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OPINION PIECE

Duration of Antibiotic Therapy for Patients with Bacteremic *Staphylococcus aureus* Community-Acquired Pneumonia

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Introduction

In a recent review article of the causes of community-acquired pneumonia (CAP) in adults, Musher et al. reported that *S. aureus* is now the third most common bacterial pathogen causing CAP [1]. Physicians treating patients with CAP will be confronted with the question of how best to treat a hospitalized patient with bacteremic *S. aureus* CAP. In this opinion piece, we will review current controversies on the topic and offer our point of view regarding management and treatment.

Controversies

1. Can patients with bacteremic *S. aureus* CAP be treated with short course antibiotic therapy?

Patients with bacteremic S. aureus CAP should not be treated with short courses of antibiotics.

A substantial proportion of patients hospitalized with community-acquired pneumonia (CAP) will reach clinical stability after 3 days of initiation of antibiotic therapy. In these patients, guideline recommendations advocate that intravenous antibiotics can be switched to oral to complete 5 to 7 days of total antibiotic therapy [2]. An important exception to the early switch and short duration of therapy approach is for patients with CAP due to *S. aureus* who are also found to be bacteremic. In these patients, we recommend a duration of therapy of at least 2 weeks. For such patients, duration of therapy should be addressed from the perspective of the bacteremia and not from the perspective of the pneumonia. From the pneumonia perspective, the patient may have a significant improvement of signs and symptoms of CAP and may reach early clinical stability, but in the clinical scenario of *S. aureus* bacteremia, the clinical improvement of pulmonary infection is no longer a marker to define duration of therapy. The number of days of antibiotic therapy should be based on the evaluation and management of *S. aureus* bacteremia, according to the presence of uncomplicated versus complicated bacteremia [3-5].

2. What should be the duration of treatment for patients with bacteremic *S. aureus* CAP?

Patients with uncomplicated bacteremic S. aureus CAP should be treated with at least 2 weeks of antibiotics.
Patients with complicated bacteremic S. aureus CAP should be treated with 4 to 6 weeks of antibiotics.

All patients with *S. aureus* bacteremia are at risk of developing metastatic infections. Some of these infections may not be clinically evident at the time the patient presents with bacteremia, such as endovascular infections (e.g. endocarditis), bone and joint infections (e.g. vertebral osteomyelitis) or nervous system infections (e.g. spinal epidural abscess). According to the level of risk of metastatic infections, bacteremia is categorized as a low risk or uncomplicated versus high risk or complicated.
For a bacteremic *S. aureus* CAP to be considered uncomplicated: there should be a rapid clinical response to initial antibiotic therapy, (e.g. temperature <100.50 F within 3 days); an echocardiogram should be negative; the patient should not have any prosthetic material (e.g. prosthetic joint); the patient should not be immunocompromised; and the bacteremia should be non-persistent (see below). If all these characteristics are present, the patient is considered to be at low risk of metastatic infection. Treatment in these patients is still recommended for a total 2 weeks to treat the possible presence of an early and unrecognized metastatic infection [3-5] (**Figure 1**).
Bacteremic *S. aureus* CAP is considered to be complicated if: there is a poor clinical response to initial antibiotic therapy, (e.g. temperature >100.50 F for more than 3 days); echocardiogram suggests the presence of a vegetation on a heart valve or a valvular abnormality which is a risk for endocarditis; a prosthetic material (e.g. prosthetic joint) is present, the patient is immunocompromised; or the bacteremia is persistent (see below). If any of these characteristics are present, the patient is considered to be at high risk of metastatic infection, even if no specific site is identified. The recommended duration of therapy in these patients is 4 to 6 weeks of intravenous therapy with an appropriate antimicrobial agent based on susceptibility data [3-5] **(Figure 1).** There are not prospective studies to define

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best duration of therapy within the 4 to 6 weeks recommended in patients with complicated bacteremia. We suggest that duration of therapy can be individualized. Patients with rapid improvement and negative repeat blood cultures may need only 4 weeks of therapy.

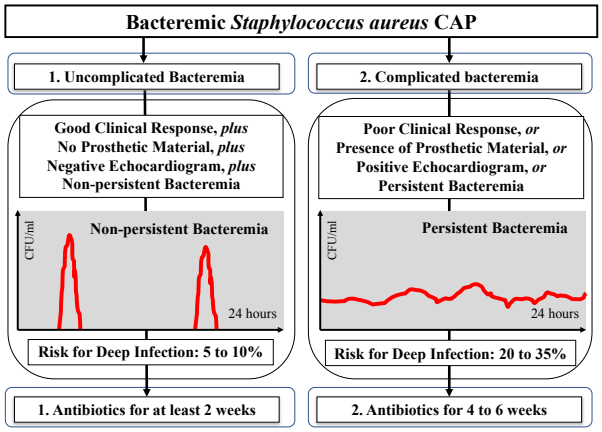

Figure 1. Duration of therapy for S. aureus bacteremia (for definitions of non-persistent and persistent bacteremia see text).

3. How to diagnose persistent *S. aureus* bacteremia in a patient with CAP?

Patients hospitalized at risk of S. aureus bacteremia should have 2 sets of blood cultures obtained at least 30 minutes apart.

In a patient with CAP due to *S. aureus*, bacteria from the alveoli can traverse lymph nodes, and be transported via lymphatic vessels into subclavian veins. After *S. aureus* enter the blood, bacteria are removed from the circulation within 10-20 minutes, primarily by macrophages in the spleen and the liver. Patients with *S. aureus* endocarditis have continuous or persistent bacteremia, where as those who have an in infection in another site, such as the lung, the kidney or soft tissue, are more likely to have intermittent or non-persistent bacteremia. Patients with non-persistent *S. aureus* bacteremia are still at risk of developing metastatic infections, since only minutes of *S. aureus* in the systemic circulation may be enough for the bacteria to attach to deep tissues. If after an initial bacteremia, *S. aureus* is able to establish a metastatic intravascular infection (e.g. endocarditis) then the presence of bacteria in the systemic circulation will be constant. Even though macrophages from the spleen and liver will continue to remove bacteria from the blood, the continuous arrival of bacteria to the systemic circulation will allow the bacteria to persist in the systemic circulation for long periods of time. This will produce a persistent type of bacteremia.

When we use blood cultures as diagnostic tests, there are several questions that we attempt to answer. First, we need to determine whether bacteremia is present. To answer this question, it is necessary to have enough blood in the laboratory, because an adequate volume sampling is an important factor for detection of bacteremia. Approximately 8 to 10 mL of blood are obtained with each set of 2 blood culture bottles, the order of 2 sets will allow 15 to 20 mL of blood to be cultured. Second, we need to determine whether the bacteria identified in the culture bottle represent a skin contaminant. To answer this second question, it is necessary to obtain each set of blood cultures from a different skin sites. Third, we need to define if persistent bacteremia is present. To answer this third question, we need to separate the timing of each of the blood cultures. As explained before, in a non-persistent bacteremia, bacteria may be present in the blood from 10 to 20 minutes. Blood cultures obtained with a time separation under 20 minutes will not be enough to define is the patient is having a persistent bacteremia. In an attempt to answer the question regarding persistent bacteremia, blood cultures should be obtained at least 30 minutes apart [6]. Patients with multiple positive blood cultures for *S. aureus* are more likely to have endocarditis, but persistently positive cultures may be present in patients with infections other than endocarditis [7,8]. Documentation of persistently positive blood cultures for *S. aureus* is a major Duke criteria for diagnosis of endocarditis [9]. To fulfill this criterion, cultures should be positive from 2 blood cultures drawn 12 hours apart, or from all of 3 blood cultures, with first and last drawn at least 1 hour apart [9]. We consider that all hospitalized patients with CAP should have 2 sets of blood cultures obtained, but the timing of the blood cultures is controversial since separating blood cultures beyond 30 minutes may create logistical problems and delay antibiotic therapy.

4. Should an Echocardiogram be obtained in all patients with bacteremic *S. aureus* CAP?

All patients with bacteremic S. aureus CAP should have an echocardiogram performed to evaluate for the presence of endocarditis.

Patients with *S. aureus* in the blood are considered at risk of infective endocarditis. At the present time *S. aureus* is the primary etiologic agent of endocarditis in industrialized countries [10]. There is agreement in the need for echocardiogram in all patients with *S. aureus* bacteremia without a clear source of bacteremia. This scenario does not apply to patients with CAP, in whom the source of bacteremia is the lung. There is also agreement in the need for echocardiogram in patients with evidence of complicated bacteremia. The disagreement is with patients with uncomplicated bacteremia. Do we need to perform an evaluation for endocarditis in a patient with CAP, who is not immunocompromised, with no prosthesis, with good initial response to therapy, and with only one out of two positive blood cultures? Even though in these patients the risk for endocarditis is low, in our opinion, all hospitalized patients with bacteremic *S. aureus* CAP should have an echocardiogram. In patients with uncomplicated bacteremia, who are at a very low risk for endocarditis, a negative transthoracic echocardiogram (TTE) may be enough to decide duration of therapy, without the need of a subsequent transesophageal echocardiogram (TEE). A TTE is readily available, of relative low cost, and with no risk for the patient. Patients with complicated bacteremia are at high risk for endocarditis. In these patients, a negative TTE should be followed with a TEE, since TEE is a more sensitive test for diagnosis of endocarditis.

5. When do we start counting the duration of therapy in patients with bacteremic *S. aureus CAP*?

Duration of therapy is counted from the day that the first negative blood culture is obtained.

Duration of therapy in patients with pneumonia is counted from the day that initial appropriate empiric therapy was initiated. In the case of *S. aureus* bacteremia, duration of therapy is counted

from the day of first negative blood culture. All patients with *S. aureus* bacteremia should have repeat blood cultures every 48 to 72 hours until blood cultures are negative. The first day of negative blood culture is the first day of duration of therapy.

6. Can we switch from intravenous to oral therapy in patients with bacteremic *S. aureus* CAP?

In patients with uncomplicated bacteremic S. aureus CAP, intravenous antibiotic therapy may be switched to oral antibiotic therapy.
Patients with complicated bacteremic S. aureus CAP should be treated only with intravenous therapy.

For the treatment of patients with *S. aureus* bacteremia we generally prefer therapy with intravenous antibiotics. A switch from intravenous to oral therapy should be done cautiously and only in special circumstances since there are no studies of oral therapy in these patients. An example may be a patient hospitalized with CAP and uncomplicated *S. aureus* bacteremia. The repeat blood cultures are negative, the patient is clinically stable, and ready to be discharged from the hospital to complete the 2 weeks of therapy at home. In these patients, the benefit of intravenous therapy for a short duration should be balanced against the risk of a IV line and cost of home IV antibiotics. In this clinical scenario, we consider that patients may be switched to an oral antibiotic that has good susceptibility and good oral absorption and to which the organism is susceptible. Virtually all available studies of treatment for complicated *S. aureus* bacteremia have been based on patients who have been treated parenterally. We base our recommendation on this body of medical literature. That being said, if a patient refuses intravenous therapy for 4-6 weeks or cannot afford it, an oral agent that is known to be bioavailable can be used instead.

Conclusions

In treating patients hospitalized for CAP, antibiotics are generally given parenterally until he patient is clinically stable, after which oral antibiotics are prescribed, the total duration not to exceed 7 days. The exception to this rule is CAP due to *S. aureus* with associated bacteremia. In these patients, treatment should address the bacteremia, not the pneumonia, and the duration of antibiotic therapy should be determine by whether the bacteremia is regarded as complicated or uncomplicated. Echocardiogram is recommended in all patients. Minimal duration of therapy is two weeks, for patients with uncomplicated bacteremia. Duration of therapy for patients for complicated bacteremia should be 4 to 6 weeks. The preferred route of therapy is intravenous, but a switch to oral therapy may be considered in special circumstances.

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