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REVIEW

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.

KEYWORDS

Community acquired pneumonia, immunisation, empirical antibiotic therapy, corticosteroids

INTRODUCTION

Community-acquired pneumonia (CAP) is an important cause of morbidity and mortality worldwide.[1-3] Reported annual incidences differ between countries, probably reflecting heterogeneity of diagnostics, reporting and socioeconomic factors.[4] 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.[5] Other common pathogens causing CAP include *Haemophilus influenzae, Mycoplasma pneumonia, 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]

Table 1. *Aetiology of CAP in hospitalised patients*

	The Netherlands 5 studies n=1047 (a)	Germany 1 study n=237 (b)	Switzerland 1 study n=318 (c)	United Kingdom 3 studies n=439 (d)	Southern Europe 19 studies n=9143 (e)	Slovenia 2 studies n=320 (f)	Nordic countries 7 studies n=1582 (g)
Streptococcus pneumoniae	31% (25-37)	13% (9-18)	13% (9-17)	35% (21-51)	23% (20-26)	9% (4-20)	30% (23-37)
Haemophilus influenzae	5% (3-10)	6% (4-10)	6% (4-9)	7% (5-10)	3% (2-4)	2% (1-7)	5% (4-8)
Staphylococcus aureus	1% (1-2)	4% (2-7)	4% (3-7)	2% (1-4)	1% (1-2)	1% (0-2)	1% (1-2)
Moraxella catarrhalis	1% (0-3)	-	2% (1-4)	2% (1-3)	0% (0-1)	1% (0-11)	1% (0-2)
Pseudomonas spp.	1% (0-3)	-	-	1% (0-3)	1% (0-2)	-	0% (0-1)
Klebsiella pneumoniae	0% (0-1)	-	1% (0-3)	1% (0-2)	0% (0-1)	-	1% (0-1)
Escherichia coli	1% (0-2)	-	-	1% (0-2)	1% (0-1)	2% (1-4)	1% (0-1)
Other gram-negatives	4% (1-12)	8% (6-13)	-	-	1% (1-2)	1% (0-3)	1% (1-3)
Mycoplasma pneumoniae	9% (4-16)	9% (6-14)	8% (5-11)	3% (2-6)	4% (3-7)	13% (3-43)	7% (5-10)
Chlamydophila pneumoniae	1% (0-3)	11% (8-16)	3% (1-5)	2% (0-24)	2% (1-5)	19% (15-24)	1% (0-3)
Chlamydophila psittaci	1% (0-4)	1% (0-3)	-	1% (0-4)	1% (0-1)	1% (0-3)	1% (0-2)
Coxiella burnetii	1% (0-1)	2% (1-5)	-	1% (0-2)	1% (1-2)	1% (0-2)	0% (0-1)
Legionella pneumophila	4% (3-7)	2% (1-4)	5% (3-8)	3% (2-5)	5% (4-7)	3% (1-5)	2% (1-3)
Viruses	9% (3-21)	10% (7-15)	-	16% (8-28)	4% (3-7)	5% (0-75)	10% (6-18)
Other agents	4% (2-8)	1% (0-3)	1% (0-3)	3% (0-6)	3% (2-5)	2% (0-8)	2% (1-5)
Unknown	36% (25-49)	33% (27-39)	61% (56-66)	40% (23-60)	44% (40-49)	43% (34-52)	38% (27-49)

A few studies included both general ward and ICU patients; complete references can be obtained from the authors. a) Boersma 1991[142], Bohte 1995[143], Braun 2004[144], Van der Eerden 2005[145], Snijders 2010[116]; b) Steinhoff 1996[146]; c) Garbino 2002[147]; d) Venkatesan 1990[148], Lim 2001[149], Howard 2005[150]; e) Levy 1988[151], Ausina 1988[152], Pachon 1990[153], Blanquer 1991[154], Almirall 2007[155], Pareja 1992[156], Falco 1991[157], Ruiz-Gonzalez 1999[158], Sopena 1999[159], Fernandez-Sabe 2003[160], Menendez 1999[161], Lorente 2000[68], Ruiz 1999[162], Cilloniz 2011[163], Zalacain 2003[164], Falguera 2001[165], Marcos 2003[166], Briones 2006[167], Angeles Marcos 2006[168]; f) Socan 1999[169], Beovic 2003[170]; g) Kerttula 1987[171], Holmberg 1987[172], Burman 1991[173], Ostergaard 1993[174], Stralin 2010[175], Hohenthal 2008[176], Johansson 2010[45].

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.[9] 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.[10-12] These patients are prone to developing CAP with both common respiratory pathogens and opportunistic pathogens. Since these immunocompromised patients have been excluded in most studies, 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 species* from 1-17% of cases, which occurred in addition to pathogens common in immunocompetent populations.[13-17] Few data are available on CAP aetiology in patients with other types of immunosuppression, although Gram-negative bacteria and fungal infections have been reported in small case series.[18-21] Summarising, the aetiology of CAP in immunocompetent patients seems unchanged with *S. pneumonia* 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.[22] 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.[26] 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.[27,28] 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.[30-32]

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.[33]

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.[34] For this reason amoxicillin is now recommended as first-choice treatment of LRTI and CAP in primary care.[29]

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.[31,35] 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.[36] CRP point-of-care testing has now been incorporated in a decision tree for antibiotic treatment in the NHG guideline for LRTI.[29] 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.[24] 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. pneumonia* in urine.[37] 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.[41-49] 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%).[50] 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.[51] 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.[50] 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.[40,52,53]

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.[54] 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.[55-58] 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

bronchitis.[55] 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.[56,58] 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.[57]

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.[59,60] 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.[61] 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 betalactam or quinolone antibiotic.[40] 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).[40] 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.[62] The last two seem to be more sensitive and cross-reactions with other streptococcal species can occur with pneumolysin.[62-65] 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.[64,66] 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.[67]

Direct testing of blood samples with PCR-based tests for *S. pneumonia* had reported sensitivities of 50-70% and specificities of 90-100% when compared with blood culture results.[62,68,69] 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.[68] 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.[70,71] 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.[69]

PCR has wider applications for 'difficult to culture' respiratory pathogens, such as *Mycoplasma pneumoniae, Legionella* species, *Chlamydophila pneumoniae, Bordetella pertussis, P. jiroveci* and *M. tuberculosis*.[72-75] For the diagnosis of acute Q fever, PCR of *Coxiella burnetii* can be used during the first three weeks after symptoms have started.[76]

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.[77]

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.[40,78,79] Patients with mild diseases can be treated with narrow-spectrum antibiotics (always covering *S. pneumonia*e) 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. pneumonia* 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.[80,81] The contents of the three severity classification systems and the recommendations for empirical treatment have been

discussed in this journal recently.[40] They are, therefore, summarised in *Box 1*.

Current guideline recommendations are based on non-experimental cohort studies only and have, therefore, been criticised.[82-84] Some studies suggest that combined treatment with a β-lactam antibiotic and macrolide improves outcome as compared with monotherapy with a β-lactam antibiotic,[85-91] and some suggest that such combination therapy improves survival in pneumococcal pneumonia.[92-95] On the contrary, other studies failed to demonstrate beneficial effects of combination therapy (versus β-lactam monotherapy) on patient outcome.[96-102] 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.[103] 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.[104] 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.[85,87,88,91,92,96,97] 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.[101]

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.

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

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.[105] These detrimental effects could be modulated through corticosteroids, as has been demonstrated in patients with bacterial meningitis and vasopressor-dependent septic shock.[106,107] In CAP patients without septic shock, however, the benefits of corticosteroids added to antibiotic treatment are less obvious.[108-110] This approach has been evaluated in six randomised trials,[111-116] four of which had less than 50 patients (*table 2*). In the largest study (304 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

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

Study	Marik 1993[113]	Confalonieri 2005[111]	Mikami 2007[115]	Snijders 2010[116]	Fernàndez 2011[112]	Meijvis 2011[114]
Country	South Africa	Italy	Japan	Netherlands	Spain	Netherlands
N	30	46	31	213	45	304
Design	Open label placebo-controlled RCT	Double-blind placebo-controlled RCT; treating physician not blinded	Open label RCT	Double-blind placebo-controlled RCT	Double-blind placebo-controlled RCT	Double-blind placebo-controlled RCT
Intervention	Hydrocortisone 10 mg/kg single dose	Hydrocortisone bolus 200 mg + 240 mg 7 days	Prednisolone 40 mg 3 days	Prednisolone 40 mg 7 days	Methyl-prednisolone bolus 200 mg + schedule§	Dexamethasone 5 mg 4 days
Setting	ICU	ICU	General ward¶	Hospital (10% ICU)	Hospital (16% ICU)	General ward¶
Age mean (SD)	36.4 (13.9)	63.5 (16.1)	72.0 (19.5)	63.5 (18.3)	63.6 (NR)	63.6 (18.5)
PSI classification	NR	NR	I: 3 (10%) II: 2 (6%) III: 9 (29%) IV: 14 (45%) V: 3 (10%)	I: 28 (13%) II: 43 (20%) III: 49 (23%) IV: 63 (30%) V: 30 (14%)	I: 0 (0%) II: 4 (9%) III: 13 (29%) IV: 25 (56%) V: 2 (4%)	I: 40 (13%) II: 64 (21%) III: 57 (18%) IV: 97 (32%) V: 46 (15%)
Mortality RR (95% CI)	0.38 (0.05-3.26)[A]	0.07 (0.004-1.10)[B ‡]	NR	1.05 (0.33-3.37)[CD] 0.76 (0.36-1.60)[CE]	0.96 (0.06-14.4)[B]	0.83 (0.35-1.94)[C]
Length of stay diff. (95% CI)	-0.3 (-4.0 to 3.4)	-8 (p=0.03) [F]	-8.7 (-18.9 to 1.5)[G] -0.3 (-3.6 to 3.0)[H]	-0.56 (-4.0 to 2.8)[D] -0.40 (-4.0 to 3.2)[E]	-2 (ns) [I]	-1 (-2 to 0)[J]
Comments	Patients with septic shock not excluded	Patients with septic shock not excluded				

PSI=Pneumonia Severity Index; ICU=intensive care unit; CI=confidence interval; NR=not reported; ¶patients admitted to the ICU on day 1 were excluded; §20 mg/6 h for 3 days + 20 mg/12 h for 3 days + 20 mg/24 h for 3 days; ‡p=0.009 (Fisher's exact test); seven patients died in the placebo group versus no patients in the intervention group; [A]ICU mortality; [B]In-hospital mortality; [C]30-day mortality; [D]Intention to treat analysis; [E]Per protocol analysis; [F]Difference in medians, no confidence interval reported; [G]PSI IV-V (n=17); [H]PSI I-III (n=14); [I]No significant difference, CI of difference cannot be retrieved. [J]Difference in medians.

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).[117] As a result, incidence of IPD, clinical outcome after infection and age distribution differ between serotypes.[118-121]

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.[122] 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.[119] 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.[123] 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 studies,

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.[124] 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.[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.[123]

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.[126] 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.[127] Conjugated vaccines have now been implemented in national immunisation programs for children across the world.[128-132]

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.[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.[134-138] Since October 2011, PCV-13 has been licensed for prevention of IPD in adults aged >50 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.[139] 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.[140] 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.[141] (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*

Topic	New trends	Current knowledge gaps
Microbiological aetiology	Larger role for opportunistic pathogens due to increasing number of immunocompromised patients.	Aetiology of CAP in immunocompromised hosts (except for HIV-patients).
Management in primary care	Implementation of point-of-care CRP test for LRTI in primary care.	Effectiveness of different methods for reducing antibiotic prescriptions for LRTI in primary care.
Management in secondary care	Streamlining broad-spectrum empirical antibiotic therapy based on pneumococcal antigen testing. Shorter duration of (intravenous) antibiotic treatment in mild to moderate-severe CAP.	Clinical relevance of PCR-based microbiological testing. Role of procalcitonin in reduction of antibiotic treatment duration. Added value of covering atypical pathogens in empirical treatment of moderate-severe CAP. Effectiveness of corticosteroids as an adjunct to antibiotic therapy
Prevention	Pneumococcal conjugate vaccine introduced in Dutch national immunisation program for children aged 0-2 years. Pneumococcal conjugate vaccine available for elderly.	Effectiveness of pneumococcal polysaccharide and of conjugate vaccines in adults. Herd immunity effects of conjugate vaccination in children.

REFERENCES

1. Fry AM, Shay DK, Holman RC, Curns AT, Anderson LJ. Trends in hospitalizations for pneumonia among persons aged 65 years or older in the United States, 1988-2002. JAMA. 2005;294:2712-9.
2. Oosterheert JJ, Bonten MJ, Hak E, Lammers JW, Schneider MM, Hoepelman IM. The increase in pneumonia-related morbidity and mortality among adults in the Netherlands and possible explanations for it. Ned Tijdschr Geneeskd. 20044;148:1765-9.
3. Welte T, Torres A, Nathwani D. Clinical and economic burden of community-acquired pneumonia among adults in Europe. Thorax. 2012;67:71-9.
4. World Health Organisation. The global burden of diseases: 2004 update. WHO Press; 2008.
5. Goossens H, Ferech M, Coenen S, Stephens P. Comparison of outpatient systemic antibacterial use in 2004 in the United States and 27 European countries. Clin Infect Dis. 2007;44:1091-5.
6. Dijkstra F, van der Hoek W, Wijers N, et al. The 2007-2010 Q fever epidemic in The Netherlands: characteristics of notified acute Q fever patients and the association with dairy goat farming. FEMS Immunol Med Microbiol. 2012;64:3-12.
7. Kauppinen MT, Herva E, Kujala P, Leinonen M, Saikku P, Syrjala H. The etiology of community-acquired pneumonia among hospitalized patients during a Chlamydia pneumoniae epidemic in Finland. J Infect Dis. 1995;172:1330-5.
8. Limonard GJ, Groot CA, Dekhuijzen PN, Nabuurs-Franssen MH. Coxiella burnetii: a genuinely novel causative agent of pneumonia in The Netherlands since May 2007. Epidemiol Infect. 2012;140:865-6.
9. Bartlett JG. Diagnostic tests for agents of community-acquired pneumonia. Clin Infect Dis. 2011;52(Suppl 4):S296-S304.
10. Martin-Mola E, Balsa A. Infectious complications of biologic agents. Rheum Dis Clin North Am. 2009;35:183-99.
11. Porter K, Babiker A, Bhaskaran K, et al. Determinants of survival following HIV-1 seroconversion after the introduction of HAART. Lancet. 2003;362(9392):1267-74.
12. Ward EM, Thun MJ, Hannan LM, Jemal A. Interpreting cancer trends. Ann N Y Acad Sci. 2006;1076:29-53.
13. Camps SM, Cervera C, Pumarola T, et al. Virological diagnosis in community-acquired pneumonia in immunocompromised patients. Eur Respir J. 2008;31:618-24.
14. Madeddu G, Porqueddu EM, Cambosu F, et al. Bacterial community acquired pneumonia in HIV-infected inpatients in the highly active antiretroviral therapy era. Infection. 2008;36:231-6.
15. Mundy LM, Auwaerter PG, Oldach D, et al. Community-acquired pneumonia: impact of immune status. Am J Respir Crit Care Med. 1995;152(4 Pt 1):1309-15.
16. Park DR, Sherbin VL, Goodman MS, et al. The etiology of community-acquired pneumonia at an urban public hospital: influence of human immunodeficiency virus infection and initial severity of illness. J Infect Dis. 2001;184:268-77.
17. Rimland D, Navin TR, Lennox JL, et al. Prospective study of etiologic agents of community-acquired pneumonia in patients with HIV infection. AIDS. 2002;16:85-95.
18. Batlle M, Ribera JM, Oriol A, et al. [Pneumonia in patients with chronic lymphocytic leukemia. Study of 30 episodes). Med Clin (Barc). 2001;116:738-40.
19. Berman SJ, Johnson EW, Nakatsu C, Alkan M, Chen R, LeDuc J. Burden of infection in patients with end-stage renal disease requiring long-term dialysis. Clin Infect Dis. 2004;39:1747-53.
20. Hoyo I, Linares L, Cervera C, et al. Epidemiology of pneumonia in kidney transplantation. Transplant Proc. 2010;42:2938-40.
21. Lossos IS, Breuer R, Or R, et al. Bacterial pneumonia in recipients of bone marrow transplantation. A five-year prospective study. Transplantation. 1995;60:672-8.
22. Verheij RA, van Dijk CE, Abrahamse H, et al. Landelijk Informatienetwerk Huisartsenzorg. Feiten en cijfers over huisartsenzorg in Nederland. Utrecht/Nijmegen: NIVEL/IQ; 2009.
23. Holm A, Nexoe J, Bistrup LA, et al. Aetiology and prediction of pneumonia in lower respiratory tract infection in primary care. Br J Gen Pract. 2007;57(540):547-54.
24. Hopstaken RM, Stobberingh EE, Knottnerus JA, 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.

25. Macfarlane J, Holmes W, Gard P, et al. Prospective study of the incidence, aetiology and outcome of adult lower respiratory tract illness in the community. Thorax. 2001;56:109-14.

26. Bont J, Hak E, Hoes AW, Macfarlane JT, Verheij TJ. Predicting death in elderly patients with community-acquired pneumonia: a prospective validation study reevaluating the CRB-65 severity assessment tool. Arch Intern Med. 2008;168:1465-8.

27. 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.

28. Van de Nadort C., Smeets HM, Bont J, Zuithoff NP, Hak E, Verheij TJ. Prognosis of primary care patients aged 80 years and older with lower respiratory tract infection. Br J Gen Pract. 2009;59:e110-e115.

29. Verheij TJ, Hopstaken RM, Prins JM, et al. NHG Standaard Acuut Hoesten (Eerste herziening). Huisarts en Wetenschap. 2011;54(2):68-92.

30. 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.

31. Cals JW, Hopstaken RM, Butler CC, Hood K, Severens JL, Dinant GJ. Improving management of patients with acute cough by C-reactive protein point of care testing and communication training (IMPAC3T): study protocol of a cluster randomised controlled trial. BMC Fam Pract. 2007;8:15.

32. van Duijn HJ, Kuyvenhoven MM, Schellevis FG, Verheij TJ. Illness behaviour and antibiotic prescription in patients with respiratory tract symptoms. Br J Gen Pract. 2007l;57:561-8.

33. Butler CC, Hood K, Verheij T, et al. Variation in antibiotic prescribing and its impact on recovery in patients with acute cough in primary care: prospective study in 13 countries. BMJ. 2009;338:b2242.

34. SWAB. Nethmap 2009 - Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in The Netherlands. 2009 Sep 21.

35. Smeets HM, Kuyvenhoven MM, Akkerman AE, et al. Intervention with educational outreach at large scale to reduce antibiotics for respiratory tract infections: a controlled before and after study. Fam Pract. 2009;26:183-7.

36. Cals JW, Schot MJ, de Jong SA, Dinant GJ, Hopstaken RM. Point-of-care C-reactive protein testing and antibiotic prescribing for respiratory tract infections: a randomized controlled trial. Ann Fam Med. 2010;8:124-33.

37. Kazandjian D, Chiew R, Gilbert GL. Rapid diagnosis of Legionella pneumophila serogroup 1 infection with the Binax enzyme immunoassay urinary antigen test. J Clin Microbiol. 1997;35:954-6.

38. Dominguez JA, Gali N, Pedroso P, et al. Comparison of the Binax Legionella urinary antigen enzyme immunoassay (EIA) with the Biotest Legionella Urin antigen EIA for detection of Legionella antigen in both concentrated and nonconcentrated urine samples. J Clin Microbiol. 1998;36:2718-22.

39. Yzerman EP, Den Boer JW, Lettinga KD, Schellekens J, Dankert J, Peeters M. Sensitivity of three urinary antigen tests associated with clinical severity in a large outbreak of Legionnaires' disease in The Netherlands. J Clin Microbiol. 2002;40:3232-6.

40. Wiersinga WJ, Bonten MJ, Boersma WG, et al. SWAB/NVALT (Dutch Working Party on Antibiotic Policy and Dutch Association of Chest Physicians) guidelines on the management of community-acquired pneumonia in adults. Neth J Med. 2012;70:90-101.

41. Andreo F, Dominguez J, Ruiz J, et al. Impact of rapid urine antigen tests to determine the etiology of community-acquired pneumonia in adults. Respir Med. 2006;100:884-91.

42. Diederen BM, Peeters MF. Rapid diagnosis of pneumococcal pneumonia in adults using the Binax NOW Streptococcus pneumoniae urinary antigen test. Int J Infect Dis. 2007;11:284-5.

43. Dominguez J, Gali N, Blanco S, et al. Detection of Streptococcus pneumoniae antigen by a rapid immunochromatographic assay in urine samples. Chest. 2001;119:243-9.

44. Gutierrez F, Masia M, Rodriguez JC, et al. Evaluation of the immunochromatographic Binax NOW assay for detection of Streptococcus pneumoniae urinary antigen in a prospective study of community-acquired pneumonia in Spain. Clin Infect Dis. 2003;36(3):286-92.

45. Johansson N, Kalin M, Tiveljung-Lindell A, Giske CG, Hedlund J. Etiology of community-acquired pneumonia: increased microbiological yield with new diagnostic methods. Clin Infect Dis. 2010;50:202-9.

46. Murdoch DR, Laing RT, Mills GD, et al. Evaluation of a rapid immunochromatographic test for detection of Streptococcus pneumoniae antigen in urine samples from adults with community-acquired pneumonia. J Clin Microbiol 2001;39:3495-8.

47. Roson B, Fernandez-Sabe N, Carratala J, et al. Contribution of a urinary antigen assay (Binax NOW) to the early diagnosis of pneumococcal pneumonia. Clin Infect Dis. 2004;38:222-6.

48. Smith MD, Derrington P, Evans R, et al. Rapid diagnosis of bacteremic pneumococcal infections in adults by using the Binax NOW Streptococcus pneumoniae urinary antigen test: a prospective, controlled clinical evaluation. J Clin Microbiol. 2003;41:2810-3.

49. Sorde R, Falco V, Lowak M, et al. Current and potential usefulness of pneumococcal urinary antigen detection in hospitalized patients with community-acquired pneumonia to guide antimicrobial therapy. Arch Intern Med. 2011;171:166-72.

50. Boulware DR, Daley CL, Merrifield C, Hopewell PC, Janoff EN. Rapid diagnosis of pneumococcal pneumonia among HIV-infected adults with urine antigen detection. J Infect. 2007;55:300-9.

51. Andreo F, Ruiz-Manzano J, Prat C, et al. Utility of pneumococcal urinary antigen detection in diagnosing exacerbations in COPD patients. Respir Med. 2010;104:397-403.

52. Guchev IA, Yu VL, Sinopalnikov A, Klochkov OI, Kozlov RS, Stratchounski LS. Management of nonsevere pneumonia in military trainees with the urinary antigen test for Streptococcus pneumoniae: an innovative approach to targeted therapy. Clin Infect Dis. 2005;40:1608-16.

53. Stralin K, Holmberg H. Usefulness of the Streptococcus pneumoniae urinary antigen test in the treatment of community-acquired pneumonia. Clin Infect Dis. 2005;41:1209-10.

54. Muller B, Becker KL, Schachinger H, et al. Calcitonin precursors are reliable markers of sepsis in a medical intensive care unit. Crit Care Med. 2000;28:977-83.

55. Christ-Crain M, Jaccard-Stolz D, Bingisser R, et al. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. Lancet. 2004;363:600-7.

56. Christ-Crain M, Stolz D, Bingisser R, et al. Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. Am J Respir Crit Care. Med. 2006;174:84-93.

57. Kristoffersen KB, Sogaard OS, Wejse C, et al. Antibiotic treatment interruption of suspected lower respiratory tract infections based on a single procalcitonin measurement at hospital admission--a randomized trial. Clin Microbiol Infect. 2009;15:481-7.

58. Schuetz P, Christ-Crain M, Thomann R, et al. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. JAMA. 2009;302:1059-66.

59. File TM, Jr., Mandell LA, Tillotson G, Kostov K, Georgiev O. Gemifloxacin once daily for 5 days versus 7 days for the treatment of community-acquired pneumonia: a randomized, multicentre, double-blind study. J Antimicrob Chemother. 2007;60:112-20.

60. Tellier G, Niederman MS, Nusrat R, Patel M, Lavin B. Clinical and bacteriological efficacy and safety of 5 and 7 day regimens of telithromycin once daily compared with a 10 day regimen of clarithromycin twice daily in patients with mild to moderate community-acquired pneumonia. J Antimicrob Chemother. 2004;54:515-23.

61. el Moussaoui R, de Borgie CA, van den Broek P, et al. Effectiveness of discontinuing antibiotic treatment after three days versus eight days in mild to moderate-severe community acquired pneumonia: randomised, double blind study. BMJ. 200610;332:1355.

62. Abdeldaim G, Herrmann B, Molling P, et al. Usefulness of real-time PCR for lytA, ply, and Spn9802 on plasma samples for the diagnosis of pneumococcal pneumonia. Clin Microbiol Infect. 2010;16:1135-41.

63. Carvalho MG, Tondella ML, McCaustland K, et al. Evaluation and improvement of real-time PCR assays targeting lytA, ply, and psaA genes for detection of pneumococcal DNA. J Clin Microbiol. 2007;45:2460-6.

64. Kee C, Palladino S, Kay I, et al. Feasibility of real-time polymerase chain reaction in whole blood to identify Streptococcus pneumoniae in patients with community-acquired pneumonia. Diagn Microbiol Infect Dis. 2008;61:72-5.

65. Vernet G, Saha S, Satzke C, et al. Laboratory-based diagnosis of pneumococcal pneumonia: state of the art and unmet needs. Clin Microbiol Infect. 2011;17(Suppl 3):1-13.

66. Johansson N, Kalin M, Giske CG, Hedlund J. Quantitative detection of Streptococcus pneumoniae from sputum samples with real-time quantitative polymerase chain reaction for etiologic diagnosis of community-acquired pneumonia. Diagn Microbiol Infect Dis. 2008;60:255-61.

67. Hirama T, Yamaguchi T, Miyazawa H, et al. Prediction of the pathogens that are the cause of pneumonia by the battlefield hypothesis. PLoS One. 2011;6:e24474.

68. Lorente ML, Falguera M, Nogues A, Gonzalez AR, Merino MT, Caballero MR. Diagnosis of pneumococcal pneumonia by polymerase chain reaction (PCR) in whole blood: a prospective clinical study. Thorax. 2000;55:133-7.

69. Smith MD, Sheppard CL, Hogan A, et al. Diagnosis of Streptococcus pneumoniae infections in adults with bacteremia and community-acquired pneumonia: clinical comparison of pneumococcal PCR and urinary antigen detection. J Clin Microbiol. 2009;47:1046-9.

70. Peters RP, de Boer RF, Schuurman T, et al. Streptococcus pneumoniae DNA load in blood as a marker of infection in patients with community-acquired pneumonia. J Clin Microbiol. 2009;47:3308-12.

71. Rello J, Lisboa T, Lujan M, et al. Severity of pneumococcal pneumonia associated with genomic bacterial load. Chest. 2009;136:832-40.

72. Kivihya-Ndugga L, van Cleeff M, Juma E, et al. Comparison of PCR with the routine procedure for diagnosis of tuberculosis in a population with high prevalences of tuberculosis and human immunodeficiency virus. J Clin Microbiol. 2004;42:1012-5.

73. Liu FC, Chen PY, Huang F, Tsai CR, Lee CY, Wang LC. Rapid diagnosis of Mycoplasma pneumoniae infection in children by polymerase chain reaction J Microbiol Immunol Infect. 2007;40:507-12.

74. Murdoch DR. Molecular genetic methods in the diagnosis of lower respiratory tract infections. APMIS. 2004;112:713-27.

75. Sotir MJ, Cappozzo DL, Warshauer DM, et al. Evaluation of polymerase chain reaction and culture for diagnosis of pertussis in the control of a county-wide outbreak focused among adolescents and adults. Clin Infect Dis. 2007;44:1216-9.

76. Wegdam-Blans MC, Nabuurs-Franssen MN, Horrevorts AM, Peeters MF, Schneeberger PM, Bijlmer HA. [Laboratory diagnosis of acute Q fever). Ned Tijdschr Geneeskd. 2010;154:A2388.

77. Oosterheert JJ, van Loon AM, Schuurman R, et al. Impact of rapid detection of viral and atypical bacterial pathogens by real-time polymerase chain reaction for patients with lower respiratory tract infection. Clin Infect Dis. 2005;41:1438-44.

78. Lim WS, Baudouin SV, George RC, et al. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. Thorax. 2009;64(Suppl 3):iii1-55.

79. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007;44(Suppl 2):S27-S72.

80. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med. 1997;336:243-50.

81. Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax. 2003;58:377-82.

82. Caballero J, Rello J. Combination antibiotic therapy for community-acquired pneumonia. Ann Intensive Care. 2011;1:48.

83. Waterer GW. Monotherapy versus combination antimicrobial therapy for pneumococcal pneumonia. Curr Opin Infect Dis. 2005;18:157-63.

84. Weiss K, Tillotson GS. The controversy of combination vs monotherapy in the treatment of hospitalized community-acquired pneumonia. Chest. 2005;128:940-6.

85. Brown RB, Iannini P, Gross P, Kunkel M. Impact of initial antibiotic choice on clinical outcomes in community-acquired pneumonia: analysis of a hospital claims-made database. Chest. 2003;123:1503-11.

86. Dudas V, Hopefl A, Jacobs R, Guglielmo BJ. Antimicrobial selection for hospitalized patients with presumed community-acquired pneumonia: a survey of nonteaching US community hospitals. Ann Pharmacother. 2000;34:446-52.

87. Garcia VE, Mensa J, Martinez JA, et al. Lower mortality among patients with community-acquired pneumonia treated with a macrolide plus a beta-lactam agent versus a beta-lactam agent alone. Eur J Clin Microbiol Infect Dis. 2005;24:190-5.

88. Gleason PP, Meehan TP, Fine JM, Galusha DH, Fine MJ. Associations between initial antimicrobial therapy and medical outcomes for hospitalized elderly patients with pneumonia. Arch Intern Med. 1999;159:2562-72.

89. Houck PM, MacLehose RF, Niederman MS, Lowery JK. Empiric antibiotic therapy and mortality among medicare pneumonia inpatients in 10 western states : 1993, 1995, and 1997. Chest. 2001;119:1420-6.

90. Metersky ML, Ma A, Houck PM, Bratzler DW. Antibiotics for bacteremic pneumonia: Improved outcomes with macrolides but not fluoroquinolones. Chest. 2007;131:466-73.

91. Tessmer A, Welte T, Martus P, Schnoor M, Marre R, Suttorp N. Impact of intravenous {beta}-lactam/macrolide versus {beta}-lactam monotherapy on mortality in hospitalized patients with community-acquired pneumonia. J Antimicrob Chemother. 2009;63:1025-33.

92. Martinez JA, Horcajada JP, Almela M, et al. Addition of a macrolide to a beta-lactam-based empirical antibiotic regimen is associated with lower in-hospital mortality for patients with bacteremic pneumococcal pneumonia. Clin Infect Dis. 2003;36:389-95.

93. Mufson MA, Stanek RJ. Bacteremic pneumococcal pneumonia in one American City: a 20-year longitudinal study, 1978-1997. Am J Med. 1999;107(1A):34S-43S.

94. Waterer GW, Somes GW, Wunderink RG. Monotherapy may be suboptimal for severe bacteremic pneumococcal pneumonia. Arch Intern Med. 2001;161:1837-42.

95. Weiss K, Low DE, Cortes L, et al. Clinical characteristics at initial presentation and impact of dual therapy on the outcome of bacteremic Streptococcus pneumoniae pneumonia in adults. Can Respir J. 2004;11:589-93.

96. Aspa J, Rajas O, de Rodriguez CF, et al. Impact of initial antibiotic choice on mortality from pneumococcal pneumonia. Eur Respir J. 2006;27:1010-9.

97. Burgess DS, Lewis JS. Effect of macrolides as part of initial empiric therapy on medical outcomes for hospitalized patients with community-acquired pneumonia. Clin Ther. 2000;22:872-8.

98. Dwyer R, Ortqvist A, Aufwerber E, et al. Addition of a macrolide to a ss-lactam in bacteremic pneumococcal pneumonia. Eur J Clin Microbiol Infect Dis. 2006;25:518-21.

99. Ewig S, Hecker H, Suttorp N, Marre R, Welte T. Moxifloxacin monotherapy versus ss-lactam mono- or combination therapy in hospitalized patients with community-acquired pneumonia. J Infect. 2011;62:218-25.

100. Loh LC, Quah SY, Khoo SK, Vijayasingham P, Thayaparan T. Addition of macrolide in treating adult hospitalized community-acquired pneumonia. Respirology. 2005;10:371-7.

101. Paul M, Nielsen AD, Gafter-Gvili A, et al. The need for macrolides in hospitalised community-acquired pneumonia: propensity analysis. Eur Respir J. 2007 Sep;30(3):525-31.

102. Stahl JE, Barza M, DesJardin J, Martin R, Eckman MH. Effect of macrolides as part of initial empiric therapy on length of stay in patients hospitalized with community-acquired pneumonia. Arch Intern Med. 1999;159:2576-80.

103. Kovaleva A, Remmelts HH, Rijkers GT, Hoepelman AI, Biesma DH, Oosterheert JJ. Immunomodulatory effects of macrolides during community-acquired pneumonia: a literature review. J Antimicrob Chemother. 2012;67:530-40.

104. Grobbee DE, Hoes AW. Confounding and indication for treatment in evaluation of drug treatment for hypertension. BMJ. 1997;315:1151-4.

105. Garnacho-Montero J, Garcia-Cabrera E, Diaz-Martin A, et al. Determinants of outcome in patients with bacteraemic pneumococcal pneumonia: importance of early adequate treatment. Scand J Infect Dis. 2010;42:185-92.

106. Begg N, Cartwright KA, Cohen J, et al. Consensus statement on diagnosis, investigation, treatment and prevention of acute bacterial meningitis in immunocompetent adults. British Infection Society Working Party. J Infect. 1999;39:1-15.

107. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med. 2008;36:296-327.

108. De Pascale G, Bello G, Antonelli M. Steroids in severe pneumonia: a literature review. Minerva Anestesiol. 2011;77:902-10.

109. Salluh JI, Povoa P, Soares M, Castro-Faria-Neto HC, Bozza FA, Bozza PT. The role of corticosteroids in severe community-acquired pneumonia: a systematic review. Crit Care. 2008;12(3):R76.

110. Sibila O, Agusti C, Torres A. Corticosteroids in severe pneumonia. Eur Respir J. 2008;32:259-64.

111. Confalonieri M, Urbino R, Potena A, et al. Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. Am J Respir Crit Care Med. 2005;171:242-8.

112. Fernandez-Serrano S, Dorca J, Garcia-Vidal C, et al. Effect of corticosteroids on the clinical course of community-acquired pneumonia: a randomized controlled trial. Crit Care. 2011;15:R96.

113. Marik P, Kraus P, Sribante J, Havlik I, Lipman J, Johnson DW. Hydrocortisone and tumor necrosis factor in severe community-acquired pneumonia. A randomized controlled study. Chest. 1993;104:389-92.

114. Meijvis SC, Hardeman H, Remmelts HH, et al. Dexamethasone and length of hospital stay in patients with community-acquired pneumonia: a randomised, double-blind, placebo-controlled trial. Lancet. 2011;377:2023-30.

115. Mikami K, Suzuki M, Kitagawa H, et al. Efficacy of corticosteroids in the treatment of community-acquired pneumonia requiring hospitalization. Lung. 2007;185:249-55.

116. Snijders D, Daniels JM, de Graaff CS, van der Werf TS, Boersma WG. Efficacy of corticosteroids in community-acquired pneumonia: a randomized double-blinded clinical trial. Am J Respir Crit Care Med. 2010;181:975-82.

117. van der Poll T, Opal SM. Pathogenesis, treatment, and prevention of pneumococcal pneumonia. Lancet. 2009;374:1543-56.

118. Harboe ZB, Thomsen RW, Riis A, et al. Pneumococcal serotypes and mortality following invasive pneumococcal disease: a population-based cohort study. PLoS Med. 2009 May 26;6(5):e1000081.

119. Jansen AG, Rodenburg GD, de Greeff SC, et al. Invasive pneumococcal disease in the Netherlands: Syndromes, outcome and potential vaccine benefits. Vaccine. 2009;27:2394-401.

120. Jansen AG, Rodenburg GD, van der Ende A, et al. Invasive pneumococcal disease among adults: associations among serotypes, disease characteristics, and outcome. Clin Infect Dis. 2009;49:e23-e29.

121. Weinberger DM, Harboe ZB, Sanders EA, et al. Association of serotype with risk of death due to pneumococcal pneumonia: a meta-analysis. Clin Infect Dis. 2010;51:692-9.

122. Siber GR, Mäkelä PH. Pneumococcal Vaccines. Washington DC: ASM Press; 2008.

123. Health Council of the Netherlands. Pneumococcal vaccine in elderly adults and risk groups. The Hague: Health Council of the Netherlands; 2003. Report No.: publication no. 2003/10.

124. Huss A, Scott P, Stuck AE, Trotter C, Egger M. Efficacy of pneumococcal vaccination in adults: a meta-analysis. CMAJ. 2009;180:48-58.

125. Moberley SA, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev. 2008;(1):CD000422.

126. Lucero MG, Dulalia VE, Nillos LT, et al. Pneumococcal conjugate vaccines for preventing vaccine-type invasive pneumococcal disease and X-ray defined pneumonia in children less than two years of age. Cochrane Database Syst Rev. 2009;(4):CD004977.

127. Direct and indirect effects of routine vaccination of children with 7-valent pneumococcal conjugate vaccine on incidence of invasive pneumococcal disease--United States, 1998-2003. MMWR Morb Mortal Wkly Rep. 2005;54:893-7.

128. Black S, Shinefield H, Fireman B, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Northern California Kaiser Permanente Vaccine Study Center Group. Pediatr Infect Dis J. 2000;19:187-95.

129. Cutts FT, Zaman SM, Enwere G, et al. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. Lancet. 2005;365:1139-46.

130. Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, Pierce N. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. N Engl J Med. 2003;349:1341-8.

131. Pilishvili T, Lexau C, Farley MM, et al. Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. J Infect Dis. 2010;201:32-41.

132. Whitney CG, Pilishvili T, Farley MM, et al. Effectiveness of seven-valent pneumococcal conjugate vaccine against invasive pneumococcal disease: a matched case-control study. Lancet. 2006;368:1495-502.

133. Rodenburg GD, de Greeff SC, Jansen AG, et al. Effects of pneumococcal conjugate vaccine 2 years after its introduction, the Netherlands. Emerg Infect Dis. 2010;16:816-23.

134. Dransfield MT, Nahm MH, Han MK, et al. Superior immune response to protein-conjugate versus free pneumococcal polysaccharide vaccine in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2009;180:499-505.

135. Goldblatt D, Southern J, Andrews N, et al. The immunogenicity of 7-valent pneumococcal conjugate vaccine versus 23-valent polysaccharide vaccine in adults aged 50-80 years. Clin Infect Dis. 2009;49:1318-25.

136. de Roux A, Schmole-Thoma B, Siber GR, et al. Comparison of pneumococcal conjugate polysaccharide and free polysaccharide vaccines in elderly adults: conjugate vaccine elicits improved antibacterial immune responses and immunological memory. Clin Infect Dis. 2008;46:1015-23.

137. Kumar D, Rotstein C, Miyata G, Arlen D, Humar A. Randomized, double-blind, controlled trial of pneumococcal vaccination in renal transplant recipients. J Infect Dis. 2003;187:1639-45.

138. Kapetanovic MC, Roseman C, Jonsson G, Truedsson L. Heptavalent pneumococcal conjugate vaccine elicits similar antibody response as standard 23-valent polysaccharide vaccine in adult patients with RA treated with immunomodulating drugs. Clin Rheumatol. 2011;30:1555-61.

139. Smith KJ, Wateska AR, Nowalk MP, Raymund M, Nuorti JP, Zimmerman RK. Cost-effectiveness of adult vaccination strategies using pneumococcal conjugate vaccine compared with pneumococcal polysaccharide vaccine. JAMA. 2012;307:804-12.

140. French N, Gordon SB, Mwalukomo T, et al. A trial of a 7-valent pneumococcal conjugate vaccine in HIV-infected adults. N Engl J Med. 2010;362:812-22.

141. Hak E, Grobbee DE, Sanders EA, et al. Rationale and design of CAPITA: a RCT of 13-valent conjugated pneumococcal vaccine efficacy among older adults. Neth J Med. 2008;66:378-83.

142. Boersma WG, Lowenberg A, Holloway Y, Kuttschrutter H, Snijder JA, Koeter GH. Pneumococcal capsular antigen detection and pneumococcal serology in patients with community acquired pneumonia. Thorax. 1991;46:902-6.

143. Bohte R, van Furth R, van den Broek PJ. Aetiology of community-acquired pneumonia: a prospective study among adults requiring admission to hospital. Thorax. 1995;50:543-7.

144. Braun JJ, de Graaff CS, de Goey J, Zwinderman AH, Petit PL. [Community-acquired pneumonia: pathogens and course in patients admitted to a general hospital). Ned Tijdschr Geneeskd. 2004;148:836-40.

145. van der Eerden MM, Vlaspolder F, de Graaff CS, Groot T, Jansen HM, Boersma WG. Value of intensive diagnostic microbiological investigation in low- and high-risk patients with community-acquired pneumonia. Eur J Clin Microbiol Infect Dis. 2005;24:241-9.

146. Steinhoff D, Lode H, Ruckdeschel G, et al. Chlamydia pneumoniae as a cause of community-acquired pneumonia in hospitalized patients in Berlin. Clin Infect Dis. 1996;22:958-64.

147. Garbino J, Sommer R, Gerber A, et al. Prospective epidemiologic survey of patients with community-acquired pneumonia requiring hospitalization in Switzerland. Int J Infect Dis. 2002;6:288-93.

148. Venkatesan P, Gladman J, Macfarlane JT, et al. A hospital study of community acquired pneumonia in the elderly. Thorax. 1990;45:254-8.

149. Lim WS, Macfarlane JT, Boswell TC, et al. Study of community acquired pneumonia aetiology (SCAPA) in adults admitted to hospital: implications for management guidelines. Thorax. 2001;56:296-301.

150. Howard LS, Sillis M, Pasteur MC, Kamath AV, Harrison BD. Microbiological profile of community-acquired pneumonia in adults over the last 20 years. J Infect. 2005;50:107-13.

151. Levy M, Dromer F, Brion N, Leturdu F, Carbon C. Community-acquired pneumonia. Importance of initial noninvasive bacteriologic and radiographic investigations. Chest. 1988;93:43-8.

152. Ausina V, Coll P, Sambeat M, et al. Prospective study on the etiology of community-acquired pneumonia in children and adults in Spain. Eur J Clin Microbiol Infect Dis. 1988;7:342-7.

153. Pachon J, Prados MD, Capote F, Cuello JA, Garnacho J, Verano A. Severe community-acquired pneumonia. Etiology, prognosis, and treatment. Am Rev Respir Dis. 1990;142:369-73.

154. Blanquer J, Blanquer R, Borras R, et al. Aetiology of community acquired pneumonia in Valencia, Spain: a multicentre prospective study. Thorax. 1991;46:508-11.

155. Almirall J, Boixeda R, Bolibar I, Bassa J, Sauca G, Vidal J, et al. Differences in the etiology of community-acquired pneumonia according to site of care: a population-based study. Respir Med. 2007;101:2168-75.

156. Pareja A, Bernal C, Leyva A, Piedrola G, Maroto MC. Etiologic study of patients with community-acquired pneumonia. Chest. 1992;101:1207-10.

157. Falco V, Fernandez de ST, Alegre J, Ferrer A, Martinez Vazquez JM. Legionella pneumophila. A cause of severe community-acquired pneumonia. Chest. 1991;100:1007-11.

158. Ruiz-Gonzalez A, Falguera M, Nogues A, Rubio-Caballero M. Is Streptococcus pneumoniae the leading cause of pneumonia of unknown etiology? A microbiologic study of lung aspirates in consecutive patients with community-acquired pneumonia. Am J Med. 1999;106:385-90.

159. Sopena N, Sabria M, Pedro-Botet ML, et al. Prospective study of community-acquired pneumonia of bacterial etiology in adults. Eur J Clin Microbiol Infect Dis. 1999;18:852-8.

160. Fernandez-Sabe N, Carratala J, Roson B, et al. Community-acquired pneumonia in very elderly patients: causative organisms, clinical characteristics, and outcomes. Medicine (Baltimore). 2003;82:159-69.

161. Menendez R, Cordoba J, de la Cuadra P, et al. Value of the polymerase chain reaction assay in noninvasive respiratory samples for diagnosis of community-acquired pneumonia. Am J Respir Crit Care Med. 1999;159:1868-73.

162. Ruiz M, Ewig S, Marcos MA, et al. Etiology of community-acquired pneumonia: impact of age, comorbidity, and severity. Am J Respir Crit Care Med. 1999;160:397-405.

163. Cilloniz C, Ewig S, Polverino E, et al. Microbial aetiology of community-acquired pneumonia and its relation to severity. Thorax. 2011;66:340-6.

164. Zalacain R, Torres A, Celis R, et al. Community-acquired pneumonia in the elderly: Spanish multicentre study. Eur Respir J. 2003;21:294-302.

165. Falguera M, Sacristan O, Nogues A, et al. Nonsevere community-acquired pneumonia: correlation between cause and severity or comorbidity. Arch Intern Med. 2001;161:1866-72.

166. Marcos MA, Jimenez de Anta MT, de la Bellacasa JP, et al. Rapid urinary antigen test for diagnosis of pneumococcal community-acquired pneumonia in adults. Eur Respir J. 2003;21:209-14.

167. Briones ML, Blanquer J, Ferrando D, Blasco ML, Gimeno C, Marin J. Assessment of analysis of urinary pneumococcal antigen by immunochromatography for etiologic diagnosis of community-acquired pneumonia in adults. Clin Vaccine Immunol. 2006;13:1092-7.

168. Angeles MM, Camps M, Pumarola T, et al. The role of viruses in the aetiology of community-acquired pneumonia in adults. Antivir Ther. 2006;11:351-9.

169. Socan M, Marinic-Fiser N, Kraigher A, Kotnik A, Logar M. Microbial aetiology of community-acquired pneumonia in hospitalised patients. Eur J Clin Microbiol Infect Dis. 1999;18:777-82.

170. Beovic B, Bonac B, Kese D, et al. Aetiology and clinical presentation of mild community-acquired bacterial pneumonia. Eur J Clin Microbiol Infect Dis. 2003;22:584-91.

171. Kerttula Y, Leinonen M, Koskela M, Makela PH. The aetiology of pneumonia. Application of bacterial serology and basic laboratory methods. J Infect. 1987;14:21-30.

172. Holmberg H. Aetiology of community-acquired pneumonia in hospital treated patients. Scand J Infect Dis. 1987;19:491-501.

173. Burman LA, Trollfors B, Andersson B, et al. Diagnosis of pneumonia by cultures, bacterial and viral antigen detection tests, and serology with special reference to antibodies against pneumococcal antigens. J Infect Dis. 1991;163:1087-93.

174. Ostergaard L, Andersen PL. Etiology of community-acquired pneumonia. Evaluation by transtracheal aspiration, blood culture, or serology. Chest. 1993;104:1400-7.

175. Stralin K, Olcen P, Tornqvist E, Holmberg H. Definite, probable, and possible bacterial aetiologies of community-acquired pneumonia at different CRB-65 scores. Scand J Infect Dis. 2010;42:426-34.

176. Hohenthal U, Vainionpaa R, Meurman O, et al. Aetiological diagnosis of community acquired pneumonia: utility of rapid microbiological methods with respect to disease severity. Scand J Infect Dis. 2008;40:131-8.