New trends in the prevention and management of community-acquired pneumonia


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ABSTRACT

Community-acquired pneumonia (CAP) is an important cause of morbidity and mortality worldwide. This review summarises current trends and knowledge gaps in CAP management and prevention. Although Streptococcus pneumoniae is the most frequent cause of CAP, identification of the microbial cause of infection remains unsuccessful in most episodes, and little is known about the aetiology of CAP in immunocompromised patients. Urinary antigen testing has become standard care for diagnosing Legionella infection, and pneumococcal urinary antigen testing is now recommended in the Dutch guidelines to streamline antibiotic therapy in patients hospitalised with CAP. In primary care C-reactive protein determination is recommended to improve antibiotic prescription for lower respiratory tract infections. In patients hospitalised with CAP, three strategies are considered equally effective for choosing empirical antibiotic treatment. Yet, more (and better designed) studies are needed to determine the best strategy, as well as to determine optimal (which usually means the minimum) duration of antibiotic therapy and the role of adjuvant treatment with corticosteroids. The effectiveness of the 23-valent pneumococcal polysaccharide vaccine in preventing invasive pneumococcal disease and pneumococcal CAP remains debated, and whether the newer conjugate vaccines are more effective remains to be determined. Many of these questions are currently being addressed in large-scaled trials in the Netherlands, and their results may allow evidence-based decisions in CAP management and prevention.

INTRODUCTION

Community-acquired pneumonia (CAP) is an important cause of morbidity and mortality worldwide." Reported annual incidences differ between countries, probably reflecting heterogeneity of diagnostics, reporting and socioeconomic factors. A universal finding, however, is that S. pneumoniae is the most commonly identified bacterial pathogen for CAP in all age groups. The purpose of this review is to summarise new developments in the field of prevention and management of bacterial CAP, and to discuss potential consequences for the Netherlands.

MICROBIOLOGICAL AETIOLOGY OF CAP

Although many micro-organisms can cause CAP, most episodes are caused by a few pathogens only. Table 1 displays proportions of pathogens documented in patients hospitalised with CAP in European countries, in which the diagnostic workup included blood cultures together with at least one other test, such as serology, polymerase chain reaction (PCR) for respiratory pathogens or urinary pneumococcal antigen testing. In most studies S. pneumoniae is the most frequently detected pathogen, accounting for 20-40% of CAP episodes. This proportion seems to be higher in studies from northern and western European countries compared with those from southern Europe. This may result from lower diagnostic sensitivity of blood and sputum cultures due to antibiotic use prior to hospital admission in southern countries. Other common pathogens causing CAP include Haemophilus influenzae, Mycoplasma pneumoniae, Legionella pneumophila and respiratory viruses. Chlamydophila pneumoniae and Coxiella burnetii are relatively rare causes of CAP, but may cause epidemics, as recently witnessed in the Netherlands during a Q-fever outbreak.6-8

KEYWORDS

Community acquired pneumonia, immunisation, empirical antibiotic therapy, corticosteroids
In 30-60% of CAP episodes the aetiology remains unknown, and this proportion has remained unchanged over time, despite the introduction of antigen testing and PCR-based testing. This has been attributed to less microbiological testing in clinical care or increased use of antibiotics prior to diagnostic testing. Therefore, although there are no discernible signs of major changes in the microbial aetiology of CAP over time, it is unknown whether such changes could have been masked by the suggested changes in clinical practice.

In addition the patient population affected is changing, with increasing numbers of severely immune-compromised patients, due to more frequent use of immune-modulating treatment modalities as well as to better survival of patients with serious illnesses. These patients are prone to developing CAP with both common respiratory tract infections (LRTI) and CAP. As a consequence, the microbial aetiology of infection is seldom established. In studies with a standardised microbiological work-up, the prevalence of opportunistic pathogens such as *Pneumocystis jirovecii*, atypical mycobacteria and fungi may have been underestimated. Among HIV-infected patients hospitalised with CAP, the reported prevalence of *P. jirovecii* has ranged from 9-31% and of *Mycobacterium avium* species from 1-17% of cases, which occurred in addition to pathogens common in immunocompetent populations.

### Table 1. Aetiology of CAP in hospitalised patients

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>The Netherlands</th>
<th>Germany</th>
<th>Switzerland</th>
<th>United Kingdom</th>
<th>Southern Europe</th>
<th>Slovenia</th>
<th>Nordic countries</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 studies</td>
<td>1 study</td>
<td>3 studies</td>
<td>3 studies</td>
<td>2 studies</td>
<td>7 studies</td>
<td>1582 (g)</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>31% (23-37)</td>
<td>13% (9-18)</td>
<td>13% (9-17)</td>
<td>35% (21-51)</td>
<td>23% (20-26)</td>
<td>9% (4-20)</td>
<td>30% (23-37)</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>5% (3-10)</td>
<td>6% (4-10)</td>
<td>6% (4-9)</td>
<td>7% (5-10)</td>
<td>3% (2-4)</td>
<td>2% (1-7)</td>
<td>5% (4-8)</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>1% (1-2)</td>
<td>4% (2-7)</td>
<td>4% (3-7)</td>
<td>2% (1-4)</td>
<td>1% (1-2)</td>
<td>1% (0-2)</td>
<td>1% (1-2)</td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
<td>1% (0-3)</td>
<td>-</td>
<td>2% (1-4)</td>
<td>2% (1-3)</td>
<td>0% (0-1)</td>
<td>1% (0-11)</td>
<td>1% (0-2)</td>
</tr>
<tr>
<td><em>Pseudomonas spp.</em></td>
<td>1% (0-3)</td>
<td>-</td>
<td>-</td>
<td>1% (0-3)</td>
<td>1% (0-2)</td>
<td>-</td>
<td>0% (0-1)</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>0% (0-1)</td>
<td>-</td>
<td>1% (0-3)</td>
<td>1% (0-2)</td>
<td>0% (0-1)</td>
<td>-</td>
<td>1% (0-1)</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>1% (0-2)</td>
<td>-</td>
<td>-</td>
<td>1% (0-2)</td>
<td>1% (0-1)</td>
<td>2% (1-4)</td>
<td>1% (0-1)</td>
</tr>
<tr>
<td>Other gramm-negatives</td>
<td>4% (1-12)</td>
<td>8% (6-13)</td>
<td>-</td>
<td>1% (1-2)</td>
<td>1% (0-3)</td>
<td>1% (0-3)</td>
<td>1% (0-3)</td>
</tr>
<tr>
<td><em>Mycoplasma pneumoniae</em></td>
<td>9% (4-16)</td>
<td>9% (6-14)</td>
<td>8% (5-11)</td>
<td>3% (2-6)</td>
<td>4% (3-7)</td>
<td>13% (3-43)</td>
<td>7% (5-10)</td>
</tr>
<tr>
<td><em>Chlamyphilus pneumoniae</em></td>
<td>1% (0-3)</td>
<td>11% (8-16)</td>
<td>3% (1-5)</td>
<td>2% (0-24)</td>
<td>2% (1-5)</td>
<td>19% (15-24)</td>
<td>1% (0-3)</td>
</tr>
<tr>
<td><em>Chlamyphilus psittaci</em></td>
<td>1% (0-4)</td>
<td>1% (0-3)</td>
<td>-</td>
<td>1% (0-4)</td>
<td>1% (0-1)</td>
<td>1% (0-3)</td>
<td>1% (0-2)</td>
</tr>
<tr>
<td><em>Coxiella burnetii</em></td>
<td>1% (0-1)</td>
<td>2% (1-5)</td>
<td>-</td>
<td>1% (0-2)</td>
<td>1% (1-2)</td>
<td>1% (0-2)</td>
<td>0% (0-1)</td>
</tr>
<tr>
<td><em>Legionella pneumophila</em></td>
<td>4% (3-7)</td>
<td>2% (1-4)</td>
<td>5% (3-8)</td>
<td>3% (2-5)</td>
<td>5% (4-7)</td>
<td>3% (1-5)</td>
<td>2% (1-1)</td>
</tr>
<tr>
<td>Viruses</td>
<td>9% (3-21)</td>
<td>10% (7-15)</td>
<td>-</td>
<td>16% (8-28)</td>
<td>4% (3-7)</td>
<td>5% (0-75)</td>
<td>10% (6-18)</td>
</tr>
<tr>
<td>Other agents</td>
<td>4% (2-8)</td>
<td>1% (0-3)</td>
<td>1% (0-3)</td>
<td>3% (0-6)</td>
<td>3% (2-5)</td>
<td>2% (0-8)</td>
<td>2% (1-3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>16% (23-49)</td>
<td>33% (27-59)</td>
<td>61% (56-66)</td>
<td>40% (23-60)</td>
<td>44% (40-49)</td>
<td>43% (14-52)</td>
<td>38% (27-49)</td>
</tr>
</tbody>
</table>


In patients with other types of immunosuppression, although Gram-negative bacteria and fungal infections have been reported in small case series.23-25 Summarising, the aetiology of CAP in immunocompetent patients seems unchanged with *S. pneumoniae* remaining most prevalent, but less is known about pathogen distribution in the growing population of immunocompromised patients.

### Diagnostics and management of CAP in primary care

Most patients with CAP are treated in primary care settings, with reported annual incidences (based on the International Classification of Primary Care) of 7.0/1000 patients in 2009. Most general practitioners (GP) must rely on clinical signs and symptoms to diagnose lower respiratory tract infections (LRTI) and CAP. As a consequence, the microbial aetiology of infection is seldom established. In studies with a standardised microbiological work-up, 13-65% of LRTI episodes were caused by respiratory viruses, mostly influenza and rhinoviruses, and the most frequent bacterial causes of infection were *S. pneumoniae*, *H. influenzae* and *M. pneumoniae*. As in hospitalised patients, no pathogen was detected in 40-60% of episodes.23-25
Consequently, treatment decisions in primary care are almost always empiric, and identification of patients at risk for a complicated course of disease or death is important. Among 315 elderly patients with CAP diagnosed in primary care in the Netherlands, 7% were referred to hospitals upon first presentation and 15% within 30 days.16 Age and presence of comorbidity, especially cardiovascular diseases and diabetes, are predictors for death or need of hospitalisation within 30 days after diagnosis of LRTI.23-28 The Guidelines of the Dutch College of General Practitioners (Nederlands Huisartsen Genootschap, NHG), therefore, recommend antibiotic treatment for these high-risk patients.29 Yet, antibiotics remain overprescribed, either because of the GP's previous experiences and beliefs or concerns about the severity of the disease, or the (GP's perception of) patient's expectations.30-34

In 13 European countries, the proportion of antibiotic prescriptions for LRTI in primary care ranged from 20% in Spain to almost 90% in Slovakia, and was 42% in the Netherlands.35 Although antibiotic resistance among respiratory pathogens is low, 11.5% and 7% of S. pneumoniae, isolated from primary care and hospital settings, respectively, are currently resistant to doxycycline.36 For this reason amoxicillin is now recommended as first-choice treatment of LRTI and CAP in primary care.37 Education of GPs and patients has been proposed as a means to improve antibiotic prescription in primary care. GP group education meetings, to improve knowledge of guidelines, and communication techniques aiming at better agreement with patients' expectations had different success rates.38-39 Furthermore, point-of-care determination of the C-reactive protein (CRP) blood level may assist in distinguishing high- and low-risk patients when clinical signs and symptoms of CAP are not conclusive.40 CRP point-of-care testing has now been incorporated in a decision tree for antibiotic treatment in the NHG guideline for LRTI.41 Implementation of CRP point-of-care testing in primary care is currently being evaluated in the ‘CRP Rapid Testing in Adults and Children in Primary Care’ (CaTCH) study. Furthermore, antibiotic prescription could be improved through better determination of the microbial causes of LRTI.42-44 Whether a combined approach of GP education, training in patient communication techniques and implementation of point-of-care tests is a cost-effective manner to reduce overprescription of antibiotics for LRTI in primary care remains to be determined.

**DIAGNOSTICS AND MANAGEMENT IN SECONDARY CARE**

Establishing a microbiological diagnosis of CAP still relies predominantly on the traditional culture techniques introduced by Koch and Pasteur in the 19th century. Yet, there is an urgent need for more precise and more rapid diagnostic tests in order to guide targeted antibiotic treatment and to prevent unnecessary use of antibiotics.9 In this respect, urinary antigen testing for Legionella and pneumococci, procalcitonin-based guidance of antibiotic therapy, and PCR-based testing of respiratory samples and whole blood have been evaluated.

**Urinary antigen testing**

The immunochromatographic membrane assays Binax Now (Binax) can detect L. pneumophila type I antigen or capsular polysaccharide antigens of S. pneumoniae in urine.27 The test for Legionella has a high sensitivity for type I species (70-100%, with higher sensitivity for severe CAP) and high specificity (95-100%).37-39 Legionella serotype I accounts for 90% of all infections caused by Legionella. The current Dutch guideline recommends to test for Legionella antigens in urine within 12 hours in patients with moderately severe CAP.40 For the pneumococcal urinary antigen test, reported specificities and sensitivities ranged from 90-100% and from 50-80%, respectively, depending on the reference standards that were used.44-46 The pooled positive predictive value of 20 studies was 79% (95% CI 70-88%) with a pooled negative predictive value of 92% (95% CI 89-96%).46 False-positive results may occur in children and COPD patients due to extensive colonisation with pneumococci, or after recent pneumococcal infection, as antigens may remain detectable for months.47 The sensitivity of this test is much more difficult to determine, especially in patients with non-bacteraemic episodes of pneumococcal CAP. In patients with bacteraemic pneumococcal CAP, though, 15-20% had negative urinary antigen tests, which might result from sequestration of antigen-antibody immune complexes with decreased antigen shedding in the urine.48 The positive predictive value of this test might be used to de-escalate initial broad-spectrum antibiotic therapy to a more narrow-spectrum treatment with penicillin or amoxicillin.49-54-55

**Procalcitonin**

Procalcitonin (PCT), a precursor of calcitonin, is a soluble protein that can be elevated in plasma during bacterial infection, sepsis and severe inflammatory reactions such as pancreatitis.44 PCT levels might be used to reduce total antibiotic exposure in patients with CAP. There have been four randomised trials comparing PCT-guided antibiotic treatment to standard care in patients hospitalised with CAP.51-55 In the first study a PCT-based approach reduced antibiotic use by 49% in patients admitted with suspected LRTI. The major effects were achieved in patients with a clinical diagnosis of acute
In subsequent studies daily PCT monitoring reduced the median length of antibiotic treatment from 12 to five days in a single-centre study and from 8.7 to 5.7 days in a multicentre study. In a fourth study a single PCT measurement at admission reduced the mean length of antibiotic treatment from 6.8 to 5.1 days, with equal proportions of patients starting with antibiotics at admission.

Yet, the optimal duration of antibiotic treatment for CAP is unknown. In two randomised trials treatment of five and seven days (with a fluoroquinolone or with a macrolide) had comparable clinical efficacies. In a Dutch study on hospitalised patients with mild or moderate-to-severe CAP (PSI score ≤110), who had significantly improved within three days after start of antibiotic treatment, clinical outcome was comparable for those patients who were randomised to discontinuation of antibiotic therapy after day 3 and those who continued antibiotics for five more days. PCT was not used in any of these studies. The Dutch guideline now recommends to treat mild and moderately severe CAP for five days, when using a beta-lactam or quinolone antibiotic. Furthermore, patients can safely switch from intravenous to oral antibiotics as soon as clinical improvement occurs (e.g. decrease in fever and respiratory rate, haemodynamic stability). Whether PCT measurement can further reduce antibiotic use in the Netherlands remains to be determined.

Nucleic acid amplification tests
Detection of microbial nucleic acid with nucleic acid amplification tests such as PCR in respiratory samples or blood may overcome the problem of culture-negative results after antibiotic therapy, and the inherent diagnostic delay of culture procedures and susceptibility testing. Real-time PCR combines amplification and detection in one reaction (reducing cross-contamination) and allows quantification of the infection load. Multiplex systems allow identifying multiple pathogens within the same time and in a single specimen.

PCR for specific pathogens
PCR is commonly used for certain respiratory viral pathogens (e.g. influenza, RSV, hMPV), but not yet for bacterial pathogens. PCR-based tests for S. pneumoniae have relied on the amplification of three different gene targets: pneumolysin, autolysin, and the DNA-fragment Spn9802. The last two seem to be more sensitive and cross-reactions with other streptococcal species can occur with pneumolysin. Reported sensitivity and specificity of PCR-based tests for S. pneumoniae in respiratory samples were 79% and 88%, respectively, and antibiotic therapy of less than 24 hours did not reduce sensitivity. As with culture techniques, PCR results cannot distinguish between colonisation and infection, although quantification of bacterial DNA load or relating this to the number of human epithelial cells may help in doing so.

Direct testing of blood samples with PCR-based tests for S. pneumoniae had reported sensitivities of 50-70% and specificities of 90-100% when compared with blood culture results. The true sensitivity, though, might be higher than for culture-based methods, but this is difficult to determine in the absence of a reliable reference standard. Yet, false-positive results can also occur and might be related to contamination or extensive pneumococcal colonisation. In bacteraemic patients, increased pneumococcal DNA loads in blood have been associated with increased mortality, need for mechanical ventilation and increased length of hospital stay. The clinical consequences of these tests remain to be determined. In one study of bacteraemic patients, pneumococcal urinary antigen testing appeared to be more sensitive, cheaper and less labour intensive than PCR-based testing of blood.

PCR has wider applications for ‘difficult to culture’ respiratory pathogens, such as Mycoplasma pneumoniae, Legionella species, Chlamydia pneumoniae, Bordetella pertussis, P. jiroveci and M. tuberculosis. For the diagnosis of acute Q fever, PCR of Coxiella burnetii can be used during the first three weeks after symptoms have started.

Up till now, large clinical validation studies for the use of PCR-based tests of respiratory samples in CAP diagnosis and management are lacking. In the only randomised controlled trial, a real-time multiplex PCR for respiratory viruses and atypical pathogens was evaluated in two Dutch hospitals. The test was associated with a higher diagnostic yield, but did not reduce antibiotic use and increased health care costs.

Management of CAP in secondary care
As the microbiological cause of CAP cannot be predicted reliably on clinical symptoms, guidelines recommend basing initial treatment choices on the severity of disease presentation. Patients with mild diseases can be treated with narrow-spectrum antibiotics (always covering S. pneumoniae) with careful monitoring of treatment response within 48 hours. On the other hand, in those with severe CAP a broader spectrum is recommended that includes at least S. pneumoniae and Legionella. In those with moderately severe CAP, empirical coverage of S. pneumonia is always needed, but coverage of Legionella can be based on the results of urinary antigen testing in most patients. Dutch guidelines recommend to use either of three scoring systems: the CURB-65 score, the Pneumonia Severity Index score (PSI) or the pragmatic classification. The contents of the three severity classification systems and the recommendations for empirical treatment have been determined.

discussed in this journal recently. They are, therefore, summarised in Box 1.

Current guideline recommendations are based on non-experimental cohort studies only and have, therefore, been criticised. Some studies suggest that combined treatment with a β-lactam antibiotic and macrolide improves outcome as compared with monotherapy with a β-lactam antibiotic and some suggest that such combination therapy improves survival in pneumococcal pneumonia. On the contrary, other studies failed to demonstrate beneficial effects of combination therapy (versus β-lactam monotherapy) on patient outcome. Better results of regimens that combine a macrolide and β-lactam antibiotic or in which fluoroquinolones are used as monotherapy might result from coverage of atypical pathogens, less resistance, synergy between β-lactams and macrolides, and anti-inflammatory effects of macrolides. A major pitfall for observational studies is confounding by indication, which arises when factors contributing to the endpoint differ between treatment groups because of the physician’s treatment decision. For instance, patients who received combination therapy might have had a higher suspicion of atypical pathogens because they were younger, and therefore, had a better prognosis. In several of the aforementioned cohort studies, either with or without beneficial effects for combination therapy, there is clear evidence of such confounding bias. This was elegantly demonstrated in one study by using a propensity analysis to predict treatment on the basis of clinical variables. These propensity scores differed significantly between treatment groups and the benefit of combination therapy in the crude analysis disappeared after adjustment for the propensity score in multivariate analysis.

As a result the relative effectiveness of empirical treatment of CAP with β-lactam monotherapy, combination therapy with a β-lactam and macrolide, or fluoroquinolone monotherapy is unknown. This is addressed in a multicentre cluster randomised cross-over trial in seven Dutch hospitals (CAP-START study, http://clinicaltrials.gov/ct2/show/NCT01660204). In each hospital one of the three treatment regimens will be used as standard empirical therapy during a period of four consecutive months, after which preferred treatment changes to one of the other two regimens. The order of regimens is randomised per hospital to control for inter-hospital variables and seasonal effects.

Corticosteroids as Adjunctive Treatment of CAP

Morbidity and mortality of patients hospitalised with CAP has been attributed to an imbalanced immune response yielding organ failure and septic shock. These detrimental effects could be modulated through corticosteroids, as has been demonstrated in patients with bacterial meningitis and vasopressor-dependent septic shock. In CAP patients without septic shock, however, the benefits of corticosteroids added to antibiotic treatment are less obvious. This approach has been evaluated in six randomised trials, four of which had less than 50 patients (table 2). In the largest study (104 patients) four days of dexamethasone 5 mg was associated with a median reduction in hospital stay of one day (95% CI 0-2 days) in patients hospitalised with CAP not requiring immediate ICU admission. However, patients requiring ICU admission after several days in hospital were excluded from analysis. The other large study (213 patients) failed to demonstrate significant reductions in length of stay or mortality in patients randomised to additional treatment with seven days of prednisolone 40 mg versus placebo. Based on these two studies there is no clear evidence that adjunctive treatment with corticosteroids is beneficial in patients with CAP in the absence of septic shock. The effects of corticosteroids as an adjunct to antibiotic therapy

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**Box 1. Current guideline recommendations for treatment of CAP**

*Mild CAP*
CURB-65: 0-1
PSI: 1-2
Pragmatic: Ambulatory treatment
Recommendation for empirical treatment: Amoxicillin, second choice doxycycline

*Moderately severe CAP*
CURB-65: 2
PSI: 3-4
Pragmatic: Treatment on hospital ward (non-ICU wards)
Recommendation for empirical treatment: Amoxicillin (if no risk factors for Legionella infection and with a urinary Legionella antigen test to be done within 12 hours).

*Severe CAP*
CURB-65: >2
PSI: 5
Pragmatic: Treatment in ICU ward
Recommendation for empirical treatment: Moxifloxacin or levofloxacin, penicillin/amoxicillin with ciprofloxacin, or 2nd or 3rd generation cephalosporin with a macrolide
is currently being evaluated in two placebo-controlled trials, one in Switzerland aiming to include 800 patients hospitalised with CAP (http://clinicaltrials.gov/ct2/show/NCT00973154) and one in Spain targeting for 120 CAP patients with PSI class V (http://clinicaltrials.gov/ct2/show/NCT00908713).

**PREVENTION OF CAP BY PNEUMOCOCCAL IMMUNISATION**

Based on differences in polysaccharide capsules, 91 different serotypes of *S. pneumonia* have been identified. Capsule polysaccharides have antiphagocytic activity, and are therefore relevant in the pathogenesis of CAP and invasive pneumococcal diseases (IPD). As a result, incidence of IPD, clinical outcome after infection and age distribution differ between serotypes.

The first human experiment of pneumococcal vaccination, based on administration of a mixture of polysaccharides, was conducted in 1911, and the first hexavalent-vaccine was registered in 1946. However, these vaccines were soon withdrawn because of the discovery of penicillin.

In the late 1970s, a 14-valent pneumococcal polysaccharide vaccine (PPV) was registered in the United States, which was replaced by a 23-valent PPV (Pneumovax/ Pneumo 23) in 1983, containing purified capsular antigens from 23 serotypes that cover approximately 87% of the isolates causing IPD in adults in the Netherlands. The vaccine induces T-cell independent B-cell responses, yielding antibodies in adults but not in young children. As immunological memory is not induced, revaccination needs to be repeated every five years. In the Netherlands, this vaccine is only recommended for patients with a high risk of IPD, such as those with (functional) asplenia, sickle cell anaemia and with liquor leakage or prior pneumococcal meningitis after skull trauma. For patients with immune suppression due to (non)-Hodgkin's disease, HIV or organ transplantation, immunisation is not strictly recommended, but can be applied.

Despite its use in many countries worldwide, the efficacy of the 23-PPV remains debated. Based on a recent meta-analysis quantifying combined risk ratios (based on a random-effects model) of (quasi)randomised

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**Table 2. Randomised controlled trials on corticosteroids in CAP**

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Design</th>
<th>Intervention</th>
<th>Setting</th>
<th>Age mean (SD)</th>
<th>PSI classification</th>
<th>Mortality RR (95% CI)</th>
<th>Length of stay diff. (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marik 1993</td>
<td>South Africa</td>
<td>Open label placebo-controlled RCT</td>
<td>Hydrocortisone 10 mg/kg single dose</td>
<td>ICU</td>
<td>39.4 (13.9)</td>
<td>NR</td>
<td>0.38 (0.09-3.26)</td>
<td>-0.3 (-4.0 to 3.4)</td>
<td>Patients with septic shock not excluded</td>
</tr>
<tr>
<td>Confalonieri 2005</td>
<td>Italy</td>
<td>Double-blind placebo-controlled RCT; treating physician not blinded</td>
<td>Hydrocortisone bolus 200 mg + 240 mg 7 days</td>
<td>General ward</td>
<td>63.5 (16.1)</td>
<td>I: 3 (10%)</td>
<td>0.09 (0.00-4.10)</td>
<td>-8 (p=0.03)</td>
<td>Patients with septic shock not excluded</td>
</tr>
<tr>
<td>Mikami 2007</td>
<td>Japan</td>
<td>Double-blind placebo-controlled RCT</td>
<td>Prednisolone 40 mg 3 days</td>
<td>Hospital (10% ICU)</td>
<td>72.0 (15.3)</td>
<td>I: 28 (13%)</td>
<td>1.05 (0.33-3.17)</td>
<td>-8.7 (-18.9 to 1.5)</td>
<td>NR</td>
</tr>
<tr>
<td>Snijders 2010</td>
<td>Netherlands</td>
<td>Double-blind placebo-controlled RCT</td>
<td>Prednisolone 40 mg 7 days</td>
<td>Hospital (16% ICU)</td>
<td>63.5 (18.3)</td>
<td>II: 43 (20%)</td>
<td>0.76 (0.36-1.60)</td>
<td>-0.3 (-3.6 to 3.0)</td>
<td>-0.56 (4.0 to 2.8)</td>
</tr>
<tr>
<td>Fernández 2011</td>
<td>Spain</td>
<td>Double-blind placebo-controlled RCT</td>
<td>Methyl-prednisolone bolus 200 mg + schedule§</td>
<td>General ward</td>
<td>63.6 (18.5)</td>
<td>III: 49 (23%)</td>
<td>0.96 (0.06-14.4)</td>
<td>-0.40 (4.0 to 3.2)</td>
<td>-0.2 (ns)</td>
</tr>
<tr>
<td>Meijvis 2011</td>
<td>Netherlands</td>
<td>Double-blind placebo-controlled RCT</td>
<td>Dexamethasone 5 mg 4 days</td>
<td>General ward</td>
<td>63.6 (18.5)</td>
<td>IV: 63 (30%)</td>
<td>2.4 (%)</td>
<td>-1 (-2 to 0)</td>
<td>-</td>
</tr>
</tbody>
</table>
PPV did not prevent infection (presumptive pneumococcal pneumonia, all-cause pneumonia and death from all causes) in trials with a double-blind design and with adequate allocation of treatment.\textsuperscript{123} Also the risk ratio of pneumococcal bacteraemia was close to one (RR 0.90 (0.46-1.77)), even without trial quality taken into account. These findings differ markedly from the reported effect of PPV on the occurrence of IPD (OR 0.26, 95% CI 0.15-0.46) based on ten studies in the most recent Cochrane review.\textsuperscript{125} Yet, only five trials were included in both analyses. The different outcomes result from differences in study selection, illustrating the large variety in study populations and outcome definitions. Large randomised controlled trials are lacking and interpretation of observational studies suffers from the ‘healthy vaccinee’ effect, which implies that subjects who have access to vaccination are usually in a better health condition than those who do not receive vaccination. Furthermore, there is no evidence that PPV prevents IPD in patients with chronic underlying medical illnesses. Therefore, we concur with the conclusion reached by the Dutch Health Council in 2003 that there is no convincing evidence that PPV prevents pneumonia or IPD in adults and that PPV vaccination, as an adjunct to annual influenza vaccination, is not recommended.\textsuperscript{126}

Since the turn of the century, pneumococcal conjugate vaccines (PCV) are available, with either seven (serotypes 4,6B, 9V, 14, 18C, 19F, 23F), ten (additional serotypes 1,5, 7F) or 13 (additional serotypes 3, 19A, 6A) polysaccharide capsular antigens conjugated to a protein. The last mentioned induces T-cell dependent immune responses, yielding adequate antibody responses in adults and young children, and immunological memory. The efficacy of conjugated pneumococcal vaccines in preventing pneumococcal disease in young children has been well established, with estimated vaccine efficacies of 80% (95% CI 58-90%) and 27% (95% CI 15-36%) for vaccine type IPD and X-ray confirmed pneumonia, respectively.\textsuperscript{127} Moreover, in the United States introduction of PCV-7 vaccination among children was associated with declines in IPD rates in the elderly, presumably because of vaccine-induced herd immunity.\textsuperscript{128} Conjugated vaccines have now been implemented in national immunisation programmes for children across the world.\textsuperscript{129-132}

In the Netherlands PCV-7 was introduced in the national immunisation program (‘Rijks Vaccinatie Programma’) in 2006, and was replaced by a ten-valent vaccine in 2011. Incidences of vaccine-serotype IPD in children <2 years had declined by 67% in 2008 (from 24.3 in 2005 to 8.0 cases/100,000 persons), but at that time, vaccine-serotype specific as well as overall IPD rates had not declined significantly among the elderly.\textsuperscript{133} In adults, a single dose of PCV-7 yields higher or at least equal immune responses to a single dose of 23-PPV, both in immune-competent and in immune-compromised adults.\textsuperscript{134-137} Since October 2011, PCV-13 has been licensed for prevention of IPD in adults aged ≥65 years in Europe. A model-based cost-effectiveness analysis suggests that in the United States replacement of 23-PPV vaccination with PCV-13, either at the age of ≥65 years – as currently recommended in the US – or routinely at the age of 50 and 65 years might reduce pneumococcal disease burden in an economically acceptable way, but model estimates were critically sensitive to vaccine efficacy in prevention of non-bacteraemic pneumococcal CAP and the magnitude of herd immunity created by children’s vaccination.\textsuperscript{138}

Up till now, effectiveness of PCV-7 vaccination in adults has only been determined in HIV-infected patients who had recovered from IPD in Blantyre, Malawi.\textsuperscript{139} After a median follow-up of 1.2 years unadjusted vaccine efficacy to prevent a new episode of vaccine serotype IPD (PCV-7 serotypes + serotype 6A) was 74% (95% CI 30-90%), but there were no significant beneficial effects on all-cause IPD (adjusted HR 0.80 (95% CI 0.45-1.44)) or mortality (adjusted HR 1.24 (95% CI 0.88-1.75)). The effectiveness of PCV in preventing bacteraemic and non-bacteraemic CAP in immune-competent elderly is unknown. This is being addressed in an ongoing placebo-controlled double-blind trial evaluating the efficacy of PCV-13 in 84,496 elderly (≥65 years) in the Netherlands.\textsuperscript{140} (http://clinicaltrials.gov/ct2/show/NCT00744263) The results of this study are expected in 2013.

**CONCLUSION**

We have reviewed some, but certainly not all, trends and controversies in the diagnosis, management and prevention of CAP. The most important trends and knowledge gaps for the prevention and management of CAP are summarised in table 3 (see page 344). Our daily clinical approach in patients with CAP has changed considerably in some aspects, such as the general approach to base empirical treatment on the severity of disease presentation rather than on the presumed involved pathogens, the frequent use of urinary antigen testing for Legionella and the shorter duration of (intravenous) antibiotic treatment. In other respects changes have not (yet) occurred, such as determination of microbial aetiology, defining optimal antibiotic strategies and duration of therapy, prevention through vaccination and the use of immunomodulating therapy. Large and well-designed studies are under way, some of them being conducted in the Netherlands, which may change our practices in the near future.
Table 3. New trends and current knowledge gaps in the management of CAP

<table>
<thead>
<tr>
<th>Topic</th>
<th>New trends</th>
<th>Current knowledge gaps</th>
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<tbody>
<tr>
<td>Microbiological aetiology</td>
<td>Larger role for opportunistic pathogens due to increasing number of immunocompromised patients.</td>
<td>Aetiology of CAP in immunocompromised hosts (except for HIV-patients).</td>
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<td>Management in secondary care</td>
<td>Streamlining broad-spectrum empirical antibiotic therapy based on pneumococcal antigen testing.</td>
<td>Clinical relevance of PCR-based microbiological testing.</td>
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<td>Shorter duration of (intravenous) antibiotic treatment in mild to moderate-severe CAP.</td>
<td>Role of procalcitonin in reduction of antibiotic treatment duration.</td>
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<td>Prevention</td>
<td>Pneumococcal conjugate vaccine introduced in Dutch national immunisation program for children aged 0-2 years.</td>
<td>Added value of covering atypical pathogens in empirical treatment of moderate-severe CAP.</td>
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<tr>
<td></td>
<td>Pneumococcal conjugate vaccine available for elderly.</td>
<td>Effectiveness of corticosteroids as an adjunct to antibiotic therapy.</td>
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<td></td>
<td></td>
<td>Herd immunity effects of conjugate vaccination in children.</td>
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REFERENCES


