Cite this article as: BMJ, doi:10.1136/bmj.38993.560984.BE (published 7 November 2006)

Research

BMJ

Effectiveness of early switch from intravenous to oral antibiotics in severe community acquired pneumonia: multicentre randomised trial

Jan Jelrik Oosterheert, Marc J M Bonten, Margriet M E Schneider, Erik Buskens, Jan-Willem J Lammers, Willem M N Hustinx, Mark H H Kramer, Jan M Prins, Peter H Th J Slee, Karin Kaasjager, Andy I M Hoepelman

Abstract

Objectives To compare the effectiveness of an early switch to oral antibiotics with the standard 7 day course of intravenous antibiotics in severe community acquired pneumonia.
Design Multicentre randomised controlled trial.
Setting Five teaching hospitals and 2 university medical centres in the Netherlands.
Participants 302 patients in non-intensive care wards with severe community acquired pneumonia. 265 patients fulfilled the study requirements.
Intervention Three days of treatment with intravenous antibiotics followed, when clinically stable, by oral antibiotics or by 7 days of intravenous antibiotics.
Main outcome measures Clinical cure and length of hospital stay.
Results 302 patients were randomised (mean age 69.5 (standard deviation 14.0), mean pneumonia severity score 112.7 (26.0)). 37 patients were excluded from analysis because of early dropout before day 3, leaving 265 patients for intention to treat analysis. Mortality at day 28 was 4% in the intervention group and 6% in the control group (mean difference 2%, 95% confidence interval −3% to 8%). Clinical cure was 83% in the intervention group and 85% in the control group (2%, −7% to 10%). Duration of intravenous treatment and length of hospital stay were reduced in the intervention group, with mean differences of 3.4 days (3.6 (1.5) *v* 7.0 (2.0) days; 2.8 to 3.9) and 1.9 days (9.6 (5.0) *v* 11.5 (4.9) days; 0.6 to 3.2), respectively.
Conclusions Early switch from intravenous to oral antibiotics in patients with severe community acquired pneumonia is safe and decreases length of hospital stay by 2 days.
Trial registration Clinical Trials NCT00273676.

Introduction

Community acquired pneumonia is a common and potentially fatal infection with high healthcare costs.[1–3] When patients are first admitted to hospital antibiotics are usually given intravenously to provide optimal concentrations in the tissues. The duration of intravenous treatment is an important determinant of length of hospital stay.[4] Conventionally, intravenous treatment is continued until definite clinical cure. A switch to treatment with oral antibiotics may allow early discharge and reduce drug costs, but may increase the rate of treatment failure, readmission, and death; it may also increase the workload for family members or healthcare professionals outside the hospital.

The concept of early transition from intravenous to oral antibiotics in the treatment of community acquired pneumonia has been evaluated before, but only in mild to moderately severe disease and rarely in randomised trials.[4–14] For patients with more severe forms of the disease, effects on outcome and length of hospital stay have not been determined in randomised trials. Therefore, we conducted a multicentre randomised trial to evaluate the effectiveness of an early switch from intravenous to oral antibiotics compared with a seven day intravenous treatment regimen in patients with severe community acquired pneumonia.

Patients and methods

Study design

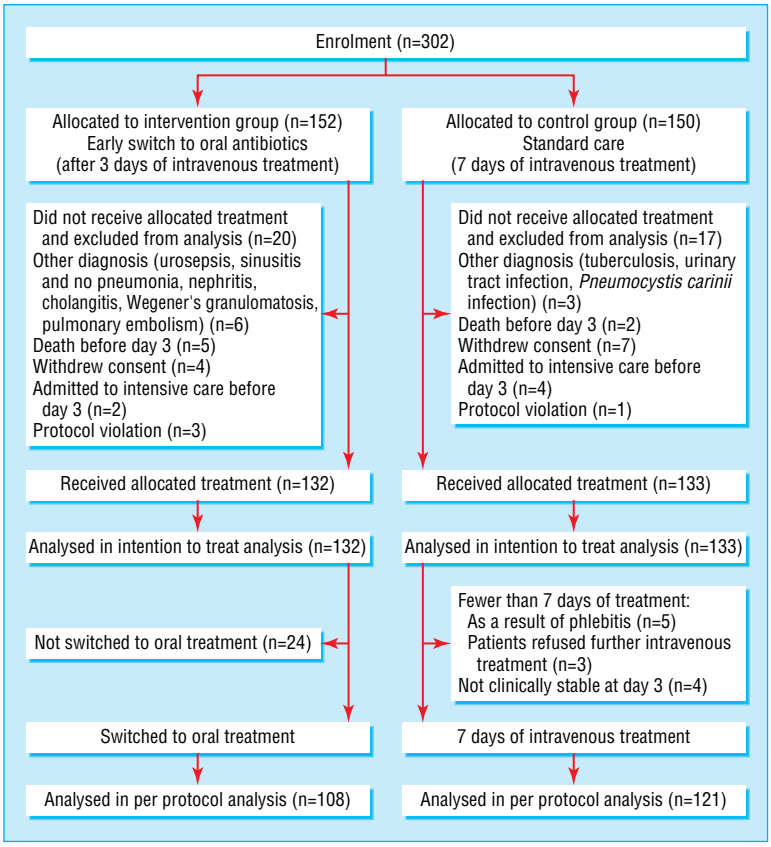
We performed a multicentre, randomised open label clinical trial in two university medical centres and five teaching hospitals in the Netherlands. All patients gave written informed consent before enrolment.

An independent central randomisation centre used computer generated tables to allocate treatment. Patients were randomised to the intervention group, where clinically stable patients (defined as respiratory rate <25/min, oxygen saturation $>90\%$ or arterial oxygen pressure >55 mm Hg, haemodynamically stable, >1°C decrease in temperature in case of fever, absence of mental confusion, and the ability to take oral drugs[10]) were switched from intravenous to oral antibiotics on the third day in hospital to complete a total of 10 days of antibiotic treatment, or to the control group, where patients received a standard regimen of seven days of intravenous treatment. Additional antibiotic treatment thereafter was left to the discretion of the treating doctor. The attending consultant chose the antibiotics on the basis of Dutch treatment guidelines.[15]

Primary outcome measure was clinical cure. Secondary outcome measure was the length of hospital stay.

Patients

Adult patients (≥ 18 years) with severe community acquired pneumonia admitted to general hospital wards were eligible for inclusion in our study. We defined pneumonia as a new or progressive infiltrate on a chest radiograph plus at least two other criteria (cough, sputum production, rectal temperature >38°C or <36.1°C, auscultatory findings consistent with pneumonia, leucocytosis ($>10^9$ white blood cells/litre or $>15\%$ bands), C reactive protein more than three times the upper limit of normal, or positive culture of blood or pleural fluid).[16] Severe



Flow of participants through trial

pneumonia was defined as pneumonia severity index class IV or V or fulfilling the American Thoracic Society criteria for severe community acquired pneumonia.[17 18] We excluded patients who needed mechanical ventilation in an intensive care unit and those with cystic fibrosis; a history of colonisation with Gram negative bacteria due to structural damage to the respiratory tract; malfunction of the digestive tract; life expectancy of less than one month because of underlying disease (assessed independently by the doctor caring for the patient); infections other than pneumonia that needed antibiotic treatment; and severe immunosuppression (neutropenia ($<0.5\times10^9$ neutrophils/litre) or a CD4 count $<200/mm^3$).

Baseline, follow-up, and outcome measurements

Patients were followed up for 28 days. On admission (day 0), we performed physical examination, chest radiography, and blood sampling for arterial blood gases, haematological analysis, and biochemical markers. We recorded demographic and clinical data and initial intravenous treatment. During follow-up, in-hospital clinical data were recorded. We evaluated clinical stability after three days of intravenous treatment in both groups and evaluated preset discharge criteria (temperature <37.8°C, oxygen saturation >92%, normal blood pressure, heart rate <100/min, respiratory rate <25/min, absence of mental confusion, and ability to take oral drugs) daily thereafter. Patients discharged within 28 days were asked to return to the outpatient clinic 28 days after inclusion, where history, physical examination, blood chemistry analysis, and chest radiograph were performed.

We used questionnaires to measure the effect of early discharge on adverse events, compliance, and how the route of administration affected freedom of movement.

Treatment failure was defined as death, still in hospital at day 28 of the study, or clinical deterioration (increase in temperature after initial improvement or the need for mechanical ventilation, switch back to intravenous antibiotics, or readmission for pulmonary reinfection after discharge). Clinical cure was defined as discharged in good health without signs and symptoms of pneumonia and no treatment failure during follow-up.[16]

Microbiological analyses

We used standard procedures to collect, culture, and evaluate sputum and blood samples. Sputum samples were considered adequate and subsequently cultured if 25 or more polymorphonuclear neutrophils and fewer than 10 epithelial cells were present in each high power field.

We used Binax NOW-tests to detect *Legionella pneumophila* and *Streptococcus pneumoniae* antigens in urine. Acute and convalescent serology samples were collected and evaluated for *Mycoplasma pneumoniae*, *L pneumophila*, and *Chlamydia pneumonia*. Any non-contaminating micro-organism cultured from a blood or sputum sample or detected by urinary antigen testing was considered a cause for the episode of pneumonia. We considered the following results indicative of infection: for *M pneumoniae*, a fourfold or greater increase in titre in paired sera or a single titre of 1:40 or greater[19] (immune fluorescence agglutination, Serodia-MycoII, Fujirebio); for *L pneumophila*, a fourfold increase in the antibody titre to 1:128 or greater, or single titres of 1:256 or more[20]; and for *C pneumoniae*, detection of IgM above established values, seroconversion of IgG between acute and convalescence samples, high amounts of IgG in single titres, or a combination of these (enzyme linked immunosorbent assay, Savyon Diagnostics).

Table 1 Multicentre randomised trial of early switch from intravenous to oral antibiotics in severe community acquired pneumonia. Patient's characteristics at baseline. Values are number (percentage) unless stated otherwise

Characteristic	Treatment group	
	Intervention (n=150)	Control (n=152)
Men	102 (68)	97 (64)
Mean (SD) age (years)	69.9 (13.8)	69.0 (14.2)
Nursing home patients	7 (5)	5 (3)
Mean (SI) pneumonia severity score	111.6 (26.3)	113.7 (25.8)
Pneumonia severity class		
II	11 (7)	7 (5)
III	14 (9)	11 (7)
IV	93 (62)	111 (73)
V	32 (21)	23 (15)
Mean (SD) leucocyte count (10^9/l)	17.2 (9.9)	15.7 (8.5)
Mean (SD) C reactive protein (mg/l)	209.1 (151.6)	199.2 (151.4)
Mean (SD) heart rate (/min)	103.3 (22.0)	108.2 (23.0)
Mean (SD) respiratory rate (/min)	26.5 (8.7)	26.6 (8.5)
Mean (SD) temperature (°C)	38.5 (1.2)	38.6 (1.2)
Mean (SD) oxygen saturation (%)	93.3 (5.3)	92.1 (8.3)
Mean (SD) arterial oxygen pressure (mm Hg)	68.4 (20.9)	67.3 (23.1)
Presenting symptom		
Myalgia	43 (29)	44 (29)
Nausea	34 (23)	40 (26)
Diarrhoea	14 (9)	25 (17)
Headache	30 (20)	39 (26)
Dyspnoea	129 (86)	131 (86)
Chest pain	54 (36)	47 (31)
Sore throat	12 (8)	16 (11)
Productive cough	94 (63)	90 (59)
Haemoptysis	16 (11)	18 (12)
Confusion	34 (23)	43 (28)
Fever	100 (67)	93 (61)
Comorbidities		
Malignancy	32 (21)	35 (23)
Liver disease	0 (0)	3 (2)
Heart failure	20 (13)	17 (11)
Cerebrovascular disease	11 (7)	16 (11)
Renal disease	16 (11)	46 (30)
Initial treatment		
Amoxicillin ±clavulanic acid	90 (60)	84 (55)
Cephalosporin (2nd and 3rd generation)	28 (19)	31 (20)
Fluoroquinolone	0 (0)	1 (1)
Amoxicillin ±clavulanic acid +macrolide	15 (10)	11 (7)
Cephahlosporin +macrolide	4 (3)	8 (5)
Other	13 (9)	17 (11)

Sample size and statistical analysis

To demonstrate equivalence in effectiveness of the two treatment groups, we initially set the sample size at 250 patients in each group on the basis of an expected cure rate of 85% in the intravenous group and a 75% cure rate in the switch group ($\alpha = 0.05$, two sided; $1\text{-}\beta = 0.80$). We calculated the absolute difference in cure rate including 95% confidence interval. Equivalence was rejected if the lower limit of the confidence interval exceeded −10%.

Differences in continuous variables are shown as absolute differences with corresponding 95% confidence intervals. We used χ^2 statistics to compare dichotomous data. Differences in percentage cure rate are shown with 95% confidence intervals. We performed intention to treat analysis and per protocol analysis of patients who had received antibiotics for at least the duration dictated by the study protocol and who were clinically stable at day 3 after admission to hospital and eligible for an early switch from intravenous to oral antibiotics.

Table 2 Micro-organisms identified in multicentre randomised trial of early switch from intravenous to oral antibiotics in severe community acquired pneumonia. Values are number of patients (percentage)

Micro-organism	Treatment group	
	Intervention (n=150)	Control (n=152)
Streptococcus pneumoniae	29 (19)	47 (31)
Isolated from sputum	6 (4)	16 (11)
Isolated from blood	9 (6)	16 (11)
Positive urinary antigen test	19 (13)	28 (19)
Staphylococcus aureus	7 (5)	5 (3)
Isolated from sputum	5 (3)	4 (3)
Isolated from blood	2 (1)	1 (1)
*Haemophilus influenzae**	6 (4)	3 (2)
*Mycoplasma catharralis**	5 (3)	0 (0)
Chlamydia pneumoniae†	8 (5)	7 (5)
Mycoplasma pneumoniae†	2 (1)	6 (4)
Legionella pneumophila	4 (3)	6 (4)
Serological evidence	4 (3)	6 (4)
Positive urinary antigen test	2 (1)	3 (2)
Other	17 (11)	24 (16)
Unknown cause	84 (56)	71 (47)

*Isolated from sputum.
†Based on serological evidence.

Results

Characteristics of the patients and treatment assignment

Between July 2000 and March 2004, we considered all patients admitted to hospital with community acquired pneumonia for inclusion. Because enrolment was slower than expected fewer than the precalculated 500 patients were included. In total, 302 patients were randomised: 150 were assigned to the control group to receive a standard course of seven days' intravenous treatment and 152 were randomised to the early switch group (figure). Baseline characteristics were similar in both groups. More than 80% of patients were in pneumonia severity class IV or V. Most patients received empirical monotherapy with amoxicillin or amoxicillin plus clavulanic acid (n=174; 58%) or a cephalosporin (n=59; 20%), which is in line with Dutch prescribing policies (table 1). The most frequently identified micro-organism was *S pneumoniae* (n=76; 25%, table 2). Atypical pathogens were detected in 33 patients (11%) (table 2). Before day 3, 37 (12%) patients were excluded from analysis, leaving 132 patients for analysis in the intervention group and 133 in the control group. Reasons for exclusion were the initial diagnosis of community acquired pneumonia was replaced by another diagnosis (n=9), consent was withdrawn (n=11), the protocol was violated (n=4), admission to an intensive care unit for mechanical ventilation (n=6), and death (n=7). After three days of intravenous treatment, 108/132 (81%) patients in the intervention group were switched to oral treatment, of whom 102 (94%) received amoxicillin plus clavulanic acid (500+125 mg every eight hours).

In the control group, five patients did not receive intravenous antibiotics for all seven days because of phlebitis associated with intravenous treatment; none of them needed treatment for line related sepsis. Overall duration of antibiotic treatment was 10.1 days in the intervention group and 9.3 days in the control group (mean difference 0.8 days, 95% confidence interval −0.6 to 2.0).

Clinical outcome

In intention to treat analysis, treatment failed in 22 (17%) and 20 (15%) patients in the intervention group and the control group (−2%, −10% to 7%; table 3). In the control group, nine (7%) patients were still in hospital on day 28, eight (6%) had deterio-

Table 3 Outcomes in multicentre randomised trial of early switch from intravenous to oral antibiotics in severe community acquired pneumonia. Intention to treat analysis. Values are number of patients (percentage) unless stated otherwise

Clinical outcome	Treatment group		Mean difference (95% CI)
	Intervention (n=132)	Control (n=133)	
Death after day 3	5 (4)	8 (6)	2% (–3% to 8%)
Clinical cure	110 (83)	113 (85)	2% (–7% to 10%)
Clinical failure:	22 (17)	20 (15)	–2% (–10% to 7%)
Clinical cure but still in hospital	9 (7)	6 (5)	–2% (–4% to 8%)
Clinical deterioration	8 (6)	6 (5)	–1% (–4% to 7%)
Death	5 (4)	8 (6)	2% (–3% to 8%)
Clinical deterioration and death	13 (10)	14 (11)	1% (–1% to 8%)
Mean (SD) length of hospital stay (days)	9.6 (5.0)	11.5 (4.9)	1.9 (0.6 to 3.2)
Mean (SD) duration of intravenous treatment (days)	3.6 (1.5)	7.0 (2.0)	3.4 (2.8 to 3.9)

rated clinically, and eight (6%) had died. In the intervention group, six (5%) patients were still in hospital, six (5%) had deteriorated clinically, and five (4%) had died.

The duration of intravenous treatment was significantly shorter in the intervention group (mean 3.6 (SD 1.5) *v* 7.0 (2.0) days, mean difference 3.4, 2.8 to 3.9; table 3). Average time to meet the discharge criteria was 5.2 (2.9) days in the intervention group and 5.7 (3.1) days in the control group (0.5 days, – 0.3 to 1.2) Total length of hospital stay was 9.6 (5.0) and 11.5 (4.9) days for patients in the intervention group and control group (1.9 days, 0.6 to 3.2). Per protocol analysis showed comparable results for clinical outcome and length of hospital stay (table 4). Patients meeting discharge criteria were not always discharged immediately; the main reasons were incomplete resolution of all clinical criteria of pneumonia or comorbid illness, the anticipated lack of continued care after discharge, and doctor's considerations.

Overall, patients treated with oral or intravenous antibiotics had the same problems with regard to mobility and other side effects.

Discussion

Patients admitted to hospital with severe community acquired pneumonia can be managed more efficiently by an early switch from intravenous to oral drugs—81% of patients could be switched to oral antibiotics on day 3, which reduced the average length of hospital stay by at least 1.9 days. Our findings can probably be generalised, as our patients were similar to other cohorts with this disease in terms of average length of stay in the control group, aetiology, and mortality rate.[8 14]

Table 4 Outcomes in multicentre randomised trial of early switch from intravenous to oral antibiotics in severe community acquired pneumonia. Per protocol analysis. Values are number of patients (percentage) unless stated otherwise

Clinical outcome	Treatment group		Mean difference (95% CI)
	Intervention (n=108)	Control (n=121)	
Death after day 3	1 (1)	8 (7)	5% (0% to 12%)
Clinical cure	93 (86)	101 (83)	–3% (–12% to 7%)
Clinical failure	15 (14)	20 (17)	3% (–7% to 12%)
Clinical cure but still in hospital	6 (6)	6 (5)	–1% (–7% to 6%)
Clinical deterioration	8 (7)	6 (5)	–2% (–9% to 5%)
Death	1 (1)	8 (7)	6% (0% to 12%)
Clinical deterioration plus death	9 (8)	14 (12)	4% (–6% to 12%)
Mean (SD) length of hospital stay (days)	9.0 (4.7)	11.3 (4.7)	2.3 (1.0 to 3.6)
Mean (SD) duration of intravenous treatment (days)	3.3 (1.1)	7.5 (2.0)	4.2 (3.7 to 4.6)

Strengths and limitations

Our study provides evidence that an early switch from intravenous to oral antibiotics is safe in patients with severe community acquired pneumonia. In most previous studies, a non-randomised design was used,[4 5 9] specific patient populations in military hospitals or moderately ill patients were studied,[6] sample sizes were small,[8] or the patients were switched relatively late—for example, after two to three consecutive days without fever.[8 14]

Our study had several limitations. The number of patients included was lower than calculated before the start of the study. Because results show small and non-significant differences in rates of treatment failure, however, it is highly unlikely that an early switch is more than 10% less effective. Moreover, mortality rates were even lower in the intervention group.

The effects of switching treatment may have been overestimated for two reasons. Firstly, in patients who were clinically stable at day 3, protocol dictated an intravenous to oral switch, but it is uncertain how many patients would have been switched in daily practice. With growing confidence in the safety of an early switch strategy this effect might decrease. Secondly, the minimum duration of intravenous treatment for the control group of seven days was also dictated by protocol, and shorter durations would have decreased the benefits of an early switch as long as failure rates remained the same.

In contrast, the effects of switching treatment could have been underestimated for two reasons. Firstly, the protocol did not cover discharge, and doctors' views on continued stay in hospital strongly influenced delayed discharge of clinically stable patients. With growing confidence, this phenomenon may decrease. Although clinical instability at discharge is associated with adverse clinical outcomes, clinical deterioration after reaching clinical stability is rare.[21] In our study, only three (2%) patients were restarted on intravenous drugs after being switched to oral treatment. Secondly, the protocol only allowed patients to be switched to oral drugs when they were clinically stable on day 3. Patients who were clinically stable before day 3 could possibly be switched earlier, which could enhance the benefits of this strategy.

What is already known on this topic

An early switch to treatment with oral antibiotics in community acquired pneumonia may allow early discharge and reduce drug and treatment costs

Studies have evaluated only patients with mild to moderately severe disease, rarely in a randomised design

What this study adds

Early transition to oral antibiotics can safely be implemented in clinical practice in patients with severe community acquired pneumonia who do not need treatment in intensive care

Such a strategy leads to a reduced length of hospital stay

Funding: Dutch Health Insurance Council, grant OG 99-64.

Contributors: JJO coordinated the study, helped supervise enrolment and follow-up, analysed and interpreted the data, and wrote the paper. MJMB, EB, MMES, J-WJL, and AIMH designed the study protocol, and helped supervise enrolment and follow-up, interpret the data, and prepare the paper. EB and MJMB supervised the statistical analysis. J-WJL, WMNH, MHHK, JMP, PHThJS, and KK helped in enrolment and follow-up and helped prepare the final version of the paper. AIMH is guarantor.

Competing interests: None declared.

Ethical approval: Ethics committees of participating institutions.The study was presented in part at the Interscience Conference on Antimicrobial Agents and Chemotherapy, abstract O-1607, Washington DC, USA, 2004.

1 Guest JF, Morris A. Community-acquired pneumonia: the annual cost to the National Health Service in the UK. *Eur Respir J* 1997;10:1530-4.
2 Marston BJ, Plouffe JF, File TM Jr, Hackman BA, Salstrom SJ, Lipman HB, et al. Incidence of community-acquired pneumonia requiring hospitalization. Results of a population-based active surveillance study in Ohio. The Community-Based Pneumonia Incidence Study Group. *Arch Intern Med* 1997;157:1709-18.
3 Pinner RW, Teutsch SM, Simonsen L, Klug LA, Graber JM, Clarke MJ, et al. Trends in infectious diseases mortality in the United States. *JAMA* 1996;275:189-93.
4 Ramirez JA, Vargas S, Ritter GW, Brier ME, Wright A, Smith S, et al. Early switch from intravenous to oral antibiotics and early hospital discharge: a prospective observational study of 200 consecutive patients with community-acquired pneumonia. *Arch Intern Med* 1999;159:2449-54.
5 Rhew DC, Weingarten SR. Achieving a safe and early discharge for patients with community-acquired pneumonia. *Med Clin North Am* 2001;85:1427-40.
6 Siegel RE, Halpern NA, Almenoff PL, Lee A, Cashin R, Greene JG. A prospective randomized study of inpatient iv antibiotics for community-acquired pneumonia. The optimal duration of therapy. *Chest* 1996;110:965-71.
7 Omidvari K, de Boisblanc BP, Karam G, Nelson S, Haponik E, Summer W. Early transition to oral antibiotic therapy for community-acquired pneumonia: duration of therapy, clinical outcomes, and cost analysis. *Respir Med* 1998;92:1032-9.
8 Castro-Guardiola A, Viejo-Rodriguez AL, Soler-Simon S, Armengou-Arxe A, Bisbe-Company V, Penarroja-Matutano G, et al. Efficacy and safety of oral and early-switch therapy for community-acquired pneumonia: a randomized controlled trial. *Am J Med* 2001;111:367-74.
9 Ramirez JA, Srinath L, Ahkee S, Huang A, Raff MJ. Early switch from intravenous to oral cephalosporins in the treatment of hospitalized patients with community-acquired pneumonia. *Arch Intern Med* 1995;155:1273-6.
10 Weingarten SR, Riedinger MS, Hobson P, Noah MS, Johnson B. Evaluation of a pneumonia practice guideline in an interventional trial. *Am J Respir Crit Care Med* 1996;153:1110-5.
11 Rhew DC, Riedinger MS, Sandhu M, Bowers C, Greengold N, Weingarten SR. A prospective, multicenter study of a pneumonia practice guideline. *Chest* 1998;114:115-9.
12 Marrie TJ, Lau CY, Wheeler SL, Wong CJ, Vandervoort MK, Feagan BG. A controlled trial of a critical pathway for treatment of community-acquired pneumonia. CAPITAL study investigators. Community-acquired pneumonia intervention trial assessing levofloxacin. *JAMA* 2000;283:749-55.
13 Ramirez JA, Bordon J. Early switch from intravenous to oral antibiotics in hospitalized patients with bacteremic community-acquired Streptococcus pneumoniae pneumonia. *Arch Intern Med* 2001;161:848-50.
14 van der Eerden MM, de Graaff CS, Vlaspolder F, Bronsveld W, Jansen HM, Boersma WG. Evaluation of an algorithm for switching from IV to PO therapy in clinical practice in patients with community-acquired pneumonia. *Clin Ther* 2004;26:294-303.
15 Van Kasteren MEE, Wijnands WJ, Stobbering EE, Janknegt R, van der Meer JW. Optimization of the antibiotics policy in the Netherlands. II. SWAB guidelines for the antimicrobial therapy of pneumonia in patients at home and as nosocomial infections. The Netherlands Antibiotic Policy Foundation. *Ned Tijdschr Geneeskd* 1998;142:952-6.
16 Chow AW, Hall CB, Klein JO, Kammer RB, Meyer RD, Remington JS. General guidelines for the evaluation of new anti-infective drugs for the treatment of respiratory tract infections. *Clin Infect Dis* 1992;15(suppl 1):s62-88.
17 American Thoracic Society. Guidelines for the management of adults with community acquired pneumonia. *Am J Respir Crit Care Med* 2001;163:1730-54.
18 Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, et al. A prediction rule to identify low-risk patients with community acquired pneumonia. *N Engl J Med* 1997;336:243-50.
19 Jacobs E. Serological diagnosis of Mycoplasma pneumoniae infections: a critical review of current procedures. *Clin Infect Dis* 1993;17(suppl 1):S79-82.
20 Stout JE, Yu VL. Legionellosis. *N Engl J Med* 1997;337:682-7.
21 Halm EA, Fine MJ, Kapoor WN, Singer DE, Marrie TJ, Siu AL. Instability on hospital discharge and the risk of adverse outcomes in patients with pneumonia. *Arch Intern Med* 2002;162:1278-84.

(Accepted 22 September 2006)

doi 10.1136/bmj.38993.560984.BE

Department of Internal Medicine and Infectious Diseases, University Medical Centre, PO Box 85500, 3508 GA Utrecht, Netherlands
Jan Jelrik Oosterheert *research associate*
Marc J M Bonten *professor of infectious diseases*
Margriet M E Schneider *infectiologist*
Andy I M Hoepelman *professor of medicine*

Julius Centre for Health Sciences and Primary Care, University Medical Centre
Erik Buskens *associate professor of epidemiology*

Department of Pulmonology, University Medical Centre
Jan-Willem J Lammers *professor of pulmonology*

Department of Internal Medicine, Diakonessenhuis, Utrecht
Willem M N Hustinx *infectiologist*

Department of Internal Medicine, Meander Medical Centre, Amersfoort, Netherlands
Mark H H Kramer *internist/haematologist*

Department of Internal Medicine, Division of Infectious Diseases, Tropical Medicine and Aids, Academic Medical Centre, Amsterdam, Netherlands
Jan M Prins *infectiologist*

Department of Internal Medicine, St Antonius Hospital, Nieuwegein, Netherlands
Peter H Th J Slee *internist*

Department of Internal Medicine, Rijnstate Hospital, Arnhem, Netherlands
Karin Kaasjager *internist*

Correspondence to: A I M Hoepelman i.m.hoepelman@umcutrecht.nl