Lower respiratory tract infections in adults : a clinical diagnostic study in general practice

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Chapter VIII

Summary and perspectives

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8.1 Introduction

We have investigated the problems general practitioners meet in the diagnostic process of lower respiratory tract infections (LRTIs). The study described in this thesis focused on LRTIs in adult patients in routine general practice.
Our research questions were:

- Which pathogens are involved in patients with LRTIs in a general practice setting?
- What is the range of findings on chest radiographs in patients with LRTIs in general practice and are these findings related to the aetiology of the infection?
- To what extent can prediction rules from existing literature be applied to assess the presence of pneumonia in our group of Dutch general practice patients with LRTIs?
- Is it possible to predict the presence of a bacterial infection in patients with LRTIs in general practice?
- Can the presence of *Mycoplasma pneumoniae* be predicted by information obtained from medical history taking, physical examination and simple laboratory tests?

These questions will be discussed in the next paragraphs, taking the results of our investigations and information from the literature into account, as well as the every day practice of the general practitioner.

8.2 Case-definition

In the present study LRTI has been defined as:
'any abnormality on pulmonary auscultation and at least two of the following three signs and symptoms: (a) fever >38°C, or fever in the past 48 hours, (b) dyspnoea or cough (productive or non-productive) and (c) tachypnoea, malaise or confusion'. Our case-definition is in line with the strictly formulated case-definitions that have been in use since 1993. These case-definitions are clear as to the criteria patients should meet to be included into a study.[1-6]
Two more or less distinct groups of diagnoses can be distinguished as a result of these case-definitions. One results in the diagnosis lower respiratory tract **illness**. It includes criteria for cough and other lower respiratory tract symptoms and signs but not for chest examination. The use of this case-definition resulted in a study population in which about 6% of the included patients turned out to have pneumonia on the chest X-ray.[2] The second case-definition leads to a diagnosis of lower respiratory tract **infection**, as it sets criteria for chest

examination as well as for cough and other lower respiratory tract symptoms. Studies that used the second case-definition resulted in study populations of which 12% of the included patients had pneumonia.[1,3,4] In studies in which the presence of fever had been added to the case-definition of lower respiratory tract **infection** the percentages of patients with pneumonia on the chest X-ray were much higher, ranging from 38% to 46%.[5,6]
We added abnormalities on chest auscultation to our case-definition, meaning that patients without an abnormality on chest auscultation were not diagnosed with LRTI. In this respect we differed from other investigations.[1-6] We required abnormalities on chest auscultation to enable us to exclude those patients who were only suffering from upper respiratory tract infections. Our case-definition resulted in a patient population in which 20% of the included patients had pneumonia. In the various study populations with lower respiratory tract infection we studied, the percentages of patients with pneumonia ranged from 12% and 46%.
It is clear that as a consequence of the differences in case-definitions the study populations also show large differences. These differences restrict the segment of the patients with LRTI in which the investigation took place as can be seen from the percentages of chest X-ray confirmed pneumonia in the studies.

8.3 Incidence

The incidence rates of LRTI in general practice in the Netherlands are based on patients who attend a physician and are estimated in the Dutch "National Public Health Compass" as 36 cases of acute bronchitis and 8 cases of pneumonia per 1000 enlisted persons per year for acute bronchitis and pneumonia, respectively.[7] These incidence rates are sex and age related. It is feasible that the real incidence rates are higher, since not every person with complaints of the respiratory tract attends a physician. These figures are not based on case-definitions and therefore have to be regarded with caution. A study[1] using a clear case-definition performed in the United Kingdom found an incidence rate of LRTI of 44 cases per 1000 per adult population per year, which is similar to the combined incidence rates for acute bronchitis and pneumonia in the Dutch "National Public Health Compass".

8.4 Aetiology of Lower Respiratory Tract Infections

Which pathogens are involved in patients with LRTIs in a general practice setting?
(Chapter 3)

We included 145 patients who met our case-definition of LRTI. The mean age was 51 years and 54% were women. At least one pathogen was detected in 63% of the patients. A bacterial infection was found in 30% and a viral infection in 39% of the patients. In 6% of these patients dual infections were found, i.e. a mixed bacterial and viral aetiology. Bacterial infections were mainly caused by *Mycoplasma pneumoniae*in 9% of the patients and *Haemophilus influenzae*, in another 9% of the patients and by *Streptococcus pneumoniae* in 6%. The Influenza A virus was the pathogen most frequently found, followed by *Mycoplasma pneumoniae* and *Haemophilus influenzae*. This study is the first to use a case-definition to establish the aetiology of LRTI in patients attending a general practitioner in the Netherlands.
The amount of pathogens found is in accordance with other studies performed in general practice in which one or more pathogens were found in 44 to 67% of the included patients.[1,2,3,6,8,9] High proportions of viruses were seen in the studies from Israel[3], Sweden[6] and Norway[8]. The proportions of *Mycoplasma pneumoniae* and of *Haemophilus influenzae* are similar to that of other studies[2,3], but are not in concordance with the study by Lagerström et al.[6] (who found 21% *Haemophilus influenzae*). The proportion of *Streptococcus pneumoniae* is comparable to studies in Israel[3] and Norway[8], but not to several English studies[1,2,9] , which showed percentages of 17 to 36%. Studies that used special tests for pneumococcal antibiodies or pneumococcal immune complexes in serum, sputum or urine showed higher proportions of this pathogen.
Thus, the differences in the results of the studies can be accounted for by the many differences in the study populations and diagnostic methods. We included patients who visited the GP's surgery as well as those seen on home visits by the GP. The data collection was done at the patients' homes, in most cases by the same investigator. Thus, even patients who were bedridden and elderly people could also be included. The study period covered three winter seasons, eliminating the year-to-year and seasonal variation in pathogens. There were differences between general practitioners in the number of patients they included, which may have introduced selection bias. However, the consequences are difficult to determine. The implications of the differences in diagnostic methods between studies have been discussed in detail in chapter 3.
In contrast to what is generally thought the present study shows that a substantial part of the LRTIs do have a viral aetiology and therefore do not need to be treated with antibiotics. We observed, however, that 99% of the patients in the study were treated with antibiotics. Hence it becomes important for the

general practitioner to know the aetiology of the disease to be able to select those patients who will potentially benefit from antibiotic treatment. The aetiology can be investigated in several ways, directly as well as indirectly. Direct methods are tests that detect the pathogen(s), for instance culture or serology. At the present direct methods for the fast detection of pathogens at the bedside are not widely available. Indirect methods are based on the prediction of the pathogen(s) by using clinical information or on chest radiography. The question is whether there is a genuine relationship between clinical data and findings on the chest X-ray and aetiology. The relation between an infiltrate on the chest X-ray and aetiology will be discussed in the next paragraph.

8.5 Radiology of lower respiratory tract infections

What is the range of findings on chest radiographs in patients with LRTIs in general practice and are these findings related to the aetiology of the infection? (Chapter 4)

An abnormality on the chest radiograph was observed in 72 (56%) of the 129 patients of whom the chest X-ray could be reviewed in detail. The most frequent findings were pneumonia and non-infectious features (predominantly signs of COPD), both in 26 (20%) patients. Findings related to an infection (pneumonia and airways disease) were seen in 45 (35%) patients. Pathogens were identified in 84 patients (65%) of which, 41 (32%) were bacterial (including dual infections) and 43 (33%) were a single viral micro-organism. Nineteen (29%) of the patients with a bacterial infection had signs of infection (pneumonia or airways disease) on the chest X-ray; 12 of them (29%) showed an infiltrate. However, half of the patients in whom a bacterial pathogen was detected did not show signs of infection on the chest X-ray. The difference between the proportions of pneumonia in patients with a bacterial and patients with a viral aetiology showed an Odds ratio of 4.0 (95% confidence interval 1.2-13.8). An infiltrate on the chest X-ray as predictor of a bacterial infection compared to a viral infection gave a sensitivity of 29%, specificity of 91%, positive predictive value of 75% and negative predictive value of 57% at the observed prevalence of 41/84. For the broader category “signs of infection” on the chest X-ray these characteristics were 46% (sensitivity), 79% (specificity), 68% (positive predictive value) and 61% (negative predictive value), respectively. The results of the present study show that a patient with an LRTI and an infiltrate on the chest X-ray has a four times higher chance to have a bacterial infection than a viral infection compared to a patient without signs of pneumonia on the chest X-ray. If the presence of an infiltrate on the chest X-ray had been used as a criterion to start antibiotic therapy 26 patients would have been treated. Of these 26 patients twelve did have a bacterial infection, four had a viral infection and

in ten no aetiological diagnosis could be made. Twenty-nine patients with a bacterial infection would not have been treated with antibiotics. Patients with an infiltrate on the chest X-ray have a probability of a bacterial infection between 46% and 85%. These estimates are based on assumptions of minimal (all unknown cases assumed to be non bacterial) and maximal (all unknown cases assumed to be bacterial) prevalence. However, patients *without* an infiltrate on the chest X-ray still have a probability of 28% to 62% of having a bacterial infection. For the broader category "signs of infection" on the chest X-ray the probability of a bacterial infection is between 42% and 80%, for patients without these "signs of infection" the probability is between 26% and 60%.
We may conclude that findings indicating pneumonia or an infection on the chest X-ray are of limited value when the decision has to be made to treat a patient with LRTI with antibiotics or not. Making chest X-rays in patients with LRTI is not common practice in general practice, although it is recommended in the Dutch guideline "Acute cough" in case there is uncertainty about the diagnosis in seriously ill patients.[10] Therefore we decided to explore if clinical signs and symptoms could be used as an alternative for an chest X-ray when establishing the diagnosis pneumonia.

8.6 Prediction of pneumonia

To what extent can prediction rules from existing literature be applied to assess the presence of pneumonia in our group of Dutch general practice patients with LRTI? (Chapter 5)

Four diagnostic rules to predict pneumonia were derived from our dataset; the models 'Prediction I' (based on a logistic regression analysis of our data set), 'Prediction II' ('Prediction I' with the addition of CRP≥20 mg/), 'textbook' (based on predictive variables for pneumonia mentioned in textbooks) and 'GP' (based on variables that general practitioners indicated as predictive for pneumonia). A literature search resulted in another six rules; the models 'Singal'[11], Heckerling'[12], 'Melbye'[13], 'Gonzalez Ortiz'[5], 'Hopstaken I'[4] and 'Hopstaken II'[4]. These ten diagnostic rules were applied to our dataset. Two models 'Prediction II' and 'Hopstaken II', both with the added variable CRP≥20mg/l, showed significant areas under curve of ROC 0.67 (95% Confidence interval (CI) 0.55,0.72) and 0.69 (95% CI 0.58, 0.80), respectively. However, the predictive value for the presence of pneumonia remained limited for daily practice. The positive predictive values of these models increased from 44% (Model 'Prediction I') to 50% (Model 'Prediction II') and from 43% (Model 'Hopstaken I) to 47% (Model Hopstaken II') by adding of CRP. Given a pre-test probability of 20%, the post-test probability was 50% for Model 'prediction II' and 47% for Model 'Hopstaken II'. The negative predictive value

was 82% for Model 'prediction II' and 84% for Model 'Hopstaken II', with a pre-test probability of non-pneumonia of 80%.
The additional value of CRP-measurement is in line with the findings in other investigations in which it was shown to have some value in the diagnosis of pneumonia[14,15,16] and infectious diseases in general.[17,18,19]
We have tested the applicability of diagnostic rules[4,5,11-13], developed to detect pneumonia in general practice or ambulant setting without making a chest X-ray. None of these diagnostic rules came up to our expectations. These diagnostic rules consist of clinical information (medical history taking and physical examination) that can easily be obtained at the bedside, the so-called clinical rules. Possible differences between the study populations of the various studies are discussed in detail in chapter 5. Our findings are in line with the conclusions of two review papers, which described the poor performance of medical history taking and physical examination in diagnosing pneumonia.[20,21]
The conclusion is that diagnostic rules are not sufficient to diagnose pneumonia, and performing a chest X-ray is necessary to confirm it. The diagnosis of pneumonia is of limited value, however, to determine the aetiology of an LRTI, as was discussed in paragraph 8.5. This raised the question: "Could we predict the aetiology of the infection by means of clinical information". This is discussed in the next paragraph.

8.7 Prediction of bacterial infections with the use of clinical information

Is it possible to predict the presence of a bacterial infection in patients with LRTIs in general practice? (Chapter 6)

The results of the present study show that information obtained from medical history taking and physical examination can be used to differentiate between a bacterial and a viral infection in patients with LRTI who show abnormalities on auscultation of the chest. The presence of headache, fever and painful lymph nodes is associated with a bacterial infection, the presence of diarrhoea and rhinitis with a viral infection. By means of logistic regression we developed a scoring system based on the above-mentioned parameters to identify the presence of a bacterial infection. This diagnostic rule was transformed to what we called the 'Simplified score' to make it applicable in daily practice. Addition of a chest X-ray (i.e. an infiltrate on the chest X-ray) to the diagnostic rule was of some value and resulted in an area under curve of the ROC of 0.83 (95% CI, 0.74, 0.92) compared to 0.77 (95% CI, 0.67, 0.87) for the 'Simplified score'.

This 'Simplified score' was defined as:

diarrhoea, rhinitis if present score –1
headache, painful cervical lymph nodes, fever if present score +1,
if absent (any sign/ symptom) score 0.

Patients with a score of ≥1 were classified as having a bacterial infection and patients with a score of <1 were classified as having a viral infection. When we considered the test characteristics of the 'Simplified score' with cut-off point of ≥1 to detect a bacterial infection, the 'Simplified score' had a sensitivity of 91% (95% CI, 82-100%), a specificity of 47% (95% CI, 33-61%), a positive predictive value of 55% (95% CI, 42-68%) and a negative predictive value of 89% (95% CI, 70-98%). When we compared these characteristics to the use of pneumonia on the chest X-ray as a test for the presence of a bacterial infection (chapter 4), these figures were 29% (95% CI, 15-43%), 84% (95% CI, 76-92%), 46% (95% CI, 27-65%) and 72% (95% CI, 63-81%), respectively. Only prescribing antibiotics to those patients with the diagnosis bacterial infection established with the 'Simplified score' could reduce the use of antibiotics in adult patients with LRTI with 30%. With the use of an infiltrate on the chest X-ray as a test the reduction in antibiotic use is 80%. With the 'Simplified score' three (4%) patients who actually had a bacterial infection would not have been treated with antibiotics compared to 29 (35%) patients when using the chest X-ray as a criterion for antibiotic treatment.

To develop a of the diagnostic rule to predict the aetiology, two patient groups were created, one group with a single bacterial infection (n=35) and one group with a single viral infection (n=49). Patients with a dual infection and patients without a diagnosis based on aetiology were left out of the analysis. This meant that the data of only 84 patients were used for the analysis, which is a relatively small number of patients. At this point we have encountered some statistical issues as was also discussed by Hopstaken et al.[22] Converting the results of our study to every day practice should therefore be done with some caution. We recommend validation of the diagnostic rule in another population. Detailed information on this discussion is presented in paragraph 6.8 Addendum II.

In our study the general practitioners were free in their choice of management. They treated nearly all the patients with antibiotics, presuming that they had an LRTI with bacterial aetiology and were seriously ill. Not all patients who have an LRTI, even with a possible bacterial origin benefit from antibiotic treatment, though, as is the case in patients who suffer from acute bronchitis, which was shown in a Cochrane review.[23] It should be taken into account that general practitioners have their own responsibility in the treatment of patients, with or without antibiotics, as was also recommended by the Dutch Practice guideline "acute cough".[10] Our 'Simplified score', based on information that can easily be obtained in general practice, could be a step forward to a more selected prescription of antibiotics. Moreover, not all bacterial pathogens that cause LRTI have the same susceptibility to antibiotic drugs. The three most frequently

found micro-organisms are *Mycoplasma pneumoniae*, *Haemophilus influenzae* and *Streptococcus pneumoniae*, as is shown in chapter 3. Amoxicillin is the treatment of choice, covering *Haemophilus influenzae* and *Streptococcus pneumoniae*, but *Mycoplasma pneumoniae* is not susceptible to this drug. We investigated whether the presence of *Mycoplasma pneumoniae* can be predicted with the help of clinical signs and symptoms. This subject will be discussed in the next paragraph.

8.8 Prediction of *Mycoplasma pneumoniae*

Can the presence of Mycoplasma pneumoniae be predicted by information obtained from medical history taking, physical examination and simple laboratory investigations? (Chapter 7)

Recently, molecular diagnostic methods such as real-time polymerase chain reaction (PCR) for a rapid detection of *Mycoplasma pneumoniae* on throat swabs has become available and was applied to our population. *Mycoplasma pneumoniae* was detected in 12 out of 106 patients in whom the real-time PCR test could be done. Patients with a *Mycoplasma pneumoniae* infection had a lower mean age (43 years) compared to patients without *Mycoplasma pneumoniae* infection (mean age 51). The highest frequency of *Mycoplasma pneumoniae* infections was seen in the age group 41-50 years. The presence of chills, an elevated ESR (reference value adjusted for age and sex) and CRP (>50 mg/l) levels were associated with a *Mycoplasma pneumoniae* infection and rhinitis was associated with the absence of a *Mycoplasma pneumoniae* infection.
A relationship between age and *Mycoplasma pneumoniae* infection was found by Farr et al.[24] and Beović et al.[25], who found that patients with *Mycoplasma pneumoniae* pneumonia were younger (mean age of about 35) than patients with pneumococcal pneumonia (mean age 54 to 57). This is in contrast to the findings of Dorigo-Zetsma et al., who did not find differences in rates of *Mycoplasma pneumoniae* infection between age groups including children.[26]
We found that the presence of chills and high levels of CRP were associated with a *Mycoplasma pneumoniae* infection, which is in accordance with the findings of Beović et al.[25] However, they also found high levels of CRP in patients with a *Streptococcus pneumnoniae* infection.[25] We also found the association between rhinitis and the absence of a *Mycoplasma pneumoniae* infection in infections (chapter 6). Rhinitis is also present in our diagnostic rule for a bacterial infection: absence being associated with bacterial infections in general.[27] Comparison of the prediction of *Mycoplasma pneumoniae* and the prediction of a bacterial infection is discussed in detail in chapter 7.
We conclude that none of the clinical findings can predict the presence of *Mycoplasma pneumoniae*.

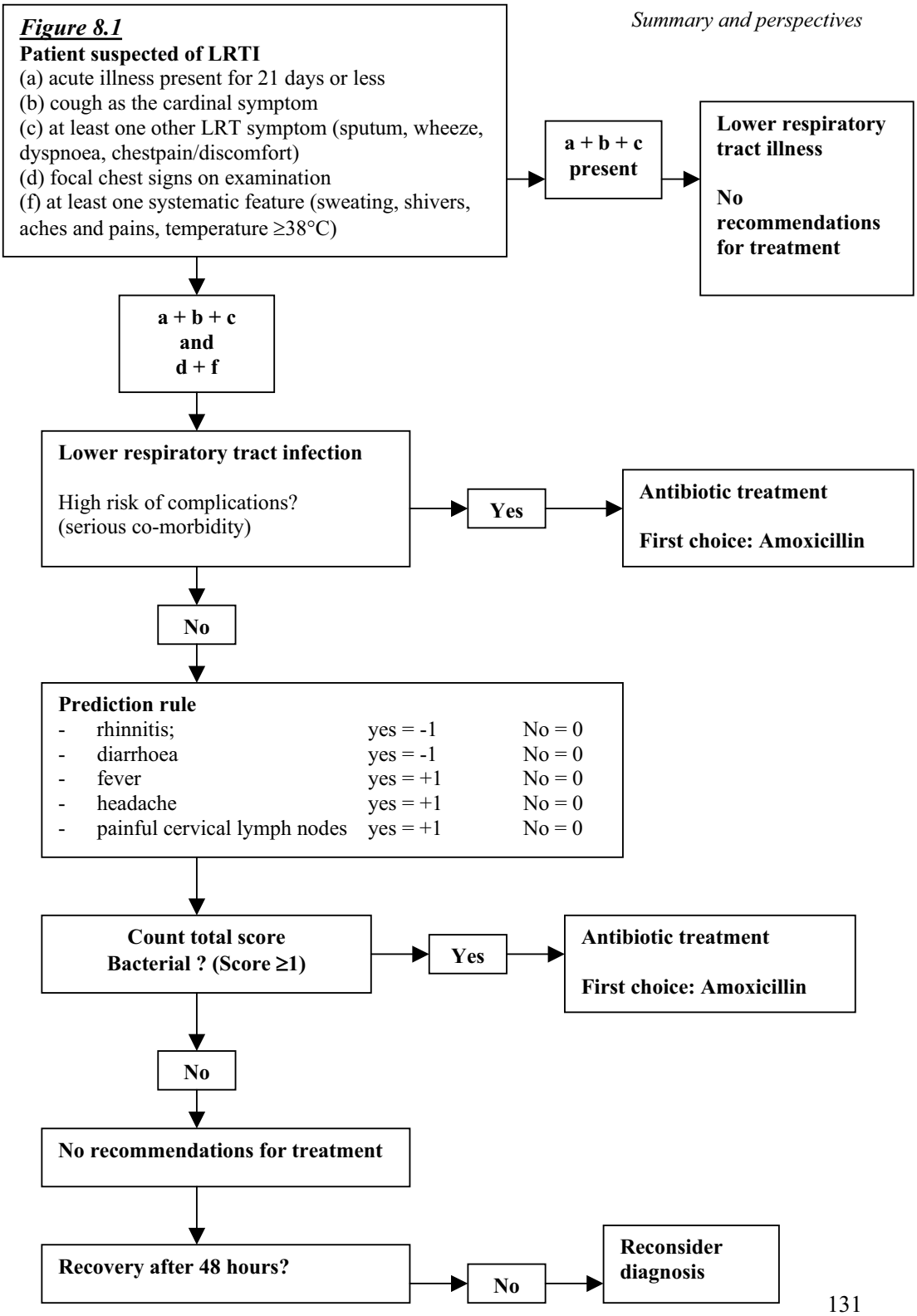
8.9 Perspectives

From this thesis the conclusion may be drawn that, although the majority of patients who suffer from LRTI are treated with antibiotics, a substantial part of these patients will not benefit from this treatment, because the infection is of a viral origin. A method to select patients with bacterial LRTI is needed to restrict the use of antibiotics in these patients. Chest X-rays or clinical decision rules to diagnose pneumonia do not suffice and bedside laboratory-tests to detect bacteria are as yet widely available. The clinical diagnostic rule we developed to predict the presence of a bacterial infection, which we developed, is at the moment the best option to restrict antibiotic use in patients with LRTI.
Figure 8.1 shows how the prediction rule may be used, by means of an algorithm. In the first step a distinction is made between a lower respiratory tract **illness** and lower respiratory tract **infection**. The definition of Macfarlane et al. is useful to make this distinction. [2,28] A lower respiratory tract **illness**, which possibly could include diagnoses such as asthma, does not necessarily imply a treatment with antibiotics. Next, the risk of complications is estimated for patients with lower respiratory tract **infection**. Patients with serious co-morbidity (i.e. heart failure or chronic obstructive pulmonary disease) or patients aged 75 and over run a high risk of complications and they should be treated with antibiotics. (See, the Dutch Practice Guideline "Acute cough"[10]) Our diagnostic rule for the prediction of a bacterial infection could be applied, however, on patients with lower respiratory tract **infections** who do not run a risk of complications. A score of ≥1 is a sign of a bacterial infection and therefore merits antibiotic treatment. For patients with a score <1 a management of wait-and-see with follow up is recommended. When there is no recovery the diagnosis should be reconsidered. (See, the Dutch Practice Guideline "Acute cough"[10]) The antibiotic treatment of first choice is amoxicilin, for the treatment of *Streptococcus pneumoniae* and *Haemophilus influenzae*, which still causes the most serious LRTIs.

We expect that a reduction in the use of antibiotics of about 30% may be achieved by applying this algorithm in the management of patients with LRTI. Before this approach is implemented in practice, however, it should be validated in future studies. This proposal differs in several respects from the recommendation done in the Dutch Practice Guideline "Acute cough" [10]: the use of a strict definition for LRTI, the use of chest X-ray and the choice of amoxicillin as first choice of antibiotic. We feel that using a strict definition helps to focus a well-defined medical problem for which information about aetiology is known. The chest X-ray is not common use in general practice, mainly because it is impractical for severely ill bedridden patients. We found that the value of the chest X-ray appeared to be limited in discriminating between a bacterial and a viral infection in patients with LRTI. We think that in

seriously ill patients suspected of having pneumonia, the results of the chest X-ray do not contribute to solving the problem of treating the LRTI. The chest X-ray may be useful in other cases, though. The Dutch Practice Guideline "Acute cough"[10] recommends doxycycline as the treatment of first choice for LRTI. This antibiotic has a very broad spectrum including the three most frequently encountered bacterial pathogens in LRTI: *Streptococcus pneumoniae, Haemophilus influenzae* and *Mycoplasma pneumoniae.* Of these three micro-organisms *Streptococcus pneumoniae* forms the greatest threat to the patient. The authors of the Dutch Practice guideline assumed 4% resistance of *Streptococcus pneumoniae* to tetracyclines. Based on more recent studies tetracycline resistance seems to have increased over the years. In 2002 seven percent of the *Streptococcus pneumoniae* isolates in the Netherlands was resistant to tetracyclines.[29] We feel that this level of resistance, which is heading towards inadequate therapy, is too high to accept in the seriously ill patients we decided to treat with antibiotics according to our algorithm. Penicillin resistance of pneumococci is not a clinical problem in the Netherlands at the moment. Thus, the most dangerous pathogen is treated effectively with amoxicillin.
International guidelines for the treatment of community-acquired pneumonia in adults generally have recommendations for outpatient treatment that are based on the local antibiotic resistance. In North America and Canada macrolides are first choice of treatment, whereas in Europe, Asia and South Africa β-lactams (mainly high dose of amoxicillin) are first choice.[30] We decided not to advice macrolides as first choice for two reason: the prevalence of microlides resistance of *Haemophilus influenzae* is high (between 70-90%) and in countries with a wide spread use a rapid rise in resistance has been noted.[29,31]

Figure 8.1


Patient suspected of LRTI
(a) acute illness present for 21 days or less
(b) cough as the cardinal symptom
(c) at least one other LRT symptom (sputum, wheeze, dyspnoea, chestpain/discomfort)
(d) focal chest signs on examination
(f) at least one systematic feature (sweating, shivers, aches and pains, temperature ≥38°C)
a + b + c present
Lower respiratory tract illness
No recommendations for treatment
a + b + c and d + f
Lower respiratory tract infection
High risk of complications? (serious co-morbidity)
Yes
Antibiotic treatment
First choice: Amoxicillin
No
Prediction rule
- rhinnitis; yes = -1 No = 0
- diarrhoea yes = -1 No = 0
- fever yes = +1 No = 0
- headache yes = +1 No = 0
- painful cervical lymph nodes yes = +1 No = 0
Count total score
Bacterial ? (Score ≥1)
Yes
Antibiotic treatment
First choice: Amoxicillin
No
No recommendations for treatment
Recovery after 48 hours?
No
Reconsider diagnosis

8.10 References

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