

Early Switch From Intravenous to Oral Antibiotics in Hospitalized Patients With Bacteremic Community-Acquired *Streptococcus pneumoniae* Pneumonia

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Background: The identification of *Streptococcus pneumoniae* bacteremia in hospitalized patients with community-acquired pneumonia is considered by some investigators to be an exclusion criterion for early switch from intravenous to oral therapy.

Objective: To determine whether the switch from intravenous to oral therapy in such patients, once the patient reaches clinical stability, is associated with poor clinical outcome.

Methods: The medical records of 400 patients with community-acquired pneumonia hospitalized at the Veterans Affairs Medical Center of Louisville (Louisville, Ky) were reviewed to identify patients with bacteremic *S pneumoniae*. Four criteria were used to define when a patient reached clinical stability and should be considered a candidate for switch therapy: (1) cough and shortness of breath are improving, (2) patient is afebrile for at least

8 hours, (3) white blood cell count is normalizing, and (4) oral intake and gastrointestinal tract absorption are adequate.

Results: A total of 36 bacteremic patients were identified. No clinical failures occurred in 18 patients who reached clinical stability and were switched to oral therapy or in 7 patients who reached clinical stability and continued intravenous therapy. Clinical failures (5 deaths) occurred in the group of 11 patients who did not reach clinical stability.

Conclusion: Once a hospitalized patient with community-acquired pneumonia reaches clinical stability, it is safe to switch from intravenous to oral antibiotics even if bacteremia caused by *S pneumoniae* was initially documented.

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THE AMERICAN Thoracic Society in 1993 suggested that, in hospitalized patients with community-acquired pneumonia (CAP), the initial intravenous therapy may be switched to oral therapy (switch therapy) once the patient shows evidence of early clinical improvement.¹ Since then, several clinical trials have documented that performing switch therapy once the patient reaches clinical stability is associated with good clinical outcome, adequate patient satisfaction, and decreased length of hospital stay.²⁻⁶

Blood cultures positive for *Streptococcus pneumoniae* in hospitalized patients with CAP have been identified as a prognostic factor that is significantly associated with mortality.⁷ Since bacteremia is associated with poor outcome, physicians are frequently reluctant to consider switch therapy in patients with bacteremic CAP. Although the identification of bacteremia is considered by some investigators to be an exclusion criterion for early switch from intravenous to

oral therapy,⁸ we have not used bacteremia as an exclusion criterion for switch therapy.^{2,4,6}

Streptococcus pneumoniae is the most common pathogen causing bacteremia in hospitalized patients with CAP. Bacteremia caused by *S pneumoniae* has been documented in up to 26% of hospitalized patients with CAP.⁹ Since controversy exists regarding the early use of oral therapy in these patients, we decided to review our experience with the treatment of hospitalized patients with bacteremic *S pneumoniae*.

Our objectives were (1) to define, in hospitalized patients with CAP and *S pneumoniae* bacteremia, whether the switch from intravenous to oral therapy is associated with poor clinical outcome and (2) to compare the population of bacteremic patients with a general population of hospitalized patients with CAP to define whether there is a difference in the percentage of patients who reach clinical stability and the time required for the patients to reach clinical stability.

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PATIENTS AND METHODS

The medical records of 400 patients hospitalized with CAP at the Veterans Affairs Medical Center of Louisville (Louisville, Ky) were reviewed to identify patients with *S pneumoniae*-positive blood cultures. Many of these patients had participated in previous clinical trials to evaluate clinical outcome after switch therapy. Diagnostic criteria for CAP were followed as previously published.^{2,4,6}

The following 4 criteria were used to define when a patient has reached clinical stability and should be considered a candidate for switch therapy: (1) cough and shortness of breath are improving, (2) the patient has been afebrile (temperature, <37.8°C) for at least 8 hours, (3) white blood cell count is normalizing, and (4) oral intake and gastrointestinal tract absorption are adequate. A patient who was able to take food by mouth without evidence of diarrhea or malnutrition was considered to have adequate oral intake and gastrointestinal tract absorption.

The clinical course was defined as *clinical improvement* in patients who met switch therapy criteria during the first 7 days of hospitalization. The clinical course was defined as *lack of improvement* in patients who did not meet criteria for switch therapy during the first 7 days of hospitalization.

All patients were treated initially with a regimen of intravenous antibiotics that was in compliance with published guidelines.¹ Cephalosporins were the most commonly used intravenous and oral antibiotics (eg, ceftriaxone sodium, cefuroxime sodium). Antibiotic therapy was defined as *switch therapy* when the patient was switched from intravenous to oral antibiotics during the first 7 days of hospitalization. The antibiotic therapy was classified as *intravenous therapy* when the patient was treated only

with intravenous antibiotics during the first 7 days of hospitalization.

According to the clinical course (improvement vs lack of improvement) and antibiotic therapy (switch therapy vs intravenous therapy), the patients were classified in 3 groups. Group A consisted of patients with clinical improvement treated with switch therapy. These patients were switched from intravenous to oral antibiotics once they met switch therapy criteria. Group B included patients with clinical improvement treated with intravenous therapy only. These patients were candidates for switch therapy during the initial 7 days of intravenous therapy, but the primary physician decided not to use oral therapy because of the presence of bacteremia. Group C consisted of patients with lack of clinical improvement treated with intravenous therapy. These patients did not meet criteria for switch therapy and were treated with intravenous antibiotics only.

The severity of CAP at the time of hospital admission was evaluated in patients in groups A, B, and C by determination of risk for mortality at 30 days,¹⁰ the Acute Physiology and Chronic Health Evaluation II score,¹¹ and the number of factors for complicated courses.¹

The clinical outcome was defined as *cured* in patients with resolution or improvement of CAP during last follow-up and *failure* in patients who died as a consequence of CAP or a complication related to CAP.

The percentage of patients who reached clinical stability and the time to reach clinical stability were calculated for the population of bacteremic patients. These data were compared with the data from a recently published study of 200 consecutive hospitalized patients with CAP.⁶ A Cox proportional hazard analysis was performed on the time to reach clinical stability data, testing the effect of the variable group.

RESULTS

From the total of 400 hospitalized patients with CAP, 36 patients were identified with blood cultures positive for *S pneumoniae* at hospital admission. All isolates were susceptible to penicillin and erythromycin. No atypical pathogens were identified in the 36 study patients. Of the 36 bacteremic patients, 18 were in group A, 7 in group B, and 11 in group C. The average risk class at time of hospitalization was 3.6 for group A, 3.3 for group B, and 4.2 for group C. The average Acute Physiology and Chronic Health Evaluation II score was 12.9 for group A, 11.6 for group B, and 17.5 for group C. The average number of risk factors for complicated course was 8.4 for group A, 7.3 for group B, and 10.4 for group C. The average patient age was 58 years for group A, 58 years for group B, and 61 years for group C. The clinical outcome of these 36 patients in groups A, B, and C is given in the **Table**.

Of the bacteremic patients, 25 (69%) were candidates for switch therapy, with a mean time to switch of 3.5 days. In the general population, 87% were candidates for switch therapy, with a mean time to switch of 2.9 days. The comparison of the bacteremic population with the general CAP population in regard to the time

to reach clinical stability is shown in the **Figure**. The groups were different ($P = .03$), with the patients in the general population having a 60% greater risk of reaching early clinical stability.

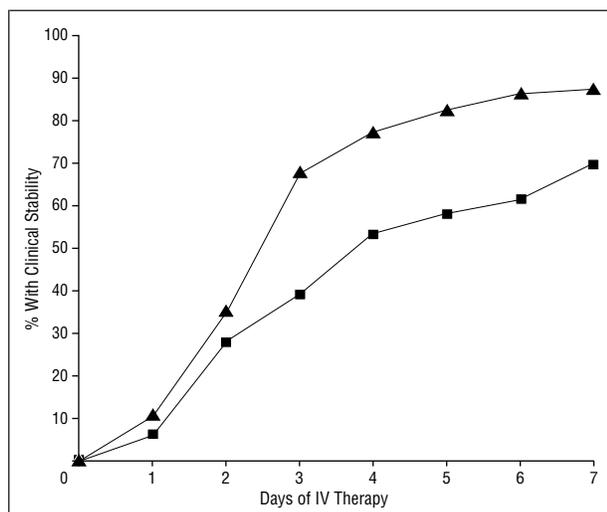
COMMENT

The result of this study indicates that, in hospitalized patients with CAP, it is safe to switch from intravenous to oral therapy as soon as the patient reaches clinical stability, even if bacteremia caused by *S pneumoniae* was initially documented. The study showed that patients with bacteremia are less likely to reach clinical stability and become candidates for switch therapy than are a general population of hospitalized patients with CAP. We also documented that, in bacteremic patients, the time to reach clinical stability is significantly longer than in nonbacteremic patients. The delay in reaching clinical stability in the bacteremic population cannot be explained as secondary to poor antibiotic selection, because all patients were initially treated with appropriate therapy against *S pneumoniae*. A clinical implication of this finding is that, in patients with bacteremia, a lack of clinical response by day 3 of therapy may not represent treatment failure but a delayed response to intravenous therapy.

Clinical Outcome of Hospitalized Patients With Bacteremic Community-Acquired *Streptococcus pneumoniae* Pneumonia

Patient Group*	No. of Patients	Clinical Course	Antibiotic Therapy	Clinical Outcome
A	18	Improvement	Switched	All cured
B	7	Improvement	Intravenous	All cured
C	11	Lack of improvement	Intravenous	Cured, 6; failure, 5

*For a description of the patient groups, see the "Patients and Methods" section.



Percentage of the population reaching clinical stability by mean time to reach stability in 36 bacteremic patients (squares) compared with 200 hospitalized patients with community-acquired pneumonia (triangles).

The fact that patients with bacteremia have a delayed clinical response to therapy should be considered during the design of antibiotic trials when 2 treatment arms are compared in relation to time to clinical stability and switch therapy. If the outcome of the clinical trial is time to switch therapy, the presence of bacteremia will act as a confounding variable.

When the data of this investigation are analyzed, it should be kept in mind that this study has several limitations because of the retrospective design and the small number of patients with bacteremia. Once patients reached clinical stability, the decision to continue intravenous therapy vs switch therapy was nonrandomized, and physicians may have decided to continue intravenous therapy in patients with more severe disease. In our evaluation of severity of disease, we were not able to see any difference in risk class, Acute Physiology and Chronic Health Evaluation II score, or number of risk factors for complicated course for the patients who reached clinical stability and were switched to oral therapy vs the patients who reached clinical stability and continued to receive intravenous therapy. The retrospective analysis of the cases seems to indicate that the only reason for some physicians to continue intravenous therapy in patients who reached clinical stability was the presence of positive blood cultures at the time of hospitalization.

Although all isolates in this study were fully susceptible to penicillin, with minimum inhibitory concen-

trations below 0.12 µg/mL, we do not consider the identification of resistance to penicillin a contraindication for switch therapy. After a recent report from the Centers for Disease Control and Prevention, in our institution we redefined susceptibility for *S pneumoniae* when implicated as a cause of CAP. *Streptococcus pneumoniae* is now considered penicillin resistant when the penicillin minimum inhibitory concentration is 4 µg/mL or greater.¹² Once treatment is switched from intravenous to oral antibiotics, it is not necessary to keep the patient in the hospital to evaluate clinical response to oral therapy.¹³ In the patients switched to oral antibiotics in this study, there was no clinical suspicion of a secondary focus of infection, such as endocarditis, meningitis, osteomyelitis, purulent pericarditis, or septic arthritis. Since the switch from intravenous to oral therapy is contraindicated in patients with *S pneumoniae* meningitis or endocarditis, these 2 complications should not be present when switch therapy is instituted in patients with CAP and *S pneumoniae* bacteremia.

In summary, our data indicate that, in hospitalized patients with CAP without clinical indication of meningitis or endocarditis, the presence of *S pneumoniae* bacteremia at the time of hospital admission is not a contraindication for switching a clinically stable patient from intravenous to oral therapy.

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Correction

Error in Abstract. In the Original Investigation by Ramirez and Bordon titled "Early Switch From Intravenous to Oral Antibiotics in Hospitalized Patients With Bacteremic Community-Acquired *Streptococcus pneumoniae* Pneumonia," published in the March 26 issue of the ARCHIVES (2001;161:848-850), an error occurred in the "Objective" statement of the abstract on page 848. This sentence should have read as follows: "To determine whether the switch from intravenous to oral therapy in such patients, once the patient reaches clinical stability, is associated with poor clinical outcome." The journal regrets the error.