

# Preventive Antibiotics for Infections in Acute Stroke

## A Systematic Review and Meta-analysis

Diederik van de Beek, MD, PhD; Eelco F. M. Wijdicks, MD, PhD; Frederique H. Vermeij, MD; Rob J. de Haan, PhD; Jan M. Prins, MD, PhD; Lodewijk Spanjaard, MD, PhD; Diederik W. J. Dippel, MD, PhD; Paul J. Nederkoorn, MD, PhD

**Objective:** To provide a systematic overview and meta-analysis of randomized clinical trials evaluating preventive antibiotics in patients with acute stroke.

**Data Sources:** The MEDLINE (1966-February 2009) and Cochrane databases and reference lists of retrieved articles.

**Study Selection:** Randomized controlled trials on preventive antibiotic treatment in stroke. For inclusion, at least case fatality or infection rate had to be recorded.

**Data Extraction:** Each study was scored for methodological key issues and appraised by the Jadad scale. We extracted the data using a predetermined protocol and included all patients who were randomized or who started therapy in an intent-to-treat analysis.

**Data Synthesis:** We identified 4 randomized clinical trials including 426 patients; 94% had ischemic stroke. Study interventions were fluoroquinolones in 2 and tetracycline or a combination of  $\beta$ -lactam antibiotic with

$\beta$ -lactamase inhibitor in 1. Therapy was started within 24 hours of stroke onset. Duration of therapy varied between 3 and 5 days. The methodological quality ranged from 2 to 5 on the Jadad scale, and studies were subject to potential bias. The proportion of patients with infection was significantly smaller in the antibiotic group than in the placebo/control group (32 of 136 [23.5%] vs 53 of 139 [38.1%] patients). The pooled odds ratio for infection was 0.44 (95% confidence interval, 0.23-0.86). Ten of 210 patients (4.8%) in the antibiotic group died, compared with 13 of 216 (6.0%) in the placebo/control group. The pooled odds ratio for mortality was 0.63 (95% confidence interval, 0.22-1.78). No major harm or toxicity was reported.

**Conclusions:** In adults with acute stroke, preventive antibiotics reduced the risk of infection, but did not reduce mortality. The observed effect warrants evaluation of preventive antibiotics in large stroke trials.

*Arch Neurol.* 2009;66(9):1076-1081

**Author Affiliations:** Departments of Neurology (Drs van de Beek and Nederkoorn), Clinical Epidemiology and Biostatistics (Dr de Haan), Infectious Diseases (Dr Prins), and Medical Microbiology (Dr Spanjaard), Center of Infection and Immunity Amsterdam (CINIMA), Academic Medical Center, Amsterdam, the Netherlands; Department of Neurology, Division of Critical Care Neurology, Mayo Clinic, Rochester, Minnesota (Dr Wijdicks); and the Department of Neurology (Drs Vermeij and Dippel), Erasmus University Medical Center, Rotterdam, the Netherlands.

**I**NFECTION IS A COMMON COMPLICATION in the acute phase after stroke and has been described in up to 40% of patients.<sup>1</sup> The most common infection after acute stroke is pneumonia, with reported rates up to 30%. Pneumonia is an early infection; about half of the cases occur within the first 48 hours after stroke onset and almost all within the first week.<sup>1</sup> The mortality and morbidity associated with pneumonia is high. In a community-based study including 14 293 patients with stroke,<sup>2</sup> pneumonia was associated with a relative risk of 3.0 for mortality (95% confidence interval [CI], 2.4-3.7) when adjusted for admission severity and propensity for pneumonia. In the United States, the annual cost of pneumonia as a complication after acute stroke has been estimated to be \$459 million.<sup>3</sup>

Over the last 3 years, several studies have evaluated preventive use of antibiotics in patients with acute stroke, with conflicting results.<sup>1</sup> Current guidelines on acute stroke management state that preventive administration of antibiotics is not indicated because this treatment has not been proven effective.<sup>4</sup> Herein we provide a systematic overview of all randomized clinical trials evaluating preventive antibiotics in patients with acute stroke.

## METHODS

We selected studies on preventive antibiotic treatment in acute stroke. Eligible patients were adults (predefined as aged 16 years or older) with acute stroke, randomized for oral or intravenous antibiotics of any type or a placebo or control group. Each study was scored for methodological key issues, such as inclusion and exclusion criteria, treatment interven-

**Table 1. Methodological Key Issues of Included Trials**

Source	Inclusion Criteria	Exclusion Criteria	Intervention	Jadad Score			Primary Outcome	Sample Size Calculation
				Randomization	Blinding	Withdrawals		
Chamorro et al <sup>6</sup>	Age >18 y; stroke; NIHSS score >4	Infection <3 mo; t > 37.7°C; epilepsy; seizures; serum creatinine >2.5 mg/dL; antibiotic use; immunosuppressant therapy <3 mo; fluoroquinolones allergy	Levofloxacin 500 mg/d IV for 3 d, started within 24 h of stroke onset	2	2	1	Infection rate within 7 d after stroke onset	Yes: 480 patients required, assuming infection rate of 30% and absolute risk reduction of 15%
Lampl et al <sup>8</sup>	Age >18 y; stroke; NIHSS score >5	Hemorrhagic stroke; infectious diseases requiring antibiotics; other CNS diseases; preexisting neurologic disability; renal failure; swallowing difficulties; tetracycline allergy	Minocycline 200 mg/d orally, 5 d, started within 6-24 h of stroke onset	1	0	1	NIHSS score at day 90	No
Harms et al <sup>9</sup>	Age >19 y; nonlacunar ischemic stroke; NIHSS score >11 in MCA territory	Clinical signs of infection; antibiotics <24 h; immunosuppressant therapy; contraindications, moxifloxacin, no others specified	Moxifloxacin 400 mg/d IV, 5 d, started within 36 h of stroke onset	2	2	1	Infection rate within 11 d after stroke onset, according to CDC criteria	Yes: 64 patients required, assuming infection rate of 40% and absolute risk reduction of 30%
Schwarz et al <sup>10</sup>	Age >17 y; ischemic stroke; mRS > 3; premonitory mRS < 2	Hemorrhagic stroke; clinical signs of infection; immunosuppressant therapy; renal insufficiency; life expectancy <90 d; allergy, penicillin or sulbactam	Mezlocillin 6 g/d plus sulbactam 1 g/d IV, 4 d, started within 24 h of stroke onset	2	0	0	Fever	No

Abbreviations: CDC, Centers for Disease Control and Prevention; CNS, central nervous system; IV, intravenously; NIHSS, National Institute of Health Stroke Scale; MCA, middle cerebral artery; mRS, modified Rankin Score; t, temperature.

tion, outcome measurements, definition of infection, and sample size calculations. Studies were also appraised by the Jadad scale, a validated 5-point scale assessing randomization (0-2 points), double-blinding (0-2 points), and withdrawals and dropouts (0-1 point).<sup>5</sup> For inclusion, studies had to be randomized and, at least, the case fatality or infection rate had to be reported. We extracted the data using a predetermined protocol and included all patients who were randomized or who started therapy in an intent-to-treat analysis. Primary outcome measures were short-term infection rate and mortality. Short-term infection rate was defined as occurrence of infection within the first 2 weeks after onset of symptoms. Because definitions of infection varied between studies, we have used infection rates as defined by the investigators. The exact timing of infection could not be ascertained (ie, there exists the chance that infection occurred before stroke was present but did not manifest until later). We did not control for age or sex in our analysis because these studies were comparative.

We extracted all medication-related adverse events. We used Mantel-Haenszel fixed-effects models because Q tests for homogeneity were all  $P > .1$ . For individual studies and meta-analyses, odds ratios (ORs) and 95% CIs are given. We calculated the 95% CIs with the formula  $10^{\exp(\log \text{ fixed effect OR} \pm 1.96 \times \log[\text{standard error}])}$ . Therefore, weighting was done by inclusion of the standard error.

## RESULTS

### DESCRIPTION OF STUDIES

In a PubMed search from 1966 through 2009, we identified 5 randomized clinical trials (published from 2005

through 2008).<sup>6-10</sup> One trial evaluated the efficacy of orally applicable gel for selective decontamination of the digestive tract and was excluded,<sup>7</sup> leaving 4 studies eligible.<sup>6,8-10</sup>

Methodological key issues are noted in **Table 1**. Inclusion criteria for stroke severity were based on the National Institute of Health Stroke Scale (NIHSS) in 3 studies, required scores ranging from greater than 4 to greater than 11.<sup>6,8,9</sup> One study used the modified Rankin Score for stroke severity.<sup>10</sup> For inclusion in this study, patients required a premonitory modified Rankin score of less than 2, a stroke severity reflected by a modified Rankin score greater than 3 on admission but subsequently were excluded if they had a life expectancy of fewer than 90 days.<sup>10</sup>

The study intervention consisted of fluoroquinolones in 2 studies (levofloxacin, moxifloxacin) and tetracycline (minocycline) or a combination of  $\beta$ -lactam antibiotic with  $\beta$ -lactamase inhibitor in 1 study. The latter 2 antibiotic regimens are off-patent antibiotics. Therapy had to be started within 24 hours of stroke onset in all studies; 1 study required a minimum duration of symptoms of 6 hours.<sup>8</sup> The duration of antibiotic therapy varied between 3 and 5 days.

The methodological quality of included studies on the Jadad scale ranged from 2 to 5. All studies were randomized, although allocation concealment was insufficient in 1 study.<sup>8</sup> Two studies had a double-blind design; both evaluated patented antibiotics (fluoroquinolones).<sup>6,9</sup> Three studies described all patients who were withdrawn after the randomization process. Reasons for withdrawal after randomization included ineligibility according to trial

**Table 2. Definitions Used for Infection**

Source	Definition
Chamorro et al <sup>6</sup>	Temperature >37.5°C in 2 determinations; >37.8°C in a single determination in patients with suggestive symptoms; white blood cell count >11 000/mL or <4000/mL; pulmonary infiltrate on chest x-rays; or cultures positive for a pathogen
Lampl et al <sup>8</sup>	Not evaluated
Harms et al <sup>9a</sup>	Pneumonia, >1 of: abnormal respiratory examination or pulmonary infiltrates in chest x-rays, or productive cough with purulent sputum, microbiological cultures from lower respiratory tract or blood cultures, leukocytosis, elevation of CRP; UTI, >1 of the following: fever (temperature >38.0°C), urine sample positive for nitrite, leukocyturia, significant bacteriuria
Schwarz et al <sup>10b</sup>	Pneumonia, new infiltrate on chest x-ray compatible with the diagnosis of infection plus at least 1 of the following: fever (temperature >38.0°C), leukocytosis >12 000/μL or leukopenia <3000/μL, purulent tracheal secretions; Tracheobronchitis, purulent tracheal secretions or sputum plus at least 1 of the following: fever (temperature >38.0°C), leukocytosis >12 000/μL or leukopenia <3000/μL; UTI, >25 leukocytes/μL in the urine if not explained by other findings; Bacteremia, bacteria in blood cultures; Sepsis, clinical evidence of an infection with at least 2 of the following: temperature >38°C or <35°C, tachycardia >90/min, tachypnea >20/min, leukocytosis >12 000/μL or leukopenia <3000/μL; Infection of unclear origin or other infections, clinical evidence of an infection of unknown origin or any other systemic infection

Abbreviations: CRP, C-reactive protein; UTI, urinary tract infection.

<sup>a</sup>Criteria modified from US Centers for Disease Control and Prevention criteria.

<sup>b</sup>Criteria from Paul Ehrlich Society for chemotherapy.

criteria or inability to complete the treatment protocol. Patients who met eligibility criteria but were excluded after the randomization process were included in the current analysis. One study did not describe withdrawals.<sup>10</sup> In this trial, patients with a life expectancy of fewer than 90 days were excluded, which resulted in an overall mortality rate of 0%.<sup>10</sup> One study did not have a blinded outcome assessment.<sup>8</sup> This was also the study that used quasirandomization.<sup>8</sup>

The primary outcome measures were the infection rate in the 2 studies and the proportion of patients with fever during admission in 1 study. The definitions used for infection differed substantially between studies. The criteria for infection are presented in **Table 2**. One study adhered to the official criteria of the US Centers for Disease Control and Prevention, but used heavily modified criteria.<sup>11</sup> Infection rates were not evaluated in all studies. One study focused on the neuroprotective effects of minocycline and did not evaluate infection rates.<sup>8</sup> The primary outcome in this trial was the difference between the NIHSS scores of individual patients at the baseline and on day 90. Overall, secondary outcomes were scores on the modified Rankin,<sup>6,10</sup> NIHSS,<sup>6,8</sup> and Bartel Index.<sup>6,9</sup> These secondary outcomes were assessed 90 days after randomization. Case fatality rates were reported in all studies.

Sample size calculations were performed in 2 studies.<sup>6,9</sup> One study was powered to detect significant effect on the rate of infection based on the assumption of a reduction from 30% to 15% (OR, 0.41), requiring 480 patients.<sup>6</sup> This study was terminated after inclusion of 130 patients because no effect was to be expected with inclusion of all 480 patients. At the moment of termination of enrollment, the proportion of patients with infection was 17% in placebo group and 18% in the levofloxacin group.<sup>6</sup>

#### EFFICACY OF ANTIBIOTIC PROPHYLAXIS

Results of the studies are noted in **Table 3**. The study populations mainly included patients with ischemic stroke

(410 of 436 included patients [94%]). One study also included patients with hemorrhage (deep hematoma, 17; lobar hematoma, 9).<sup>6</sup> The overall number of participants with infection was significantly smaller in the antibiotic group than in the placebo or control group (32 of 136 [23.5%] vs 53 of 139 [38.1%] patients) (Table 3). The number needed to treat to prevent infection was 7. The pooled OR for infection was 0.44 (95% CI, 0.23-0.86) (**Figure**). Infections were pneumonia (n=61), urinary tract infections (n=21), bronchitis (n=5), and others (n=5). The infections that were prevented by antibiotic therapy were those that occurred most frequently, pneumonia and urinary tract infections.

Ten of 210 (4.8%) patients who were treated with antibiotics died, compared with 13 of 216 (6.0%) receiving placebo or no treatment (Table 3). The number needed to treat to prevent death was 83. The pooled OR for mortality was 0.63 (95% CI, 0.22-1.78) (Figure). Case fatality rates varied between studies from 0% to 7%. Two studies had positive results on their primary outcome: 1 on improvement of baseline NIHSS score (mean [SD], 1.6 [1.9] vs 6.5 [3.8];  $P < .001$ ) and 1 on occurrence of fever ( $P < .05$ ).<sup>8,10</sup> In 1 study, the result of primary analysis was positive for the per protocol analysis only (occurrence of infections, 6 of 35 [17%] vs 13 of 31 [42%] patients;  $P = .03$ ).<sup>9</sup> In 1 study, the proportion of patients with favorable neurological outcome was statistically significantly reduced and no effect was observed on mortality.<sup>8</sup> The rate of infection was not evaluated in this study.

#### SAFETY OF ANTIBIOTIC PROPHYLAXIS

Adverse events were described in 3 articles. Antibiotic treatment was not associated with any side effects in 2 studies. The study evaluating mezlocillin plus sulbactam described exanthema and elevated liver enzymes each in 1 patient.<sup>10</sup> Antibiotic susceptibility testing of *Escherichia coli* isolates was performed in 1 study.<sup>9</sup> No difference was found in antibiotic resistance patterns between bacterial isolates from patients in the moxifloxacin and placebo groups.

**Table 3. Results of Studies**

Source	Patients and Controls, No.	Inclusion NIHSS Treatment vs Control	Treatment vs Control Mortality Rate, No./Total (%)	Death		Treatment vs Control Infection Rate, No./Total (%)	Infection		Adverse Events
				OR (95% CI)	P Value <sup>a</sup>		OR (95% CI)	P Value <sup>a</sup>	
Chamorro et al <sup>6</sup>	67 levofloxacin, 69 placebo	Median, 14 (range, 7-19) vs 11 (range, 7-18)	4/67 (6) vs 1/69 (1)	4.32 (0.44-104.00)	.2	11/67 (16) vs 13/69 (19)	0.85 (0.32-2.23)	.7	Not stated
Lampl et al <sup>8</sup>	74 minocycline, 77 controls	Mean (SD), 7.6 (3.8) vs 7.5 (3.2)	5/74 (7) vs 9/77 (12)	0.55 (0.15-1.91)	.4	Not stated	NA	NA	None
Harms et al <sup>9</sup>	39 moxifloxacin, 40 placebo	Median, 17 (range, 12-21) vs 15 (range, 12-25)	1/39 (3) vs 3/40 (8)	0.32 (0.01-4.31)	.6	6/39 (15) vs 13/40 (33)	0.38 (0.11-1.26)	.1	None
Schwarz et al <sup>10</sup>	30 mezlocillin plus sulbactam, 30 controls	Median, 17 (range, 8-28) vs 15 (range, 5-27)	0/30 vs 0/30	NA	NA	15/30 (50) vs 27/30 (90)	0.11 (0.02-0.51)	.002	Exanthema (n=1); elevated liver enzymes (n=1)

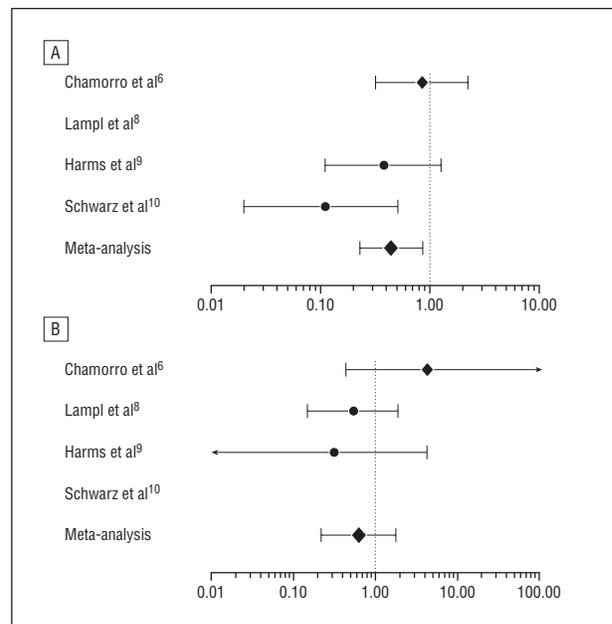
Abbreviations: CI, confidence interval; NA, not applicable; NIHSS, National Institute of Health Stroke Scale; OR, odds ratio.  
<sup>a</sup>Two-sided.

**COMMENT**

This meta-analysis of 4 trials including 426 patients shows that prophylactic antibiotic treatment reduced the occurrence of infections in adults with acute stroke from 38% to 24% (OR, 0.44; 95% CI, 0.23-0.86). The use of preventive antibiotics was not associated with a significant reduction in mortality. We have found no major harm or toxicity, although 2 patients treated with mezlocillin plus sulbactam developed exanthema or elevated liver enzymes.<sup>10</sup>

Pneumonia was the most common infection, complicating 1 of 3 cases of acute stroke. The susceptibility of acute stroke patients to aspiration pneumonia has been well recognized,<sup>1,12</sup> and its etiology is likely multifactorial. Dysphagia occurs in many patients with acute stroke and is a strong predictor of pneumonia.<sup>1,2,12</sup> Aspiration is expected if patients with a large hemispheric lesion or lower brainstem lesion do not receive swallowing precautions but may occur at the ictus. Acute stroke, ischemic stroke in particular, may also lead to stroke-induced immunodepression,<sup>13</sup> a functional decrease in cellular immune response that is related to susceptibility to infection.<sup>14</sup> Finally, sympathetic activation is increased in patients with acute stroke, resulting in gastrointestinal dysmotility,<sup>14,15</sup> which also poses a risk for aspiration pneumonia.<sup>12</sup> Pneumonia is a well-recognized predictor of poor outcome and mortality in patients after acute stroke.<sup>1,2,12</sup> Therefore, there is strong rationale to investigate the efficacy of preventive antibiotics in patients with acute stroke. Future cohort studies may elucidate the influence of the location of stroke and the effects of treatment on infection (ie, an effect of tissue plasminogen activator on infection rates).

Antibiotics can be used after acute stroke to prevent infection but may also offer neuroprotection. To prevent infections, the antimicrobial spectrum should cover the most common causative bacteria of pneumonia and urinary tract infections. *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus* and *Enterobacteriaceae* predominate in patients with aspiration pneumonia and occur within 4 days after



**Figure.** Meta-analysis of effect of preventive antibiotics on infection (A) and mortality (B) rates in patients with acute stroke. Values less than 1.0 indicate decreased infection or mortality rate; greater than 1.0, increased risk for infection or mortality.

admission (community-acquired aspiration syndrome).<sup>12</sup> The most common causative bacteria of urinary tract infections are *Escherichia coli* and *Staphylococcus saprophyticus*.<sup>16</sup> Three of the 4 study interventions adequately covered these most common bacteria.<sup>6,9,10</sup> However, minocycline has inadequate microbiological coverage in patients with acute stroke. The main rationale for treating patients with acute stroke with minocycline is the neuroprotective action of this drug. The study that evaluated preventive minocycline did not even evaluate the rate of infection.<sup>8</sup> Minocycline has several anti-inflammatory effects, reducing microglial activation, inhibits apoptotic cell death, and has a favorable effect on outcome in experimental stroke studies.<sup>17</sup> Another high potential neuroprotective antibiotic is ceftriaxone, a

$\beta$ -lactam antibiotic.<sup>18,19</sup> In a rat model of ischemic stroke, ceftriaxone reduced mortality and neurological deficits.<sup>20</sup> Neuronal survival was improved within the penumbra, and ceftriaxone led to upregulation of neurotrophins in the peri-infarct zone.<sup>20</sup> Ceftriaxone is an off-patent antibiotic with, in contrast to minocycline, a broad action against causative bacteria of infection after acute stroke. The combination of effective antibiotic and neuroprotective properties makes ceftriaxone an interesting drug for future clinical trials.

The methodological quality of included studies ranged from 2 to 5 for the 5-point Jadad score. Several biases may have diminished the reliability of our results. The first confounding factor is selection bias. The included studies had exceptionally low mortality rates, ranging from 0% to 7%. Mortality rates of acute stroke in previously reported studies ranged from 15% to 25%.<sup>21</sup> Inclusion of patients with a less severe illness in the meta-analysis, as reflected in very low case fatality rates, might overestimate the effect of antibiotics; for patients with very high mortality risk, antibiotics are probably less protective. A second bias is introduced when participants are withdrawn after randomization. One study did not describe withdrawal of patients but excluded patients with a life expectancy of fewer than 90 days. Withdrawals on the grounds of ineligibility may have been influenced by knowledge of outcome; if so, this would advantage the antibiotic regimen. Excluding participants because of an inability to complete the course of antibiotics owing to minor side effects (ie, exanthema) also clearly introduces bias in favor of the study medication. One study had positive results in the per protocol analysis only.<sup>9</sup> A third bias is introduced by competitive risks; patients who die are not able to develop an infection.

Fourth, this concise review likely has publication bias. To exclude the possibility of missing small randomized clinical trials that have been described in less well-known journals, more elaborate searches with other search engines (Excerpta Medica Database) and hand searches of congress proceedings are needed. Finally, to fully appreciate the effect of antibiotic prophylaxis on outcome after stroke, a measure of functional outcome or dependency is needed. More elaborate analyses of these trial results, combining all information into a measure of dependency after a reasonably long time span (ie, 3 months) would be desirable. Fifth, the included studies were heterogeneous with respect to study protocol. Several study interventions were used, and definitions of infection were heterogeneous. Studies were comparative; therefore, different definitions used for infection are not such a problem. Nevertheless, future studies should use standardized definitions as described by the Centers for Disease Control and Prevention.<sup>11</sup>

No difference was found in antibiotic resistance patterns between the treatment and placebo groups.<sup>9</sup> Nevertheless, increasing use of antibiotics will lead to increasing resistance rates.<sup>22</sup> The potential benefit for individual patients and the growing burden of antimicrobial resistance should be carefully weighed.

The observed effect in this meta-analysis warrants evaluation of preventive antibiotics in new stroke trials.

These trials should use functional clinical outcomes and standardized definitions of infection. Outcome measures should not only include mortality but also intensive care unit costs and hospital stay. One of the most promising candidates for an intervention is ceftriaxone, an off-patent antibiotic with broad antibacterial action and the potential for neuroprotection. To establish with certainty whether antibiotic prophylaxis has a place in the treatment of patients with acute stroke, a large randomized control trial, probably enrolling many thousands of patients, would need to be undertaken, aiming to detect even a small effect.

**Accepted for Publication:** March 9, 2009.

**Correspondence:** Diederik van de Beek, MD, PhD, Department of Neurology, Center of Infection and Immunity Amsterdam (CINIMA), Academic Medical Center, University of Amsterdam, PO Box 22660, 1100DD Amsterdam, The Netherlands (d.vandebeek@amc.uva.nl).

**Author Contributions:** *Study concept and design:* van de Beek, de Haan, Spanjaard, and Nederkoorn. *Acquisition of data:* van de Beek, Vermeij, and Nederkoorn. *Analysis and interpretation of data:* van de Beek, Wijdicks, Prins, and Dippel. *Drafting of the manuscript:* van de Beek and Wijdicks. *Critical revision of the manuscript for important intellectual content:* van de Beek, Wijdicks, Vermeij, de Haan, Prins, Spanjaard, Dippel, and Nederkoorn. *Statistical analysis:* van de Beek, de Haan, and Nederkoorn. *Obtained funding:* van de Beek. *Administrative, technical, and material support:* van de Beek and Vermeij. *Study supervision:* van de Beek, Wijdicks, Dippel, and Nederkoorn.

**Financial Disclosure:** None reported.

**Funding/Support:** This study was supported by grants from the Netherlands Organization for Health Research and Development (ZonMw; NWO-Veni 2006 grant 916.76.023) and the Academic Medical Center 2008 Fellowship (Dr van de Beek).

## REFERENCES

1. Emsley HC, Hopkins SJ. Acute ischaemic stroke and infection: recent and emerging concepts. *Lancet Neurol.* 2008;7(4):341-353.
2. Katzan IL, Cebul RD, Husak SH, Dawson NV, Baker DW. The effect of pneumonia on mortality among patients hospitalized for acute stroke. *Neurology.* 2003;60(4):620-625.
3. Katzan IL, Dawson NV, Thomas CL, Votruba ME, Cebul RD. The cost of pneumonia after acute stroke. *Neurology.* 2007;68(22):1938-1943.
4. Adams HP Jr, del Zoppo G, Alberts MJ, et al; American Heart Association/American Stroke Association Stroke Council; American Heart Association/American Stroke Association Clinical Cardiology Council; American Heart Association/American Stroke Association Cardiovascular Radiology and Intervention Council; Atherosclerotic Peripheral Vascular Disease Working Group; Quality of Care Outcomes in Research Interdisciplinary Working Group. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Circulation.* 2007;115(20):e478-e534.
5. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials.* 1996;17(1):1-12.
6. Chamorro A, Horcajada JP, Obach V, et al. The early systemic prophylaxis of infection after stroke study: a randomized clinical trial. *Stroke.* 2005;36(7):1495-1500.

7. Gosney M, Martin MV, Wright AE. The role of selective decontamination of the digestive tract in acute stroke. *Age Ageing*. 2006;35(1):42-47.
8. Lampl Y, Boaz M, Gilad R, et al. Minocycline treatment in acute stroke: an open-label, evaluator-blinded study. *Neurology*. 2007;69(14):1404-1410.
9. Harms H, Prass K, Meisel C, et al. Preventive antibacterial therapy in acute ischemic stroke: a randomized controlled trial. *PLoS ONE*. 2008;3(5):e2158.
10. Schwarz S, Al-Shajlawi F, Sick C, Meairs S, Hennerici MG. Effects of prophylactic antibiotic therapy with mezlocillin plus sulbactam on the incidence and height of fever after severe acute ischemic stroke: the Mannheim infection in stroke study (MISS). *Stroke*. 2008;39(4):1220-1227.
11. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control*. 2008;36(5):309-332.
12. Marik PE. Aspiration pneumonitis and aspiration pneumonia. *N Engl J Med*. 2001;344(9):665-671.
13. Chamorro A, Urra X, Planas AM. Infection after acute ischemic stroke: a manifestation of brain-induced immunodepression. *Stroke*. 2007;38(3):1097-1103.
14. Klehmet J, Harms H, Richter M, et al. Stroke-induced immunodepression and post-stroke infections: lessons from the Preventive Antibacterial Therapy in Stroke trial. *Neuroscience*. 2009;158(3):1184-1193.
15. Schaller BJ, Graf R, Jacobs AH. Pathophysiological changes of the gastrointestinal tract in ischemic stroke. *Am J Gastroenterol*. 2006;101(7):1655-1665.
16. Stamm WE, Hooton TM. Management of urinary tract infections in adults. *N Engl J Med*. 1993;329(18):1328-1334.
17. Yong VW, Wells J, Giuliani F, Casha S, Power C, Metz LM. The promise of minocycline in neurology. *Lancet Neurol*. 2004;3(12):744-751.
18. Lipski J, Wan CK, Bai JZ, Pi R, Li D, Donnelly D. Neuroprotective potential of ceftriaxone in in vitro models of stroke. *Neuroscience*. 2007;146(2):617-629.
19. Lee SG, Su ZZ, Emdad L, et al. Mechanism of ceftriaxone induction of excitatory amino acid transporter-2 expression and glutamate uptake in primary human astrocytes. *J Biol Chem*. 2008;283(19):13116-13123.
20. Thöne-Reineke C, Neumann C, Namsolleck P, et al. The beta-lactam antibiotic, ceftriaxone, dramatically improves survival, increases glutamate uptake and induces neurotrophins in stroke. *J Hypertens*. 2008;26(12):2426-2435.
21. van der Worp HB, van Gijn J. Clinical practice: acute ischemic stroke. *N Engl J Med*. 2007;357(6):572-579.
22. Hawkey PM. The growing burden of antimicrobial resistance. *J Antimicrob Chemother*. 2008;62(suppl 1):i1-i9.

### Announcement

**Research Letters.** The Research Letter is intended to provide a means to communicate short original research in a highly focused manner. Important, fast-breaking research that lends itself to a short communication and that can be reviewed rapidly is our objective. Papers should not exceed 600 words of text and should have fewer than 6 references. A single table or figure may be included. In general, Research Letters should be divided into the following sections: an introduction (with no heading), Methods, Results, and Comment. Research Letters should be double spaced and a word count should be provided with each letter.