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)
Stefan Schwarz, MD; Frank Al-Shajlawi, MD; Christian Sick, MD; Stephen Meairs, MD; Michael G. Hennerici, MD

Background and Purpose—Fever after stroke is a strong predictor for a negative outcome with infections as the most common cause. The aim of this pilot study was to evaluate the effects of prophylactic antibiotic therapy on the incidence and height of fever after acute ischemic stroke.

Methods—This is a randomized, controlled study of antibiotic prophylaxis in patients with ischemic stroke enrolled within 24 hours from clinical onset who presented bedridden (modified Rankin score >3) with no significant infection. Interventions included prophylactic mezlocillin plus sulbactam (3×2 g/1 g for 4 days) or conventional management. Over 10 days, body temperature was continuously monitored, and the presence of infection was daily assessed. Primary end points were incidence and height of fever; secondary end points included rate of infection and clinical outcome.

Results—Sixty patients were included (mean, 75 years; median National Institutes of Health Stroke Scale score, 16). Over the first 3 days, patients in the intervention group showed lower mean body temperatures as well as lower daily peak temperatures (P<0.05). Throughout the observation period, 15 of 30 patients in the intervention group but 27 of 30 patients in the conventionally treated group developed an infection (P<0.05). Mean interval until the diagnosis of infection was 5.1 days in the intervention group and 3.3 days in the control group (P=0.01). Clinical outcome was more favorable in patients with prophylactic therapy (P=0.01).

Conclusions—In patients with acute severe stroke, prophylactic administration of mezlocillin plus sulbactam over 4 days decreases body temperature, lowers the rate of infection, and may be associated with a better clinical outcome. (Stroke. 2008;39:1220-1227.)

Key Words: acute stroke ■ antibiotic prophylaxis ■ fever ■ hyperthermia ■ infection

The prognostic importance of body temperature during the acute phase of ischemic stroke has been increasingly recognized. Several clinical studies have consistently shown that in the early phase after stroke, fever (>37.5°C) is very common, occurring in up to 61% of patients, and is a strong predictor of an unfavorable outcome.1 A multitude of different biochemical and inflammatory mechanisms for the detrimental effects of fever during the acute phase of stroke have been identified.2 Consequently, present guidelines recommend lowering fever in patients with acute stroke.3 However, in many patients, symptomatic treatment of fever remains frustrating.4–7 Invasive catheter-based heat-exchange systems influence the body temperature more effectively but may not be suitable for the general stroke-unit setting due to technical and staff requirements, possible complications, and the substantial costs of this invasive technique.8,9 Given the prognostic significance of fever and the limitations of its present symptomatic treatment options, it appears reasonable to ascertain and treat the causes of fever, and, if possible, to prevent its occurrence altogether.

The etiology of fever after stroke is not always evident. In some patients, even a rigorous search for the cause of fever remains unsuccessful, leading to the assumption of “central” or “neurogenic” fever in these patients.10 However, systemic infections are the main origin of fever after stroke. The incidence of infection after stroke varies remarkably depending on the observation period, definitions of infection, and patient selection.1 Infections have been extensively discussed as a risk factor11 but, to a lesser extent, also as a complication of stroke due to immobilization, dysphagia, or catheterizations.10 More recently, it has been hypothesized that alleged “brain-induced immunodepression” could also contribute to the occurrence of infection after stroke.12 Considering that (1) fever is a common finding after acute stroke; (2) fever is associated with a negative outcome; (3) the

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From the Departments of Neurology (S.S., C.S., S.M., M.G.H.) and Internal Medicine (F.A.-S.), Klinikum Mannheim, University of Heidelberg, Mannheim, Germany; and the Central Institute of Mental Health (S.S.), University of Heidelberg, Mannheim, Germany.
Correspondence to Stefan Schwarz, MD, Central Institute of Mental Health, J 5, Mannheim 68159, Germany. E-mail stefan.schwarz@zi-mannheim.de
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symptomatic treatment of fever often remains ineffective; and (4) infections are the most common cause of fever after stroke, prophylactic antibiotic therapy to prevent fever after stroke emerges as an appealing concept.

The aim of this phase II, randomized pilot study was to test the primary hypothesis that prophylactic antibiotic treatment with mezlocillin and sulbactam over 4 days decreases the incidence, duration, and height of fever in the first 10 days after acute, severe ischemic stroke. Secondary objectives included the effects of antibiotic prophylactic treatment on the rate of infection and clinical outcome parameters.

**Materials and Methods**

Over a period of 2 years, 60 patients with acute ischemic stroke were enrolled in this study. All patients were being treated at the Stroke Unit of the Klinikum Mannheim of the University of Heidelberg according to present American Heart Association guidelines.3 Fever was treated using a standardized protocol (Table 1). Physiotherapy, early mobilization, and breathing exercises were performed on a regular basis.

We included patients in whom the diagnosis of an ischemic stroke, with onset of symptoms less than 24 hours ago, had been established and who were bedridden on time of inclusion (modified Rankin score [mRS] ≥3). We deliberately used the criterion of being bedridden because these patients carry the greatest risk of infection and because this simple clinical criterion would facilitate the implementation of study results into future treatment regimes. Other eligibility criteria were age ≥18 years, stable deficit as well as an estimated premorbid mRS <2.

Exclusion criteria included evidence of a significant systemic bacterial or viral infection on inclusion, renal insufficiency (serum creatinine >2 mg/dL), immunosuppressive medication, expected life expectancy of <90 days, and intolerance to penicillin antibiotics or sulbactam. Women of childbearing potential were also excluded. Any infection with the need for antibacterial therapy was defined as “significant.”

Randomization was performed using a computer-generated number sheet and by opening a numbered, sealed envelope. Patients were randomized to either conventional management or prophylactic antibiotic therapy:

1. Conventional treatment: Antibiotic therapy was initiated only after the diagnosis of an infection had been established. Fever as an isolated clinical symptom was not an indication for antibiotic treatment. If antibiotic therapy became necessary, the antibiotic drug was chosen by the treating physician according to the underlying condition.

2. Prophylactic antibiotic treatment: The patients received 2 g mezlocillin plus 1 g sulbactam over 20 minutes IV every 8 hours over a total of 4 days (12 infusions). If the diagnosis of an infection was established during or after the 4-day treatment phase, the antibiotic drug combination could either be continued or changed to another antibiotic drug regime at the discretion of the treating physician.

### Table 1. Standardized Protocol for Symptomatic Treatment of Fever

<table>
<thead>
<tr>
<th>Step</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Start treatment immediately as soon as the temperature exceeds 37.5°C</td>
</tr>
<tr>
<td>2.</td>
<td>1000 mg acetaminophen per rectum or orally; may be repeated (maximum daily dose 4 g)</td>
</tr>
<tr>
<td>3.</td>
<td>400 mg metamizole orally or IV; may be repeated (maximum daily dose 2 g)</td>
</tr>
<tr>
<td>4.</td>
<td>External cooling with cooling blankets</td>
</tr>
<tr>
<td>5.</td>
<td>Consider additional therapy with opiates (5 to 10 mg pethidine subcutaneously or IV) or neuroleptics (25 to 50 mg levopromazine orally or IV)</td>
</tr>
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</table>

### Table 2. Definitions of Significant Infection*

<table>
<thead>
<tr>
<th>Infection</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>Evidence of a new infiltrate on the chest x-ray compatible with the diagnosis of infection plus at least one of the following findings: Fever (temperature &gt;38.0°C), Leukocytosis (&gt;12,000/µL or leukopenia &lt;3000/µL), Purulent tracheal secretions</td>
</tr>
<tr>
<td>Tracheobronchitis</td>
<td>Purulent tracheal secretions or sputum plus at least one of the following findings: Fever (temperature &gt;38.0°C), Leukocytosis (&gt;12,000/µL or leukopenia &lt;3000/µL)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>Evidence of &gt;25 leukocytes/µL in the urine if not explained by other findings (eg, blood contamination); each urinary tract infection in this patient group is considered significant</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>Evidence of bacteria in blood cultures</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Clinical evidence of an infection with at least two of the following findings: Temperature &gt;38°C or &lt;35°C, Tachycardia &gt;90/min, Tachypnea &gt;20/min, Leukocytosis &gt;12,000/µL or leukopenia &lt;3000/µL</td>
</tr>
<tr>
<td>Infection of unclear origin or other infections</td>
<td>Clinical evidence of an infection of unknown origin or any other systemic infection</td>
</tr>
</tbody>
</table>

*Modified criteria of the Paul-Ehrlich-Society for chemotherapy.13,14

Core body temperature was continuously monitored in both groups. In patients who needed a urinary catheter due to incontinence or urinary obstruction, a bladder catheter with a temperature probe was inserted. Bladder catheters were not inserted solely for study-related reasons. In patients not needing a urinary catheter at the start of the study or over the entire observation period, a rectal temperature probe was inserted. Temperature values were documented on an hourly basis during the entire observation period of 10 days.

Patients’ daily mean temperature as well as daily maximum temperatures were assessed along with the length of time (hours) when the temperature was ≥37.5°C (fever), ≥38.0°C, and ≥38.5°C. The patients’ neurological status was assessed on a daily basis using the National Institutes of Health Stroke Scale (NIHSS). Blood and urine were daily taken for routine laboratory markers, including C-reactive protein, blood cell count, and urine sediment. Radiological examinations, blood cultures, and additional assessments to ascertain the cause of a suspected infection were only done when clinically indicated.13,14

Because the treatment team was not blinded, an internist blinded to the study medication assessed the evidence of significant infection (ie, with the need for antibacterial therapy) in both treatment groups using all available data along with standardized criteria for infections according to present guidelines (Table 2) on a daily basis during the study period.13,14

The final infarct location was determined using cranial CT or MRI. Combined with other data acquired during the routine workup, the infarct was categorized according to the TOAST15 and OCSP16 classifications.

The mRS was used to determine patients’ outcome at the end of the observation period at day 10 and again after 90 days. The follow-up examination at day 90 was performed by a telephone interview.
Statistical analysis was done with statistical software (JMP 5.1; SAS, Cary, NC) using nonparametric tests to detect differences between the 2 groups. For nominal data, χ² or Fisher exact tests (2-tailed) were used. Continuous or ordinal data were analyzed with the Mann-Whitney signed rank test. Differences were considered significant at values of \( P < 0.05 \).

This study had been approved by the institutional ethics committee and the German Federal Drug Administration. Informed consent was obtained from the patients or their legal substitutes.

### Results

The main patient characteristics are presented in Table 3. Significant differences between the 2 groups could not be detected, except for the initial serum creatinine, which was higher in the treatment group (\( P < 0.01 \)). However, absolute creatinine values were not notably high. The NIHSS scores indicate that most patients had a moderate to severe neurological deficit in addition to all patients being bedridden (mRS ≥3). The majority of patients had sustained embolic stroke, predominantly in the anterior circulation. Intubation and artificial ventilation was not performed in any patient. Mean body temperature on inclusion into the study was 37.1°C in both groups. Although signs of a significant infection could not be found in any patient at the time of inclusion, mean initial C-reactive protein was mildly elevated in both groups.

All patients in the treatment group completed the treatment over 4 days without additional antibiotic drugs. Serious adverse events related to the prophylactic antibiotic drug combination were not noted. Two patients in the treatment group developed minor adverse events possibly linked to the study drug: One patient had a suspected drug-induced exanthema, whereas in another patient, we noted clinically asymptomatic, mildly elevated liver enzymes. In both patients, various comedications and other conditions could also have caused these symptoms. Both adverse events were mild and self-limited, and antibiotic drug therapy was continued. With temperature monitoring generally well tolerated, we analyzed a total of 10,072 single temperature measurements from all...
patients. This means that 69% of all planned temperature measurements did actually take place. Missing measurements were due to technical problems, death during the observation period, temporary dislocation of the rectal probe, or transport of the patient away from the ward for therapeutic or diagnostic interventions.

The initial temperature on inclusion into the study and the mean daily temperatures over the first 10 days are provided in Figure 1. In both groups, patients’ temperature increased from the time of inclusion, reaching peak values at day 3, after which they fell back toward normal values. Interestingly, in the active treatment group, the rise in temperature within the first few days was markedly tapered. Throughout day 4, the mean daily temperatures in the treatment group were lower compared with the conventional treatment group. After day 3, the temperature differences between the 2 groups were no longer significant.

Figures 2 and 3 depict the duration of fever (temperature >37.5°C) and temperatures >38.0°C per day (hours) over the first 10 days. The duration of fever and temperatures >38.0°C were higher in the conventional treatment group from day 1 through day 4 (P<0.05), after day 4, the maximum temperatures were not longer different. In both groups, the peak of the patients’ mean maximum temperature was reached on day 3 (active treatment: 37.8±0.6°C, conventional treatment: 38.1±0.6°C, P<0.001).

Figure 4 provides an overview over patients remaining free of fever (>37.5°C) who were found more frequently in the treatment group from day 1 to day 3.

Infections were diagnosed more frequently in the conventional treatment group. Over the first 10 days, 15 patients with prophylactic antibiotic treatment compared with 27 conventionally treated patients developed a significant infection (Fisher exact P=0.0015, contingency coefficient=0.400). Supplemental Figure I, available online at http://stroke.ahajournals.org, shows the number of patients remaining free from infection over the observation period. In the conventional treatment group, most infections were diagnosed within the first few days. Although in patients receiving prophylactic antibiotic therapy, infections were also a frequent finding, occurring in half of the total sample, half of
the infections were diagnosed during the 6 days after prophylactic antibiotic therapy was stopped. The interval before diagnosis of the first infection was shorter in the conventional treatment group (5.1 ± 2.7 days versus 3.3 ± 2.1 days, \( P < 0.003 \)). In both groups, most infections were urinary tract infections followed by pneumonia and tracheobronchitis (Table 4).

The laboratory analyses revealed an increase in daily white blood cell count and C-reactive protein levels in both groups but no differences between the groups. Although in the active treatment group, maximum mean white blood cell count was at day 1 (10.493 ± 3.234 × 10^9/L), the control group’s maximum mean white blood cell count was observed on day 2 (10.540 ± 4.117 × 10^9/L). In the active treatment groups, C-reactive protein levels rose to a maximum mean of 55.6 ± 63.8 mg/dL on day 8. Interestingly, the peak mean C-reactive protein levels in the control group occurred earlier, on day 4 (52.7 ± 66.4 mg/dL), before dropping thereafter (at day 8: 33.6 ± 37.4 mg/dL).

NIHSS scores showed no differences at the beginning of the study. However, on day 2 and 3, NIHSS scores were lower in patients receiving antibiotic drug therapy (supplemental Figure II). This coincided with the period of time when the temperature differences were also significant.

At the end of the study, mRS did not differ between the 2 groups (Figure 5). Three patients in the conventional treatment groups and one patient in the active treatment group had died, all of them from space-occupying stroke. During short follow-up after 90 days, clinical outcome was better among patients having undergone prophylactic antibiotic treatment (\( P = 0.01 \), Figure 5).

**Discussion**

In this controlled phase II study on prophylactic antibiotic therapy with fever as the primary outcome parameter, we could demonstrate that prophylactic antibiotic therapy with mezlocillin and sulbactam decreases the incidence as well as the height of fever during the acute phase within the first 3 to 4 days after stroke. Moreover, prophylactic antibiotic therapy was associated with a lower rate of infection and an improved outcome after 90 days.

The effect size from prophylactic treatment in our study was by far larger than the results of previous studies on antipyretic medication for symptomatic therapy of fever after stroke, which had shown no or only modest temperature-lowering effects.4–7

The concept of prophylactic antibiotic therapy for patients with an excess risk of infection is not innovative. In selected surgical patient collectives, prophylactic antibiotic therapy has been the subject of various studies, yielding heterogeneous results.17–19 Only a few studies have investigated prophylactic antibiotic therapy in patients with stroke. Al-

![Figure 3](http://stroke.ahajournals.org/Downloaded_from http://stroke.ahajournals.org) Duration of marked fever (temperature >38.0°C) per day (hours) over the first 10 days after stroke under conventional treatment and prophylactic antibiotic therapy. The duration of fever >38.0°C is significantly higher in the conventional treatment group on days 2 and 3.

![Figure 4](http://stroke.ahajournals.org/Downloaded_from http://stroke.ahajournals.org) Patients remaining free of fever (>37.5°C) under conventional treatment or prophylactic antibiotic therapy. The incidence of fever throughout the observation period was lower in the active treatment group throughout the first 3 days.

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**Table 4**

<table>
<thead>
<tr>
<th>Group</th>
<th>Infections Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional treatment</td>
<td>12</td>
</tr>
<tr>
<td>Prophylactic antibiotic</td>
<td>11</td>
</tr>
</tbody>
</table>

**Figure 5**

Day 1: Fisher’s exact \( p = 0.0001 \) contingency coefficient = 0.492
Day 2: Fisher’s exact \( p = 0.0048 \) contingency coefficient = 0.367
Day 3: Fisher’s exact \( p = 0.0159 \) contingency coefficient = 0.317
ready in 1982, Majkowski et al.20 published a controlled study on prophylactic antibiotics in 103 patients with acute stroke. They reported a reduced incidence of infections in the active therapy group during the first 10 days. Yet, this study, published in a Polish-language journal during the Cold War, was not widely recognized at the time.

More recently, 2 other studies on prophylactic antibiotic therapy have been published, both concentrating on the prevention of infectious complications. Chamorro et al.21 performed a controlled study on the effects of levofloxacin over 3 days after acute stroke. This study was prematurely terminated after an interim analysis made positive effects from active treatments unlikely. Actually, outcome after 90 days was even worse in the verum group. The authors speculated that negative central nervous system effects of levofloxacin could have caused the unexpected negative effects on outcome. In this study, although hyperthermia was not their main focus, daily temperature measurements were taken revealing no differences between the groups. However, body temperature was assessed with measurements in the axilla, a method that is hardly adequate to determine the actual core body temperature. Moreover, in contrast to our data and the results from other studies,1,22,23 the authors found no increase in body temperature after admission. The results of this study are difficult to compare with our study, because Chamorro et al included patients with ischemic and hemorrhagic stroke as well as patients with an NIHSS score ≥5. Most likely, these patients were not as severely ill as our severely ill, bedridden patients. Another recent study on antibiotic prophylaxis after stroke has so far only been published as an abstract with seemingly ambiguous results.24

Also in this second study, the main focus was the incidence of infection, and despite the negative results of the previously mentioned study with levofloxacin, another fluoroquinolone antibiotic, moxifloxacin, was used.

The choice of the optimum antibiotic drug to be administered for this purpose and the optimum duration of preventive therapy remain hypothetical. We selected mezlocillin plus sulbactam, a combination of a broad-spectrum penicillin with a β-lactamase inhibitor, due to its excellent efficacy against the most common microorganisms that can be expected in this patient population.25 Cephalosporins, which rapidly induce drug-resistant bacteria, are possibly not preferable.26 Arguably, fluoroquinolones are also not the first choice in patients with stroke because, as a group, they impose a well-documented risk for central nervous system complications27 and are moreover associated with QT prolongation,28 which renders these drugs not attractive in patients with stroke.

We performed no systematic microbiological monitoring. Microorganisms causing an infection during the first days of treatment in a stroke unit that are particularly difficult to treat are not expected in this population. Theoretically, the possibility for drug-resistant bacteria to develop cannot be excluded. On the other hand, this risk appears negligible given 60 additional patients treated over a period of 2 years in a stroke unit where over 700 patients are treated per year. Previous studies on prophylactic antibiotic treatment in other settings did not support the assumption that short-term prophylactic antibiotic drug treatments facilitate the development of antibiotic drug resistance.17 However, if antibiotic prophylaxis should be implemented into the daily routine of stroke units, and a large number of patients would be treated with the same antibiotic drugs within a single ward, the development of drug resistance could constitute a point of concern.

In the present study, the incidence of infection during the first days after stroke was high. In accordance with the literature, urinary and respiratory tract infections were the most common types of infection.21,29–32 In previous studies, the incidence of infection as a complication of stroke varied enormously,

<table>
<thead>
<tr>
<th>Time to first infection, days</th>
<th>Prophylactic Antibiotic Treatment (n=30)</th>
<th>Conventional Treatment (n=30)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any infection</td>
<td>15</td>
<td>27</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>8</td>
<td>18</td>
<td>...</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>5</td>
<td>7</td>
<td>...</td>
</tr>
<tr>
<td>Tracheobronchitis</td>
<td>2</td>
<td>3</td>
<td>...</td>
</tr>
<tr>
<td>Other/unclear origin</td>
<td>2</td>
<td>2</td>
<td>...</td>
</tr>
</tbody>
</table>

Table 4. Significant Infections During the Observation Period of 10 Days

Figure 5. Outcome (mRS) at end of study and 90 days after conventional treatment or prophylactic antibiotic therapy (mRS 0 = no symptoms, mRS 6 = death). At the end of the observation period, the outcomes were not different. On follow-up at day 90, outcome was significantly better in the treatment group. mRS 0 to 2 were not observed.
This was our reason for selecting only severely ill patients who were bedridden on admission. In the study by Chamorro et al discussed previously, the cumulative rate of infection at day 7 was below 20% even in the control group. A very large sample size would be necessary to demonstrate beneficial effects from a prophylactic therapy in a population with such a small event rate, and possible side effects from the medication would gain more weight. Thus, in future studies, only severely ill patients should be considered as candidates for prophylactic antibiotic treatment.

We chose fever as the primary outcome criterion for the following reasons; first, because fever has been more consistently demonstrated as a strong negative predictor than infection per se, and second, because we had the intention to circumvent methodological problems associated with the diagnosis of infection. Especially in the early phase of a systemic infection, often characterized by a systemic response with prominent fever (systemic inflammatory response syndrome), the underlying infection may not be easy to establish. This is particularly true for urinary tract infections. It is difficult, and in many situations even impossible, to differentiate a bland, localized urinary infection from a systemic inflammatory syndrome originating from a urinary tract infection. We used the strict criteria of >25 leukocytes/mL in urine to diagnose a urinary infection if not otherwise explainable (for example, with blood contamination), because this finding is an indication for antibiotic therapy in hospitalized ill patients. Moreover, infections are an important risk factor for stroke. Thus, in patients in whom an infection is diagnosed within the first 2 or 3 days after stroke, it may be impossible to distinguish between infections that were clinically not yet evident on admission and infections that were actually acquired after stroke.

Beneficial effects associated with prophylactic antibiotic therapy were present even during the first 24 hours after inclusion and thereafter over the first 3 to 4 days only. After the first days, significant differences between the 2 groups could no longer be detected. At this time, the vast majority of patients in the control group had already been receiving antibiotic treatment due to clinical indications, which could explain this finding, whereas in the active treatment group, many patients developed an infection after termination of prophylactic antibiotic therapy.

This study has limitations. Although the design was controlled and randomized, treatment was not blinded to the treating physicians. We tried to overcome this shortcoming by blinding the internist, who assessed the evidence of an infection on a daily basis to the study drug. Moreover, our primary end point, fever, was automatically assessed. As mentioned previously, the diagnosis of infection was established using standardized criteria. Regarding the complex problems in diagnosing an incipient infection, an area of uncertainty cannot be excluded. Finally, this study was not designed or powered to detect differences in patients’ outcome. The unexpected result of an improved outcome in the active treatment group has to be viewed with caution because probably not all of the multiple predictors of outcome after stroke have been sufficiently taken into consideration.

Conclusions
This is the first study demonstrating that prophylactic antibiotic therapy with mezlocillin plus sulbactam over 4 days after acute severe ischemic stroke is well tolerated; decreases the incidence, height, and duration of fever; lowers the rate of infection; and may even be associated with an improved clinical outcome.

Based on these data, a large, randomized multicenter study using simple, practical inclusion criteria and valid functional outcome parameters is justified to test the hypothesis that prophylactic antibiotic therapy can actually improve clinical outcome in this patient group.

Acknowledgments
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Disclosures
None.

References


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