cerebrovascular event while receiving aspirin, the so-called aspirin treatment failure. Present practice patterns include increasing the dose of aspirin or switching to another antiplatelet agent, which are not unreasonable approaches but neither has definitive supportive evidence. Trials that randomly assign patients with a breakthrough event while on aspirin to a newer antiplatelet drug or higher aspirin dose, rather than reinitiation of the original aspirin dose, could provide insights into this issue. Perhaps terutroban could be called on to perform again.

*Meng Lee, *Bruce Ovbiagele*
Department of Neurology, Chang Gung Memorial Hospital at Chiayi, Chang Gung University College of Medicine, Taoyuan, Taiwan (ML); and Department of Neurosciences, University of California, San Diego, La Jolla, CA 92093, USA (BO)
ovibes@ucsd.edu

We declare that we have no conflicts of interest.

1 Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002; **324:** 71–86.
2 Bousser M-G, Amarenco P, Chamorro A, et al, on behalf of the PERFORM Study Investigators. Terutroban versus aspirin in patients with cerebral ischaemic events (PERFORM): a randomised, double-blind, parallel-group trial. *Lancet* 2011; published online May 25. DOI:10.1016/S0140-6736(11)60600-4.
3 Hass WK, Easton JD, Adams HP Jr, et al, for the Ticlopidine Aspirin Stroke Study Group. A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. *N Engl J Med* 1989; **321:** 501–07.
4 Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European Stroke Prevention Study 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci* 1996; **143:** 1–13.
5 CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996; **348:** 1329–39.
6 Gorelick PB, Richardson D, Kelly M, et al. Aspirin and ticlopidine for prevention of recurrent stroke in black patients: a randomized trial. *JAMA* 2003; **289:** 2947–57.
7 Matias-Guiu J, Ferro JM, Alvarez-Sabin J, et al. Comparison of triflusal and aspirin for prevention of vascular events in patients after cerebral infarction: the TACIP Study: a randomized, double-blind, multicenter trial. *Stroke* 2003; **34:** 840–48.
8 The ESPRIT Study Group. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. *Lancet* 2006; **367:** 1665–73.
9 Shinohara Y, Katayama Y, Uchiyama S, et al, for the CSPS 2 group. Cilostazol for prevention of secondary stroke (CSPS 2): an aspirin-controlled, double-blind, randomised non-inferiority trial. *Lancet Neurol* 2010; **9:** 959–68.
10 Chen ZM, Sandercock P, Pan HC, et al, on behalf of the CAST and IST collaborative groups. Indications for early aspirin use in acute ischemic stroke: a combined analysis of 40 000 randomized patients from the Chinese Acute Stroke Trial and the International Stroke Trial. *Stroke* 2000; **31:** 1240–49.
11 Lovett JK, Coull AJ, Rothwell PM. Early risk of recurrence by subtype of ischemic stroke in population-based incidence studies. *Neurology* 2004; **62:** 569–73.
12 Garcia Rodriguez LA, Cea Soriano L, Hill C, Johansson S. Increased risk of stroke after discontinuation of acetylsalicylic acid: a UK primary care study. *Neurology* 2011; **76:** 740–46.

# Glucocorticoid treatment in community-acquired pneumonia

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Community-acquired pneumonia is a major public health problem. While mortality decreased sharply after the introduction of antibiotics in the 1940s, since 1950 the overall acute (hospital) mortality has either remained stable or increased.[1] Equally concerning, after clinical resolution of pneumonia, patients discharged from hospital have—after adjusting for age and comorbidities—a substantial, continuing excess mortality.[2] Despite concern about immunosuppression, glucocorticoid treatment in low-to-moderate doses is beneficial and safe for a wide variety of infections; and experimental and clinical research has focused on its potential role as adjunctive treatment of pneumonia.

In *The Lancet*, Sabine Meijvis and colleagues[3] report the largest trial so far (304 patients) in which they investigated glucocorticoid treatment in patients hospitalised with community-acquired pneumonia. The treatment and control groups had much the same baseline characteristics and no patients required mechanical ventilation. 4 days' adjunctive treatment with low-dose dexamethasone led to a median duration of hospitalisation—the primary endpoint—of 6·5 days (IQR 5·0–9·0) compared with 7·5 days (5·3–11·5) for patients who received antibiotics alone, without an increased risk of adverse events. The dexamethasone group also had improved social functioning by day 30 (p=0·0091). The cost saving associated with reduction in hospital stay for this common disease has important public health relevance.[4] We congratulate the investigators for this important addition to the evidence[5] and the selection of a relevant primary endpoint. A preliminary randomised trial of patients with community-acquired pneumonia requiring admission to intensive care (higher control mortality)[6] reported improved short-term survival, and a large confirmatory trial is in progress (NCT01283009).

Over the past 60 years, our pathophysiological understanding of sepsis (most caused by pneumonia) has

evolved and has influenced, more than any other factor, the design and interpretation of glucocorticoid-treatment trials.[7] In the 1950s and 1960s, our pathophysiological knowledge of sepsis was scarce; glucocorticoid treatment was given in low doses, and duration of administration was guided by improvement in clinical variables (clinical resolution). In the two decades that followed, systemic inflammation was introduced into the pathophysiological model of sepsis. However, widely used laboratory models that misrepresented human sepsis characterised systemic inflammation as short-lasting.[7] The fundamental idea that treatment should be directed to and continued until disease resolution was omitted from the design of glucocorticoid trials in sepsis. This faulty pathophysiological model led to many negative trials investigating massive doses (methylprednisolone, up to 120 mg/kg daily) for 24–48 h.[7]

In the past two decades (panel),[8] with the availability of biomarker assays, longitudinal measurements have shown that persistent (in place of short-lived) elevation of circulating concentrations of inflammatory cytokines over time (dysregulated systemic inflammation) is the central pathogenetic process contributing to morbidity and mortality in community-acquired pneumonia, sepsis, and acute respiratory distress syndrome. For community-acquired pneumonia and sepsis studies, contrary to acute respiratory distress syndrome,[8] biomarker measurements were limited to the first 7–10 days of acute illness. Partly for this reason, most community-acquired pneumonia and sepsis trials[6] restricted duration of glucocorticoid treatment to 7 days or less, and directed it solely at the acute phase of illness (clinical resolution).

Two landmark publications have broadened the landscape of our understanding of systemic inflammation in pneumonia and its effect on acute and long-term morbidity and mortality.[9,10] With a large dataset that included nearly 1900 patients with community-acquired pneumonia, Kellum[9] and Yende[10] (for the Genetic and Inflammatory Markers of Sepsis Study) reported that increased concentrations of tumour necrosis factor (TNF) α and interleukin 6 persisted for weeks after clinical resolution of pneumonia, and that the increase in interleukin 6 at discharge predicted subsequent 90-day and 1-year mortality. These findings were much the same for patients admitted with or without severe sepsis and suggested that patients with community-acquired pneumonia discharged from hospital—irrespective of initial severity—still have long-lasting, subclinical, low-grade systemic inflammation. This inflammatory load, which is a risk factor for premature

***Panel:* Present understanding of systemic inflammation in sepsis and acute respiratory distress syndrome**

1. Systemic inflammation is a highly organised response to infectious and non-infectious threats to homoeostasis, and includes at least five major programmes: (a) tissue–host defence response, (b) acute-phase reaction, (c) sickness syndrome, (d) pain programme mediated by afferent sensory and autonomic systems, and (e) stress programme mediated by hypothalamic–pituitary–adrenal axis and locus ceruleus–norepinephrine or sympathetic nervous system
2. Tissue–host defence response is an integrated network of three simultaneously activated pathways—inflammation, coagulation, and tissue repair—which account for histological and physiological changes noted with acute and chronic organ dysfunction
3. Severity of systemic inflammation, at hospital presentation, positively correlates with clinical severity scale of pneumonia: sepsis, severe sepsis, septic shock, and acute respiratory distress syndrome
4. Severity of systemic inflammation, at intensive care unit entry, positively correlates with need for mechanical ventilation, higher Pneumonia Severity Index score, higher Acute Physiology and Chronic Health Evaluation II score, higher Simplified Acute Physiology Score III, and multiple organ dysfunction score
5. Experimental and clinical evidence shows strong cause and effect relation between persistence *vs* reduction in systemic inflammation and progression (maladaptive repair) *vs* resolution (adaptive repair) of organ dysfunction
6. Moderate degree of local inflammation is required to control infection; however, excessive release of inflammatory cytokines favours intracellular and extracellular bacterial growth and virulence, with U-shaped response
7. Inflammatory cytokine concentrations remain increased for weeks after clinical resolution of sepsis or acute respiratory distress syndrome
8. Most patients with community-acquired pneumonia have low-grade systemic inflammation at hospital discharge that correlates with 1-year mortality, independent of patient's age and comorbidity
9. Activated glucocorticoid receptor α —via downregulation of nuclear factor-κB —is most important physiological inhibitor of inflammation, affecting thousands of genes involved in stress-related homoeostasis
10. At cellular level, patients with dysregulated inflammation have inadequate glucocorticoid receptor-mediated downregulation of inflammatory transcription factor nuclear factor-κB, despite often having increased concentrations of circulating cortisol (systemic inflammation-associated glucocorticoid resistance)
11. Systemic inflammation-associated glucocorticoid resistance can be reversed by increasing glucocorticoid receptor α activation with quantitatively adequate and prolonged glucocorticoid supplementation
12. In patients with sepsis and acute respiratory distress syndrome, much evidence supports a strong association between prolonged downregulation, induced by glucocorticoid treatment, of the inflammatory response and improvement in organ physiology
13. Even short treatment with glucocorticoid is associated with downregulation of glucocorticoid receptor concentrations in most cell types and adrenal insufficiency; without 6–9 days' tapering, rebound systemic inflammation is common and associated with substantial clinical deterioration

death (mostly cardiovascular),[11] adds substantial excess mortality for years. This important shift in our understanding has important public health implications and merits priority in research funding.

For the foreseeable future, glucocorticoids—with their rapid and profound anti-inflammatory effect, safety profile,[5] and low cost—will remain the most viable candidate for first-line adjunctive treatment. In agreement with the published work on glucocorticoids, Meijvis and colleagues[3] report a rapid and sustained decrease in circulating inflammatory markers during dexamethasone administration. This finding sharply contrasts with the effect of statin treatment in community-acquired pneumonia.[12] However, in Meijvis and colleagues' study,[3] dexamethasone's early therapeutic benefits were lost within 2–3 days of discontinuation of treatment and inflammatory marker concentrations were much the same as those of controls. Within the new pathophysiological model,[9,10] the duration of glucocorticoid treatment directed at achieving clinical resolution should be deemed inadequate. We strongly urge future trials to extend the duration of anti-inflammatory treatment to achieve biological resolution and prevent rebound inflammation. A longer duration of glucocorticoid treatment—similar to those for acute respiratory distress syndrome[8] and *Pneumocystis jirovecii* pneumonia—in conjunction with secondary prevention[8] would maximise the improvement in morbidity and mortality during and after hospitalisation. We thank Meijvis and colleagues for identifying new benefits for community-acquired pneumonia and the Genetic and Inflammatory Markers of Sepsis investigators[9,10] for expanding our understanding and creating new research opportunities to improve the lives of patients with pneumonia.

*Marco Confalonieri, G Umberto Meduri*
Pneumology Department, University Hospital of Trieste, Trieste 34149, Italy (MC); and Memphis Veterans Affairs Medical Center and Division of Pulmonary, Critical Care, and Sleep Medicine, University of Tennessee Health Science Center, Memphis, TN, USA (GUM)
marco.confalonieri@aots.sanita.fvg.it

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1 Armstrong GL, Conn LA, Pinner RW. Trends in infectious disease mortality in the United States during the 20th century. *JAMA* 1999; **281:** 61–66.
2 Kaplan V, Clermont G, Griffin MF, et al. Pneumonia: still the old man's friend? *Arch Intern Med* 2003; **163:** 317–23.
3 Meijvis SCA, Hardeman H, Remmelts HHF, et al. Dexamethasone and length of hospital stay in patients with community-acquired pneumonia: a randomised, double-blind, placebo-controlled trial. *Lancet* 2011; published online June 1. DOI:10.1016/S0140-6736(11)60607-7.
4 Niederman MS, McCombs JS, Unger AN, Kumar A, Popovian R. The cost of treating community-acquired pneumonia. *Clin Ther* 1998; **20:** 820–37.
5 Annane D, Bellissant E, Bollaert PE, et al. Corticosteroids in the treatment of severe sepsis and septic shock in adults: a systematic review. *JAMA* 2009; **301:** 2362–75.
6 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:** 242–48.
7 Meduri GU. An historical review of glucocorticoid treatment in sepsis. Disease pathophysiology and the design of treatment investigation. *Sepsis* 1999; **3:** 21–38.
8 Meduri GU, Annane D, Chrousos GP, Marik PE, Sinclair SE. Activation and regulation of systemic inflammation in ARDS: rationale for prolonged glucocorticoid therapy. *Chest* 2009; **136:** 1631–43.
9 Kellum JA, Kong L, Fink MP, et al, for the GenIMS Investigators. Understanding the inflammatory cytokine response in pneumonia and sepsis: results of the Genetic and Inflammatory Markers of Sepsis (GenIMS) Study. *Arch Intern Med* 2007; **167:** 1655–63.
10 Yende S, D'Angelo G, Kellum JA, et al, for the GenIMS Investigators. Inflammatory markers at hospital discharge predict subsequent mortality after pneumonia and sepsis. *Am J Respir Crit Care Med* 2008; **177:** 1242–47.
11 Cesari M, Penninx BW, Newman AB, et al. Inflammatory markers and onset of cardiovascular events: results from the Health ABC study. *Circulation* 2003; **108:** 2317–22.
12 Yende S, Milbrandt EB, Kellum JA, et al. Understanding the potential role of statins in pneumonia and sepsis. *Crit Care Med* 2011; published online April 21. DOI:10.1097/CCM.0b013e31821b8290.

# The impact of the Brazil experience in Latin America

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See Series page 2042

See Series *Lancet* 2011; **377:** 1778, 1863, 1877, 1949, and 1962

The Brazil Series in *The Lancet* shows that rapid progress can be made in public health and clinical care when necessary conditions are met. The authors, a seasoned group of Brazilian public health leaders, are key actors in this process. They narrate what has gone right, the forces that shaped progress, the main achievements, past and present problems being faced, and challenges ahead. The papers show the key role of securing universal access to health as vital for vaccine-preventable infectious diseases, diarrhoea and malnutrition, maternal mortality, and, more recently, in controlling AIDS by providing free antiretroviral therapy at point of entry—an impressive account of joint efforts, supported by successive governments, to expand preventive and curative health care in response to growing public demand. How did this experience contribute to changes in other countries within and beyond the region?

Traditional economic thinking in the past by bilateral and multilateral international assistance was that countries

# Dexamethasone and length of hospital stay in patients with community-acquired pneumonia: a randomised, double-blind, placebo-controlled trial

*Sabine C A Meijvis, Hans Hardeman, Hilde H F Remmelts, Rik Heijligenberg, Ger T Rijkers, Heleen van Velzen-Blad, G Paul Voorn, Ewoudt M W van de Garde, Henrik Endeman, Jan C Grutters, Willem Jan W Bos, Douwe H Biesma*

## Summary

**Background** **Whether addition of corticosteroids to antibiotic treatment benefits patients with community-acquired pneumonia who are not in intensive care units is unclear. We aimed to assess effect of addition of dexamethasone on length of stay in this group, which might result in earlier resolution of pneumonia through dampening of systemic inflammation.**

**Methods** **In our double-blind, placebo-controlled trial, we randomly assigned adults aged 18 years or older with confirmed community-acquired pneumonia who presented to emergency departments of two teaching hospitals in the Netherlands to receive intravenous dexamethasone (5 mg once a day) or placebo for 4 days from admission. Patients were ineligible if they were immunocompromised, needed immediate transfer to an intensive-care unit, or were already receiving corticosteroids or immunosuppressive drugs. We randomly allocated patients on a one-to-one basis to treatment groups with a computerised randomisation allocation sequence in blocks of 20. The primary outcome was length of hospital stay in all enrolled patients. This study is registered with ClinicalTrials.gov, number NCT00471640.**

**Findings** **Between November, 2007, and September, 2010, we enrolled 304 patients and randomly allocated 153 to the placebo group and 151 to the dexamethasone group. 143 (47%) of 304 enrolled patients had pneumonia of pneumonia severity index class 4–5 (79 [52%] patients in the dexamethasone group and 64 [42%] controls). Median length of stay was 6·5 days (IQR 5·0–9·0) in the dexamethasone group compared with 7·5 days (5·3–11·5) in the placebo group (95% CI of difference in medians 0–2 days; p=0·0480). In-hospital mortality and severe adverse events were infrequent and rates did not differ between groups, although 67 (44%) of 151 patients in the dexamethasone group had hyperglycaemia compared with 35 (23%) of 153 controls (p<0·0001).**

**Interpretation** **Dexamethasone can reduce length of hospital stay when added to antibiotic treatment in non-immunocompromised patients with community-acquired pneumonia.**

**Funding** **None.**

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**Department of Internal Medicine** (S C A Meijvis MD, W J W Bos MD, Prof D H Biesma MD), **Department of Pulmonology** (H Hardeman MD, Prof J C Grutters MD), **Department of Medical Microbiology and Immunology** (G T Rijkers PhD, H van Velzen-Blad MSc, G P Voorn MD), **and Department of Clinical Pharmacy** (E M W van de Garde PhD), **St Antonius Hospital, Nieuwegein, Netherlands; Department of Internal Medicine, Gelderse Vallei Hospital, Ede, Netherlands** (H H F Remmelts MD, R Heijligenberg MD); **Division of Pharmacoepidemiology and Clinical Pharmacology, Faculty of Science, Utrecht University, Utrecht, Netherlands** (E M W van de Garde); **Department of Intensive Care Medicine, Onze Lieve Vrouwe Gasthuis, Amsterdam, Netherlands** (H Endeman MD); **and Division Heart and Lungs** (J C Grutters) **and Department of Internal Medicine** (H H F Remmelts, D H Biesma), **University Medical Centre Utrecht, Utrecht, Netherlands**

Correspondence to: Ms Sabine Meijvis, Department of Internal Medicine, St Antonius Hospital, Koekoekslaan 1, PO Box 2500, 3430 EM Nieuwegein, Netherlands **s.meijvis@antoniusziekenhuis.nl**

## Introduction

The mainstays of treatment for community-acquired pneumonia are early diagnosis and initiation of appropriate antibiotic therapy.[1] Despite preventive measures such as vaccination and advances in antibiotic treatments, community-acquired pneumonia has a high rate of mortality and morbidity and is associated with significant health-care costs.[2] Adjunctive therapy for community-acquired pneumonia might help to reduce disease severity.

In community-acquired pneumonia, locally produced pulmonary cytokines are needed to control and eliminate the primary infection. However, organ dysfunction can result from a systemic inflammatory response.[3] Therefore, a balanced cytokine response needs to be sufficient to control the local infection but not be excessive, to prevent systemic effects. An ideal intervention would reduce the systemic complications of the inflammatory response without affecting the resolution of local inflammation.

Corticosteroids are very potent inhibitors of inflammation.[4] They switch off genes that encode proinflammatory cytokines and switch on genes that encode anti-inflammatory cytokines. Treatment with low-dose corticosteroids downregulates proinflammatory cytokine transcription, which prevents an extended cytokine response and might accelerate the resolution of systemic and pulmonary inflammation in the early phase of community-acquired pneumonia.[5,6]

Although not all studies show a beneficial effect of corticosteroids, these hormones are widely given as adjunctive therapy in patients with sepsis and septic shock.[7] By contrast with the large number of studies about sepsis and septic shock, there are few controlled trials of corticosteroids as adjunctive treatment to antibiotics in pneumonia, and these trials have produced variable results.[8–10]

We postulated that adjunctive treatment of community-acquired pneumonia with intravenous dexamethasone might change the immune response and thereby reduce

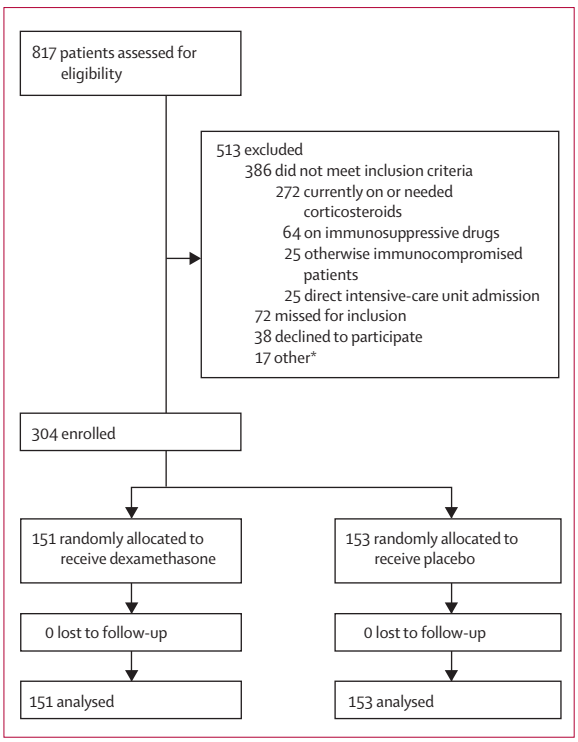


***Figure 1:*** **Study profile**
*Eg, pregnant or breastfeeding.

morbidity, leading to a decrease in patients' length of stay in hospital. Dexamethasone has potent anti-inflammatory effects and weak mineralocorticoid effects compared with other corticosteroids, thus avoiding interference with sodium reabsorption and water balance. Moreover, dexamethasone has a long-lasting effect, allowing for a once-a-day regimen.

We aimed to assess the effect of intravenous dexamethasone compared with placebo on length of hospital stay in non-immunocompromised patients who were admitted to hospital with community-acquired pneumonia.

## Methods

### Study design and patients

For the **protocol** see http://www.antoniusziekenhuis.nl/research/lopendestudies

We undertook a randomised, double-blinded, placebo-controlled trial at the 880-bed St Antonius Hospital in Nieuwegein and the 500-bed Gelderse Vallei Hospital in Ede in the Netherlands (both teaching hospitals). Patients were prospectively enrolled if they were aged 18 years or older and had confirmed community-acquired pneumonia. Diagnosis of pneumonia was confirmed when a new pulmonary infiltrate on a chest radiograph was present in combination with at least two of the following criteria: cough, sputum production, temperature more than 38°C or lower than 35°C, auscultatory findings consistent with pneumonia, C-reactive protein concentration of more than 15 mg/L, white blood cell count of more than $10\times10^9$ cells per L or fewer than $4\times10^9$ cells per L, or more than 10% of rods in leucocyte differentiation.[11]

Patients were excluded if they had a known congenital or acquired immunodeficiency or receipt of chemotherapy, any dose of oral corticosteroids, or immunosuppressive medication in the previous 6 weeks or haematological malignant disease. Patients who needed immediate admission to the intensive-care unit at presentation and pregnant or breastfeeding women were also excluded. Furthermore, patients were not eligible when pneumonia was diagnosed more than 24 h after admission or when the patient needed corticosteroid treatment. Eligible patients provided written informed consent and the study was approved by the institutional Medical Ethics Committee of the St Antonius Hospital.

### Randomisation and masking

Eligible patients were randomly allocated to receive dexamethasone or placebo by the Department of Clinical Pharmacy (St Antonius Hospital) in blocks of 20 according to a computer-generated random-number table. Randomisation was based on a one-to-one allocation of prenumbered boxes containing four ampoules (identical appearance for dexamethasone and placebo) for intravenous administration. Patients, investigators, and data assessors were masked to treatment allocation.

### Procedures

Patients in the dexamethasone group were given a bolus of 5 mg (1 mL) of dexamethasone (dexamethasone-disodiumphosphate 5 mg, Centrafarm BV, Etten-Leur, Netherlands) intravenously and patients in the placebo group were given 1 mL of sterile water for injection (Centrafarm BV) intravenously at the emergency unit, within a maximum of 12 h from admission. All patients received antibiotics before study treatment was given. For the subsequent 3 days, patients received either intravenous dexamethasone 5 mg (1 mL) or sterile water (1 mL) once a day. Selection, duration, and administration of the antibiotic treatment were decided by the medical team in charge and were done according to national guidelines.[12] The decision to transfer a patient to the intensive-care unit or hospital discharge were established by their medical team. A general rule for hospital discharge in both hospitals was that patients were clinically stable (improvement of shortness of breath, absence of hyperthermia or hypothermia, consistent decrease of C-reactive protein concentrations, and adequate oral intake and gastrointestinal absorption) and were in a condition to leave the hospital.

The primary endpoint was length of hospital stay in days until hospital discharge or death. If a patient was admitted between 2400 h and 1200 h, the day of admission was counted as 1 day; if the patient was admitted after 1200 h, the day of admission was counted as 0·5 days. Secondary endpoints included mortality, admission to intensive-care units, development of empyema,

superinfection, readmission, time courses of C-reactive protein, interleukin-6, and interleukin-10 concentrations, pulmonary function at day 30, and general health-related quality of life as measured by the RAND-36 generic health survey (see webappendix p 1).[13] Pleural effusion was defined as pleural fluid layer thickness on chest radiograph of more than 1 cm that needed additional assessment (ie, pleural puncture), and empyema was defined as pleural effusion containing bacteria. A superinfection was defined as a new infection with or without the need for antibiotic treatment. Readmission was defined as admission to hospital within 30 days from discharge. At a control visit 30 days after the day of admission, lung function was assessed by body plethysmography and carbon monoxide diffusion and helium dilution. Measurements were done in the pulmonary function laboratory of the hospital in which the patient was admitted. Other secondary objectives that were prespecified in the study protocol are beyond the scope of this report and will be reported elsewhere.

We measured concentrations of C-reactive protein with high sensitive-CRP (Roche Diagnostics GmbH, Mannheim, Germany), electrolytes, and glucose, and renal function, liver function, and haematology on the day of presentation. Subsequently we took samples at 0800 h on days 1–7, if patients were still admitted to the hospital, and at a control visit at least 30 days after admission (convalescent phase). We measured interleukin-6 and interleukin-10 concentrations by Milliplex multianalyte profiling (Millipore, Billerica, MA, USA) on the day of presentation and days 1, 2, and 4, and at the control visit. At admission, we measured total serum cortisol concentrations in blood drawn before administration of the study medication with an ELISA kit (Calbiotech, Spring Valley, CA, USA). Webappendix p 1 describes the method used for pathogen identification. Treating doctors assessed comorbidities (neoplastic disease, liver disease, congestive heart failure, renal disease, diabetes mellitus, and chronic obstructive pulmonary disease [COPD]). We calculated a pneumonia severity index score for all patients.[14]

## Statistical analyses

We calculated the sample size on the basis of the assumption that dexamethasone could reduce the overall length of stay by 2 days. With a reference length of stay of 10 days, we calculated that 150 patients were needed in each group to detect this difference with a power of 80% and a type 1 error of 5% (two-sided).

We show n (%) for categorical variables and median (IQR) for continuous variables with non-normal distribution or mean (SD) for those with normal distribution. We assessed differences in categorical variables with the $\chi^2$ test or Fisher's exact test. We analysed differences in length of stay until hospital discharge or death with the Mann-Whitney *U* test. We calculated 95% CI for differences in medians with an exact test.[15]

We also assessed differences in length of stay between treatment groups with the Kaplan-Meier method and a Cox proportional hazard regression model. In these analyses, we made adjustments because patients who died early or were admitted to intensive-care units would count as having a short length of hospital stay. If more patients in the dexamethasone group died after a short length of stay than did in the control group, an incorrect estimate of length of stay would be reported. Equally, patients admitted to the intensive-care unit were all treated with corticosteroids and study medication was stopped after intensive-care unit admission. Therefore, we performed a Kaplan-Meier method for analysis of time to discharge, in which patients who were admitted to the intensive-care unit or died were censored to show that the time of reporting was cutoff before the only event of interest for

See Online for webappendix

| | Dexamethasone group (n=151) | Placebo group (n=153) |
|---|---|---|
| Men | 84 (56%) | 87 (57%) |
| Age (years) | 64·5 (18·7) | 62·8 (18·2) |
| Race* | | |
| White | 149 (99%) | 150 (98%) |
| Other | 2 (1%) | 3 (2%) |
| Nursing-home resident | 9 (6%) | 7 (5%) |
| Current smoker | 38 (25%) | 38 (25%) |
| Antibiotic treatment before admission | 42 (28%) | 39 (25%) |
| Comorbidities† | | |
| Neoplastic disease | 9 (6%) | 10 (7%) |
| Liver disease | 2 (1%) | 0 |
| Congestive heart failure | 24 (16%) | 24 (16%) |
| Renal disease | 20 (13%) | 10 (7%) |
| Diabetes mellitus | 22 (15%) | 21 (14%) |
| Chronic obstructive pulmonary disease | 20 (13%) | 14 (9%) |
| Physical examination findings | | |
| Temperature (°C) | 38·2 (1·1) | 38·2 (1·2) |
| Systemic blood pressure (mm Hg) | 130·9 (22·7) | 132·3 (20·7) |
| Heart rate (beats per min) | 96·5 (19·4) | 97·0 (20·2) |
| Respiratory rate (breaths per min) | 24·1 (6·5) | 24·1 (6·7) |
| Altered mental status‡ | 29 (19%) | 22 (14%) |
| Laboratory parameters | | |
| C-reactive protein (mg/L) | 224·5 (143·6) | 209·6 (136·7) |
| White-blood-cell count ($10^9$ cells per L) | 14·7 (6·4) | 14·0 (6·5) |
| Total serum cortisol (μg/dL) | 23·6 (14·9–41·2) | 21·6 (13·5–39·2) |
| Pneumonia severity index score[14] | 100·2 (33·4) | 95·8 (32·5) |
| Pneumonia severity index risk class | | |
| Class 1 | 18 (12%) | 22 (14%) |
| Class 2 | 30 (20%) | 34 (22%) |
| Class 3 | 24 (16%) | 33 (22%) |
| Class 4 | 54 (36%) | 43 (28%) |
| Class 5 | 25 (17%) | 21 (14%) |

Data are n (%), mean (SD), or median (IQR). *Self-reported. †Patients could have more than one comorbidity. ‡Defined as a state of awareness that differed from the normal awareness of a conscious person, including sudden confusion, disorientation, or stupor, and scored by the treating doctor.

***Table 1:*** **Baseline characteristics of enrolled patients**

| | Dexamethasone group (n=151) | Placebo group (n=153) | p value |
|---|---|---|---|
| Length of stay (days) | 6·5 (5·0–9·0) | 7·5 (5·3–11·5) | 0·0480 |
| In-hospital mortality | 8 (5%) | 8 (5%) | 0·98 |
| Time to death (days) | 5·5 (2·6–18·9) | 8·8 (3·8–12·8) | 0·64 |
| 30-day mortality | 9 (6%) | 11 (7%) | 0·68 |
| ICU admission | 7 (5%) | 10 (7%) | 0·47 |
| Time to ICU admission (days) | 2·5 (1·5–6·5) | 1·8 (1·5–2·6) | 0·34 |
| Length of stay in ICU (days) | 21·5 (14·5–28·5) | 15·5 (10·1–28·5) | 0·23 |
| Empyema or pleural effusion | 7 (5%) | 5 (3%) | 0·54 |
| Readmission within 30 days from hospital discharge | 7 (5%) | 7 (5%) | 0·98 |

Data are median (IQR) or n (%), unless otherwise stated. ICU=intensive-care unit.

***Table 2:*** **Outcomes for all enrolled patients**

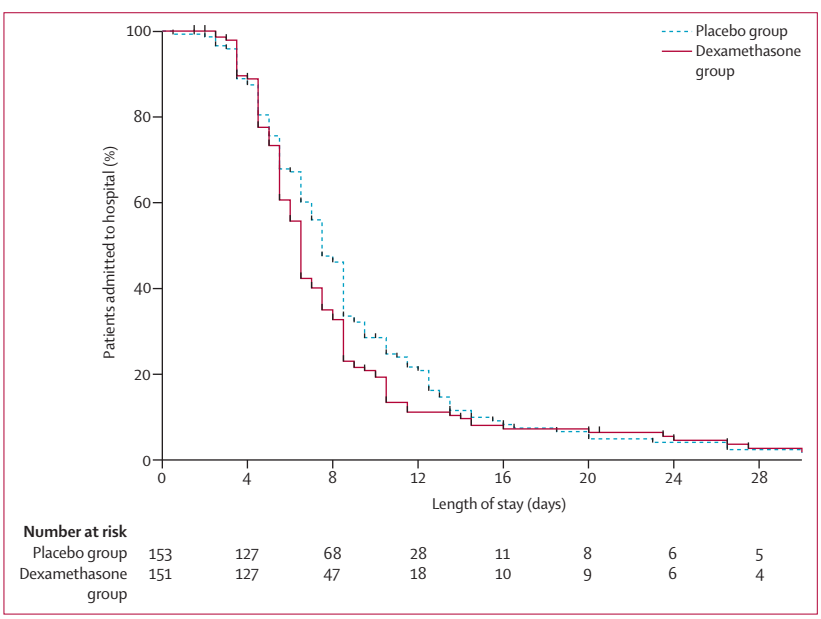


***Figure 2:*** **Kaplan-Meier analysis of the effect of dexamethasone on length of hospital stay in all enrolled patients**
Patients who died or were admitted to the intensive-care unit were censored on the day of death or the day of admission to the intensive-care unit.

the primary analysis (ie, hospital discharge) occurred. For the Kaplan-Meier method, a Gehan-Breslow-Wilcoxon test was applied because this test emphasises early differences.[16] In the Cox proportional hazard regression model, we adjusted for all baseline characteristics.

To examine differences in quality-of-life scores between the two groups, we calculated the proportion of patients with clinically meaningful changes in quality of life (ie, a change of ±10 points; webappendix p 1) between baseline and 1 month after treatment. Differences between the two treatment groups were analysed with the $\chi^2$ test. All statistical analyses were done with SPSS version 15.0. A two-tailed p value of less than 0·05 was regarded as significant, apart from for multiple comparisons of the quality of life items, in which we used a conservative value of p<0·01. Interim analyses were preplanned and done after the inclusion of 100 and 200 patients to assess the frequency of serious side-effects related to either dexamethasone or placebo. An external, independent data and safety monitoring board reviewed the results of these interim analyses.

This study is registered with ClinicalTrials.gov, number NCT00471640.

### Role of the funding source

There was no funding source for this study. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

From November, 2007, to September, 2010, we enrolled 304 patients (figure 1, table 1). 133 (44%) patients had comorbidities, with more patients having renal disease in the dexamethasone group than in the control group (table 1). 79 (52%) of 151 patients in the dexamethasone group were in pneumonia severity index risk classes 4 and 5 compared with 64 (42%) of 153 in the placebo group (table 1). Baseline characteristics of patients did not differ between the two hospitals (data not shown).

For the primary outcome, the median length of hospital stay in the dexamethasone group was 6·5 days (IQR 5·0–9·0) compared with 7·5 days (5·3–11·5) in the placebo group (95% CI of difference in medians: 0–2 days, p=0·0480; table 2). Length of hospital stay differed significantly between groups on Kaplan-Meier analysis (p=0·0478; figure 2). Adjusted for baseline characteristics, the hazard ratio for discharge was 1·46 (95% CI 1·13–1·89) favouring earlier discharge for dexamethasone-treated patients compared with controls.

All patients were treated with intravenous antibiotics within 4 h of admission to hospital according to national guidelines.[12] Antibiotic treatment was much the same in both groups (webappendix p 3). 18 (12%) of 151 patients in the dexamethasone group and 16 (10%) of 153 patients in the placebo group were treated with a macrolide alone or as part of combination therapy. Antibiotic treatment was modified on the basis on the outcome of the microbiological investigation. The mean time of switching to oral administration of antibiotics was 5·0 days (SD 4·2) in the dexamethasone group and 5·1 days (3·5) in the placebo group.

We established the microbial cause of community-acquired pneumonia in 168 (55%) of 304 patients (webappendix p 4). *Streptococcus pneumoniae, Coxiella burnetii, Chlamydophila* spp, and *Legionella* spp were the most frequently identified microorganisms. Distribution of the pathogens did not differ between groups. We noted mixed infection in 21 (7%) patients.

132 (87%) of 151 patients in the dexamethasone group and 134 (88%) of 153 patients in the placebo group completed the 4-day course of study treatment. 13 patients did not complete the course because of admission to intensive-care units, four died, and 21 had protocol violations (webappendix pp 1–2).

For secondary outcomes, hospital mortality (webappendix p 5) and rates of admission to intensive-care units did not differ between groups (table 2). None of the patients received continuous positive airway pressure or non-invasive ventilation outside the intensive-care unit. Rates of pleural effusion or empyema were less than 5% in both groups and did not differ significantly (p=0·54; table 2). Seven (5%) patients in both groups were readmitted within 30 days of hospital discharge (table 2; webappendix p 2).

In the first 4 days after admission, we noted a greater decline in C-reactive protein and interleukin-6 concentrations in the dexamethasone group than we did in the control group (figure 3). For interleukin-10, the decrease was much the same between treatment groups. The sharp decrease we noted for interleukin-6 and interleukin-10 concentrations contrasts with the more blunted kinetics of C-reactive protein. On day 10, C-reactive protein concentrations were slightly higher in the dexamethasone group than they were in the placebo group (figure 3).

Concentrations of cortisol before the start of study treatments were much the same between groups. We noted a cortisol concentration of 10 µg/dL or lower in 30 (10%) patients, including 18 (12%) of 149 patients who were tested in the placebo group and 12 (9%) of 141 patients who were tested in the dexamethasone group. In patients with low cortisol concentrations (<10 µg/dL), mortality, intensive-care unit admission, and length of stay did not differ between treatment groups.

We assessed lung function at a control visit on day 30 in 93 (61%) patients in the placebo group and 86 (57%) in the dexamethasone group. There were no differences in forced expiratory volume in 1 s ($FEV_1$), $FEV_1$/forced vital capacity, or diffusing capacity of the lung for carbon monoxide in either group (data not shown).

209 (69%) patients completed the RAND-36 quality of life survey on day 3 (114 controls and 95 patients in the dexamethasone group) and 157 (52%) patients completed it on day 30 (79 and 78). Although patients had a similar quality of life on day 3, patients in the dexamethasone group had significant improvements in social functioning by day 30 compared with controls (p=0·0091).

Hyperglycaemia (non-fasting glucose >11 mmol/L[17]) was more common in the dexamethasone group (67 [44%] patients) than it was in controls (35 [23%]; p<0·0001). However, only seven patients (5%) in the dexamethasone group and five patients (3%) in the placebo group needed additional glucose-lowering treatment during their hospital stay (p=0·57). Superinfection occurred in seven (5%) patients in the dexamethasone group and five (3%) patients in the placebo group (p=0·54). One patient in the dexamethasone group had a history of myelodysplastic syndrome, progressed to acute myeloid leukaemia on day 12 after admission, and subsequently died. Another patient in the dexamethasone group had a gastric perforation on day 3. Surgical closure of the

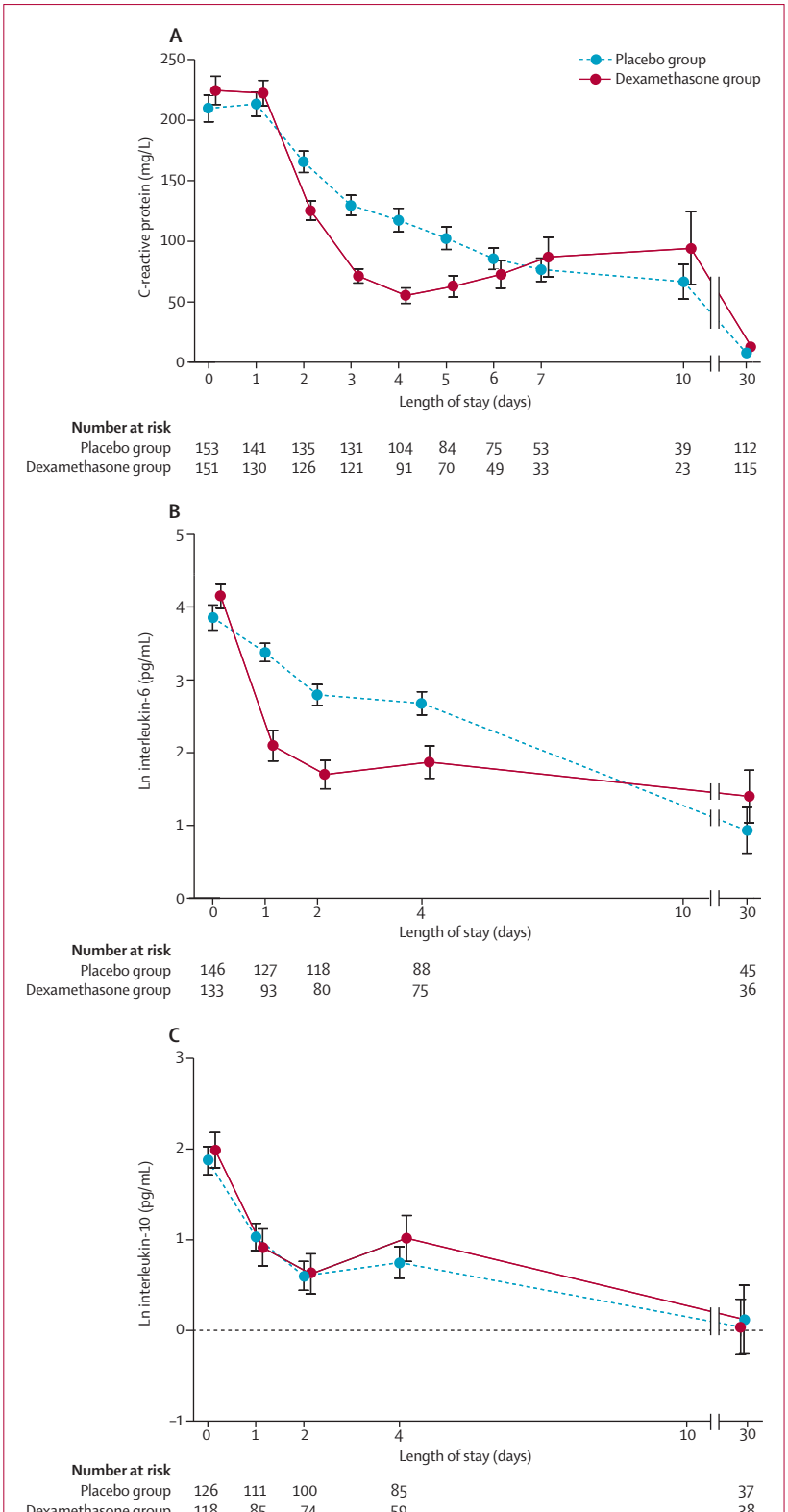


***Figure 3:*** **Mean concentrations of serum C-reactive protein (A), interleukin-6 (B), and interleukin-10 (C) from hospital admission to day 30**

Error bars show standard error. Interleukin concentrations were not tested for all enrolled patients.

perforation was done, and the patient recovered well. Two patients in the placebo group developed an acute myocardial infarction on day 1; one died 4 days after admission to the intensive-care unit and the other patient died after 3 weeks while on the ward. One patient in the placebo group required admission to the cardiac care unit because of new-onset atrial fibrillations. A masked independent monitoring committee (the Medical Ethics Committee, according to predefined regulations) adjudicated all adverse events and decided that there were no reasons for unmasking. Immunological and endocrinological data will be reported elsewhere.

## Discussion

In our trial, we noted an overall reduction in median length of hospital stay of 1 day in patients with community-acquired pneumonia who were given intravenous dexamethasone compared with controls. In a secondary analysis, patients in the dexamethasone group had a better quality of life than did controls with respect to social functioning by day 30 after admission to hospital.

These findings support our hypothesis that early administration of dexamethasone changes the immune response and thereby reduces length of hospital stay in patients with community-acquired pneumonia. This modulation is shown in the accelerated return to normal concentrations of C-reactive protein and interleukin-6 that we noted in the dexamethasone group. However, interleukin-10 concentrations were not affected by the use of dexamethasone. The published effects of glucocorticosteroids on interleukin-10 concentrations during infection are variable,[18–20] and the effect of dexamethasone on interleukin-10 is probably dose-dependent.[21]

We reported an apparent rebound effect of dexamethasone on C-reactive protein concentrations by day 10 after admission to hospital, as previous described in the published work.[22] However, this finding might be explained because, by day 10, most patients in the dexamethasone group had been discharged, whereas the remaining patients had a complicated clinical course. By contrast, on day 10 the placebo group had a high number of patients who were almost ready for discharge, and had low mean C-reactive protein concentrations. Moreover, the number of readmissions was not higher in the dexamethasone group than the control group, which would have been expected in the case of a true rebound effect.

Our results are in line with other studies that showed a beneficial effect of corticosteroids in patients with community-acquired pneumonia (panel). Confalonieri and colleagues[9] reported an improvement in oxygenation and a survival advantage in patients with severe community-acquired pneumonia who were treated with hydrocortisone for 7 days. A retrospective study[24] suggested that patients with severe community-acquired pneumonia who were treated with systemic corticosteroids had a reduced risk of mortality compared with patients who were not given adjunctive corticosteroids. A small randomised-controlled trial[8] of 31 patients with community-acquired pneumonia of any severity compared prednisolone for 3 days with placebo and reported a non-significant reduction in hospital stay from 16 to 11 days (p=0·182). However, this study was probably too small to show significant effects on length of stay. A study[23] of 213 patients—the largest so far to assess the role of prednisolone (40 mg once per day for 7 days) in community-acquired pneumonia of any severity—showed neither beneficial effects of adjunctive corticosteroids on clinical cure at day 7 or effects on length of stay. A possible explanation for the absence of effect compared with our study was the use of prednisolone once a day, which might not have been sufficient to achieve effective serum concentrations during the course of 24 h. Furthermore, this study was not powered to show differences in the length of hospital stay.

In our study, the median length of hospital stay of 7·5 days in the placebo group was reduced by 1 day by dexamethasone (13% reduction). Although the group size of the study was calculated for a 2 day reduction, we regard the noted 1 day reduction as clinically relevant.

Our study has several strengths compared with previous studies. It was the largest randomised double-blind, placebo-controlled trial undertaken to date and was done in two hospitals. We used dexamethasone, which has a comparatively long biological half-life of 36–54 h.[25] Because we provided dexamethasone once a day for 4 days, the pharmacological effects can be expected from day 1 to about day 11. Moreover, because of the long half-life of dexamethasone, a more gradual reduction in biological effects might be expected, allowing for a gradual increase in intracellular glucocorticoid receptor number and recovery of the

### *Panel:* Research in context

**Systematic review**

We searched the PubMed database with the search terms "community-acquired pneumonia" and "corticosteroids" for randomised, double-blind trials describing the effect of corticosteroids as adjunctive therapy for community-acquired pneumonia. No language restrictions were applied. The last search was done on April 15, 2011. Our search identified five published trials.[8–10,23,24]

**Interpretation**

Our study shows that a 4-day course of 5 mg dexamethasone reduces length of hospital stay in patients admitted for community-acquired pneumonia. The faster decline in concentrations of C-reactive protein and interleukin-6 that we noted in patients given dexamethasone compared with controls support the notion that dexamethasone reduces the systemic inflammatory response. Although serious adverse events were rare, the benefits of corticosteroids should be weighed against the potential side-effects.

hypothalamic-pituitary-adrenal axis. Additionally, we measured total cortisol concentrations on the day of admission to detect adrenal insufficiency. The significance of a low serum cortisol concentration in patients with community-acquired pneumonia is, however, not clear.[26] Nevertheless, in accordance with other studies, total cortisol concentrations of lower than 10 µg/dL were not associated with worse outcome than were higher concentrations.[27]

Pneumonia severity index risk classes 4 and 5 were more commonly noted in the dexamethasone group than the placebo group. This imbalance in the severity of community-acquired pneumonia could have led to an underestimation of the effect of dexamethasone because a high risk class (4 or 5) usually leads to a longer length of stay than does a low risk class (1–3).[28]

Our study had limitations. First, the results cannot be generalised to all patients with community-acquired pneumonia. In patients with COPD, pneumonia is usually coincident with bronchial obstruction, which needs treatment with systemic corticosteroids[29] and therefore led to an underrepresentation of patients with COPD in this study (only 34 [11%] of 304 patients enrolled this study had COPD compared with an incidence of around 21% of the 817 people in the screened population). Also, the microorganism *C burnetii* is somewhat overrepresented in this study because of an outbreak of Q fever in the Netherlands in spring 2009.[30] However, patients with *C burnetii* pneumonia were equally distributed between the dexamethasone and placebo groups. Another limitation was that, because of low rates of antibiotic resistance, guidelines for antibiotic treatment in the Netherlands differ from US guidelines.[12] In the Netherlands, amoxicillin is standard therapy for community-acquired pneumonia of pneumonia severity index class 1 and 2 and is combined with a fluoroquinolone or macrolide antibiotic in patients with more severe community-acquired pneumonia. All pneumococci derived from sputum or blood cultures in this study were sensitive to penicillin. A further limitation was that admission to intensive-care units during the hospital stay was defined as an endpoint of this study. Patients with severe community-acquired pneumonia who were admitted to the intensive-care unit were given corticosteroids according to the Surviving Sepsis Campaign protocol.[31] Therefore, we were unable to assess the effects of dexamethasone on mechanically ventilated patients. The study was not sufficiently powered to show an effect of dexamethasone on admission to the intensive-care unit. Finally, dexamethasone was given intravenously. Although the study protocol allowed health-care professionals to stop the intravenous administration of dexamethasone if patients were switched to oral antibiotics, most patients received the full course of study medication. Therefore, participation in the trial might have resulted in longer administration of intravenous antibiotics.

Although serious adverse events were rare, one patient in the dexamethasone group developed a gastric perforation on day 3 that could be attributed to the use of dexamethasone. Furthermore, hyperglycaemia was noted more often in the dexamethasone group than it was in the control group. Hyperglycaemia is also associated with adverse outcome in non-critically ill patients.[32] The benefits of corticosteroids should be weighed against the potential disadvantages of these drugs, such as superinfections and gastric disturbances.

#### Contributors

DHB, HE, and SCAM designed the study. SCAM, HH, and HHFR were responsible for recruitment and follow-up of the participants. WJWB, JCG, and RH were the principal investigators in Nieuwegein and Ede. GTR helped with the analysis of the cytokines. HvV-B and GPV were responsible for the microbiological data. EMWvdG supervised the packaging and labelling of the study medication and contributed to the data analysis. SCAM analysed the data and wrote the first draft of the article. All authors had access to the data and contributed substantially to the submitted report.

#### Conflicts of interest

We declare that we have no conflicts of interest.

#### References


1 Garnacho-Montero J, Garcia-Cabrera E, Diaz-Martín 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.

2 Gil-Prieto R, García-García L, Alvaro-Meca A, Méndez C, García A, de Miguel AG. The burden of hospitalisations for community-acquired pneumonia (CAP) and pneumococcal pneumonia in adults in Spain (2003–2007). *Vaccine* 2011; **29:** 412–16.

3 Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. *N Engl J Med* 2003; **348:** 138–50.

4 Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids—new mechanisms for old drugs. *N Engl J Med* 2005; **353:** 1711–23.

5 Monton C, Ewig S, Torres A, et al. Role of glucocorticoids on inflammatory response in nonimmunosuppressed patients with pneumonia: a pilot study. *Eur Respir J* 1999; **14:** 218–20.

6 Rosewicz S, McDonald AR, Maddux BA, Goldfine ID, Miesfeld RL, Logsdon CD. Mechanism of glucocorticoid receptor down-regulation by glucocorticoids. *J Biol Chem* 1988; **263:** 2581–84.

7 Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002; **288:** 862–71.

8 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.

9 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:** 242–48.

10 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.

11 Fine MJ, Singer DE, Hanusa BH, Lave JR, Kapoor WN. Validation of a pneumonia prognostic index using the MedisGroups Comparative Hospital Database. *Am J Med* 1993; **94:** 153–59.

12 Schouten JA, Prins JM, Bonten M, et al. Optimizing the antibiotics policy in The Netherlands. VIII. Revised SWAB guidelines for antimicrobial therapy in adults with community-acquired pneumonia. *Ned Tijdschr Geneeskd* 2005; **149:** 2495–500.

13 Hays RD, Morales LS. The RAND-36 measure of health-related quality of life. *Ann Med* 2001; **33:** 350–57.

14 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.

15 Campbell MJ, Gardner MJ. Calculating confidence intervals for some non-parametric analyses. *Br Med J (Clin Res Ed)* 1988; **296:** 1454–56.

16 Mike V, Stanley KE, eds. Statistics in medical research: methods and issues, with applications in cancer research. NY, USA: Wiley, 1982.

17 American Diabetes Association. Executive summary: standards of medical care in diabetes—2011. *Diabetes Care* 2011; **34** (suppl 1): S4–10.

18 Visser J, van Boxel-Dezaire A, Methorst D, Brunt T, de Kloet ER, Nagelkerken L. Differential regulation of interleukin-10 (IL-10) and IL-12 by glucocorticoids in vitro. *Blood* 1998; **91:** 4255–64.

19 Fushimi T, Okayama H, Seki T, Shimura S, Shirato K. Dexamethasone suppressed gene expression and production of interleukin-10 by human peripheral blood mononuclear cells and monocytes. *Int Arch Allergy Immunol* 1997; **112:** 13–18.

20 van der Poll T, Barber AE, Coyle SM, Lowry SF. Hypercortisolemia increases plasma interleukin-10 concentrations during human endotoxemia—a clinical research center study. *J Clin Endocrinol Metab* 1996; **81:** 3604–06.

21 Franchimont D, Martens H, Hagelstein MT, et al. Tumor necrosis factor alpha decreases, and interleukin-10 increases, the sensitivity of human monocytes to dexamethasone: potential regulation of the glucocorticoid receptor. *J Clin Endocrinol Metab* 1999; **84:** 2834–39.

22 Keh D, Boehnke T, Weber-Cartens S, et al. Immunologic and hemodynamic effects of "low-dose" hydrocortisone in septic shock: a double-blind, randomized, placebo-controlled, crossover study. *Am J Respir Crit Care Med* 2003; **167:** 512–20.

23 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.

24 Garcia-Vidal C, Calbo E, Pascual V, Ferrer C, Quintana S, Garau J. Effects of systemic steroids in patients with severe community-acquired pneumonia. *Eur Respir J* 2007; **30:** 951–56.

25 Melby JC. Clinical pharmacology of systemic corticosteroids. *Annu Rev Pharmacol Toxicol* 1977; **17:** 511–27.

26 Salluh JI, Shinotsuka CR, Soares M, et al. Cortisol levels and adrenal response in severe community-acquired pneumonia: a systematic review of the literature. *J Crit Care* 2010; **25:** 541–48.

27 Christ-Crain M, Stolz D, Jutla S, et al. Free and total cortisol levels as predictors of severity and outcome in community-acquired pneumonia. *Am J Respir Crit Care Med* 2007; **176:** 913–20.

28 Yandiola PP, Capelastegui A, Quintana J, et al. Prospective comparison of severity scores for predicting clinically relevant outcomes for patients hospitalized with community-acquired pneumonia. *Chest* 2009; **135**: 1572–79.

29 Niewoehner DE, Erbland ML, Deupree RH, et al. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. Department of Veterans Affairs Cooperative Study Group. *N Engl J Med* 1999; **340:** 1941–47.

30 Voelker R. Risk of exposure to Q fever pathogen boosted by travel in Iraq or Netherlands. *JAMA* 2010; **303:** 2345.

31 Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2004; **32:** 858–73.

32 Castellanos MR, Szerszen A, Saifan C, et al. Fasting hyperglycemia upon hospital admission is associated with higher pneumonia complication rates among the elderly. *Int Arch Med* 2010; **3:** 16.