. We recommend using the clinical prediction rule in elderly patients with LRTI in who the GP estimates a low- or medium-risk. Because of that, more patients who in reality have a low-risk will be identified as low-risk, therefore preventing unnecessary treatment or referral to hospital.

In **chapter 5** the results of this thesis and the main limitations are discussed. The studies provide the GP with new insight in antibiotic prescribing and risk factors of a poor prognosis of LRTI in elderly. A clinical prediction rule was developed and optimised and was well able to identify elderly patients with LRTI in primary care with a low- or high-risk of severe complications. The prediction rule, however, should be validated in a new cohort of patients, possibly also in younger patients and in other European countries, before it can be applied in daily practice. This should be the aim of future studies.

Chapter 6.2

Samenvatting

Lagere luchtweginfecties (LLWI), zoals acute bronchitis, exacerbaties van chronische obstructieve longaandoeningen (chronic obstructive pulmonary disease in het Engels; COPD) en longontsteking, behoren tot de meest voorkomende aandoeningen in de eerste lijn. Als de huisarts een LLWI diagnosticeert, wordt hij of zij met verschillende klinische dilemma's geconfronteerd. Heeft deze patiënt een kleine of een grote kans op een ziekenhuisopname of een fataal beloop? Is bij deze patiënt behandeling met antibiotica aangewezen of is een afwachtend beleid beter? Bij wie is de kans op een slechte prognose zo groot dat verwijzing naar het ziekenhuis en/of intensievere begeleiding noodzakelijk is?

Deze vragen zijn extra belangrijk bij oudere patiënten aangezien de incidentie van LLWI bij hen drie keer zo hoog is als in de gehele populatie (**Hoofdstuk 1**) en zij vaker ernstige complicaties ontwikkelen. Daarnaast zal het aantal ouderen de komende jaren drastisch stijgen. Het is van groot belang om patiënten die een grotere kans hebben op een gecompliceerd beloop tijdig te herkennen. Hierdoor zal er minder over- en onderbehandeling plaatsvinden met als gevolg minder bacteriële resistentie, bijwerkingen en zeer waarschijnlijk ook minder complicaties. Ook kan het leiden tot minder onnodige verwijzingen naar het ziekenhuis, terwijl patiënten die het nodig hebben juist wel tijdig zullen worden opgenomen.

Antibiotica gebruik

Antibiotica vormen een van de belangrijkste behandelmogelijkheden bij LLWI. In principe zullen patiënten bij wie de huisarts de diagnose longontsteking stelt direct worden behandeld met antibiotica aangezien een longontsteking vaak door bacteriën wordt veroorzaakt en er voldoende bewijs is voor de werkzaamheid van deze geneesmiddelen bij deze aandoening. Daarentegen is de behandeling van acute bronchitis met antibiotica controversieel omdat er onvoldoende bewijs is voor de effectiviteit van antibiotica. Hetzelfde geldt voor patiënten met milde COPD die een exacerbatie ondergaan. De Nederlandse huisartsrichtlijnen (NHG-standaarden), 'acute hoest' en 'COPD' raden aan om antibiotica voor te schrijven aan patiënten met een verhoogd risico op basis van bijvoorbeeld hoge leeftijd, de aanwezigheid van relevante comorbiditeit of een slechte longfunctie. Desalniettemin ontvangen de meeste patiënten met acute bronchitis en veel patiënten met een exacerbatie COPD antibiotica. Om het antibioticavoorschrijfgedrag te verbeteren, is het belangrijk om te onderzoeken waarom huisartsen aan de ene patiënt wel en aan de andere geen antibiotica voorschrijven. Dit onderzoek wordt beschreven in Hoofdstuk 2.

In **hoofdstuk 2.1** analyseerden we retrospectief de gegevens van episodes van oudere patiënten die de huisarts bezochten met acute bronchitis of een exacerbatie COPD. We onderzochten of antibiotica vaker werden voorgeschreven aan patiënten met comorbiditeiten die de kans op complicaties zouden kunnen verhogen. Antibiotica werden vaak voorgeschreven aan patiënten met acute bronchitis (84%), maar ook aan patiënten met een exacerbatie COPD (53%). In het geval van acute bronchitis was leeftijd de enige determinant, terwijl bij COPD exacerbaties antibiotica vaker werden voorgeschreven aan

mannelijke patiënten en aan patiënten met suikerziekte of hartfalen. Alhoewel we aantonen dat juist bij acute bronchitis geen comorbiditeiten worden meegenomen in de beslissing om wel of geen antibiotica voor te schrijven, heeft de studie als nadeel dat de invloed van klinische informatie, zoals anamnese en lichamelijk onderzoek, op het prescriptiegedrag van de huisarts niet kon worden geanalyseerd door de retrospectieve opzet van de studie.

In **hoofdstuk 2.2** wordt een prospectief onderzoek naar determinanten van antibiotica voorschrijfgedrag bij oudere patiënten met acute bronchitis gepresenteerd, waarbij ook de gegevens van de anamnese en het lichamelijk onderzoek werden meegenomen. In 82% van de episodes werd antibiotica voorgeschreven. Purulent sputum en afwijkende auscultatie met tekenen van infectie waren de enige determinanten die statistisch significant geassocieerd waren met antibioticavoorschriften. Een aantal andere karakteristieken bleek samen te hangen met een verhoogde kans op antibioticavoorschriften, maar door de geringe aantallen patiënten is een definitieve conclusie hier niet mogelijk.
Op basis van de twee in hoofdstuk 2 beschreven cohort onderzoeken concludeerden we dat antibiotica voorschrijfgedrag verbeterd zou kunnen worden als er vaker rekening zou worden gehouden met risicoverhogende kenmerken zoals de aanwezigheid van relevante comorbiditeit, koorts of een snelle hartslag.

Prognostische studies

Herkenning van patiënten met LLWI met een slechtere prognose is belangrijk als leidraad voor het beleid. Verschillende eerdere studies hebben zich hierop gericht. Echter, de meeste studies naar LLWI zijn uitgevoerd in ziekenhuispopulaties en de resultaten zijn daarom niet zonder meer toepasbaar in de huisartspraktijk. Een van die studies resulteerde in de bekende CRB-65 score (**C**onfusion (verwardheid), high **R**espiratory rate (snelle ademhaling), lage **B**loeddruk en leeftijd ouder dan **65** jaar; score 0-4) om sterfte binnen 30 dagen te voorspellen. Dit model wordt gebruikt in de Britse pneumonie richtlijnen. Het wordt aangeraden om dit model ook als een beslisregel te gebruiken bij eerstelijns patiënten met een longontsteking, terwijl CRB-65 niet in de eerste lijn is gevalideerd. De richtlijn raadt aan om patiënten met een score van ≥1 te verwijzen naar het ziekenhuis. Dat betekent dat alle patiënten van 65 jaar en ouder met een longontsteking naar het ziekenhuis verwezen zouden moeten worden. Dit is uiteraard in de praktijk niet werkbaar, maar ook niet wenselijk.

Wij hebben in een prospectieve studie de CRB-65 gevalideerd in een onderzoek bij oudere patiënten bij wie de huisarts de diagnose longontsteking had gesteld. (**Hoofdstuk 3.1**) De mortaliteit in het totale cohort was laag (3,5%). Patiënten met een score van 1,2 of ≥3 hadden een mortaliteit van respectievelijk 0.9%, 8.2% and 17.4%. De testkarakteristieken waren vergelijkbaar met de originele studie, mits er een afkapscore van ≥2 (en niet de voorgestelde grenswaarde van 1) werd gebruikt. Ook de discriminerende waarde van het model was goed. We concludeerden dat de CRB-65 in oudere patiënten met longontsteking in de eerste lijn een fatale afloop adequaat kan voorspellen. Omdat, echter, de a-priori kans op mortaliteit in de huisartspraktijk veel lager is dan in een ziekenhuispopulatie, moet het

onderscheid tussen laag- en hoogrisico patiënten gebaseerd worden op een afkapwaarde van 2 in plaats van 1.

De CRB-65 score zou dus gebruikt kunnen worden om mortaliteit te voorspellen in patiënten met een longontsteking. Echter, mortaliteit is zeldzaam in de eerste lijn en daarom zou het interessant zijn om een model te gebruiken dat ook minder ernstige (niet-fatale) eindpunten voorspelt. Daarnaast is het niet mogelijk om de score ook voor andere LLWIs zoals acute bronchitis en COPD exacerbaties te gebruiken. Dit is belangrijk omdat het in de eerste lijn moeilijker is om onderscheid te maken tussen de verschillende LLWIs aangezien aanvullend onderzoek zoals bloedonderzoek en longfoto's minder makkelijk uitgevoerd kunnen worden. Daarom hebben we een studie uitgevoerd naar prognostische factoren van een slecht beloop bij oudere patiënten die de huisarts bezochten met acute bronchitis, COPD exacerbaties en longontsteking. Op basis van deze prognostische factoren werd gepoogd een predictieregel te ontwikkelen die adequaat mortaliteit of ziekenhuisopname kan voorspellen. In **hoofdstuk 3.2** wordt deze retrospectieve cohort studie beschreven. De ontwikkelde retrospectieve predictieregel bestond uit de volgende variabelen: leeftijd ≥80 jaar, hartfalen, suikerziekte, ziekenhuisopnames in het voorafgaande jaar, prednisolon gebruik, recent antibioticagebruik en type LLWI. De regel voorspelde de kans dat de patiënt binnen 30-dagen in het ziekenhuis wordt opgenomen of komt te overlijden. De regel werd gevalideerd in het cohort van de Nederlandse Tweede Nationale Studie. Patiënten met een lage score (≤2) hadden een kans van 3% op ziekenhuisopname of overlijden en bij patiënten met een hoge score (≥7) was dit 31%. In het validatiecohort werd een vergelijkbare discriminatieve waarde van de predictieregel gevonden.

Alhoewel deze retrospectieve predictieregel eenvoudig is en de huisarts kan helpen om onderscheid te maken tussen laag- en hoogrisico patiënten, maakt deze geen gebruik van de potentieel nuttige gegevens uit de anamnese en lichamelijk onderzoek. Daarom is de retrospectieve predictieregel nogmaals prospectief gevalideerd en geoptimaliseerd met toevoeging van gegevens uit de anamnese en het lichamelijk onderzoek, in een nieuwe studie bij patiënten met LLWI in de huisartspraktijk. (**Hoofdstuk 3.3)** Validatie liet zien dat de retrospectieve regel goed onderscheid kan maken tussen laag- en hoogrisico patiënten. Tijdens de procedure van de optimalisatie werden de originele regressiecoëfficienten van de retrospectieve regel gebruikt. Hierdoor werd voorkomen dat de klinische predictieregel te veel zou zijn afgestemd op het cohort waar die in ontwikkeld werd (overfitting). De uiteindelijke klinische predictieregel, waarin dus ook enkele items van anamnese en lichamelijk onderzoek waren opgenomen, bleek beter in staat om laag- en hoogrisico patiënten te selecteren. Laagrisico patiënten (score ≤8) hadden een kans van 2% op ziekenhuisopname of overlijden en bij hoogrisico patiënten (score ≥14) was de kans 33%. De klinische predictieregel kan gebruikt worden als een beslisregel: laagrisico patiënten zijn geschikt voor behandeling thuis, terwijl hoogrisico patiënten intensief begeleid moeten worden, thuis of in het ziekenhuis.

Huisarts of predictieregel?

Het toepassen van een predictieregel zal ongetwijfeld bevorderd kunnen worden als de meerwaarde ten opzichte van de prognose zoals door de huisarts wordt ingeschat *zonder* gebruik van de regel, is aangetoond. Toch zijn er vrijwel geen studies bekend waarin de prognose ingeschat op basis van een predictieregel, wordt vergeleken met de prognose door de behandelend arts. In **hoofdstuk 4** worden twee predictieregels (de CRB-65 en de klinische predictieregel zoals ontwikkeld door de onderzoeksgroep) bij patiënten met LLWI vergeleken met de prognose door de huisarts. Met behulp van de CRB-65 werden laag- en hoogrisico patiënten vaker verkeerd geclassificeerd dan wanneer de klinische predictieregel zou worden toegepast. Over het algemeen konden huisartsen de absolute kans van individuele patiënten goed inschatten indien deze in de extreme groepen zaten (laag en hoog risico). Echter, de meerwaarde van de klinische predictieregel ligt in een betere classificatie van de groep patiënten bij wie de huisarts het risico als “gemiddeld” inschatte. Deze groep was namelijk groot; in 68% van de populatie werd door de huisarts een gemiddeld risico ingeschat. Ruim de helft (59%) van die groep werd door de klinische regel als laagrisico geclassificeerd en deze patiënten bleken ook een laag risico te hebben. Het lijkt er op dat huisartsen te defensief oordelen als ze een laagrisico patiënt moeten identificeren. Hetzelfde aantal hoogrisico patiënten werd geïdentificeerd door huisartsen als door de klinische predictieregel (16% en 13% respectievelijk). De CRB-65 herkende slechts een klein aantal hoogrisico patiënten (3%). Ons onderzoek toont aan dat huisartsen dus goed in staat zijn om hoogrisico patiënten met LLWI te herkennen. In deze groep zijn de CRB-65 en de klinische predictieregel niet van aanvullende waarde. Wij raden aan om de klinische predictieregel te gebruiken bij oudere patiënten met een LLWI bij wie de huisarts het risico als laag of middelhoog inschat. Hierdoor worden veel meer patiënten die in werkelijkheid een laag risico hebben, ook als laagrisico ingeschat waardoor onnodige behandelingen en verwijzingen voorkomen kunnen worden.

In **hoofdstuk 5** worden de resultaten van dit proefschrift en de belangrijkste tekortkomingen besproken. De studies voorzien de huisarts van nieuwe inzichten in antibiotica voorschrijfgedrag en risicofactoren voor een slechte prognose van LLWIs bij ouderen. De door ons ontwikkelde en geoptimaliseerde klinische predictieregel lijkt goed in staat bij oudere patiënten met een LLWI in de huisartspraktijk diegenen met een hoog- of laagrisico op ernstige complicaties te identificeren. De regel zal echter eerst moeten worden gevalideerd in een nieuw cohort van patiënten, mogelijk ook bij jongere patiënten en in andere Europese landen, voordat de regel kan worden toegepast in de dagelijkse praktijk. Toekomstige studies zouden zich hierop moeten richten.

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Curriculum vitae

CURRICULUM VITAE

Jettie Bont was born on February 28th, 1973 in Amsterdam, The Netherlands. She graduated from Secondary school in 1991 at the Casimir College in Amstelveen. In 1992 she did her Propedeuse in Medical Biology at the University of Amsterdam. In 1993 she started medical school at the same university. In her second year she went to Kenya to do a 'junior' internship and in her third year she did a research project in Stockholm, Sweden, on HIV in pregnant women. She finished medical school in 2000 (cum laude). Next, she did residencies in Internal -, Emergency and Respiratory Medicine at the Academic Medical Center of Amsterdam. In 2001 she started her vocational training at the department of General Practice/ Family Medicine at the University of Amsterdam. The next year she switched to Utrecht and combined it with this PhD-project, under the guidance of Prof.dr. T.J.M. Verheij, Prof.dr. A.W. Hoes and dr. E. Hak. In the same period she chaired the Board of the Dutch association of GP-trainees (LOVAH), until she got her specialist status in General Practice/ Family Medicine in 2005. In 2006 she joined the national Board of the Dutch Association of General Practitioners and started working as a general practitioner.