I believe that 3 major issues about doxycycline are often overlooked.

First, updated data on the pharmacokinetics of oral doxycycline remain both scarce and controversial. Indeed, whereas Cunha [1] reported peak serum doxycycline concentrations of $\sim4 \mu g/mL$ after administration of a 100-mg oral dose, Sakellari et al. [2] observed mean peak serum concentrations of 2.35 $\mu g/mL$ 2 h after administration of the same dose. Our experience with 6 healthy volunteers who received a 100-mg tablet is closer to that of Sakellari et al. [2], because we observed a mean peak serum level of 1.37 $\mu g/mL$ 2 h after administration of the dose (Bantar et al., unpublished data).

Second, the use of doxycycline for treating outpatients with CAP has probably been promoted on the basis of data published in some guidelines on the in vitro efficacy of this drug against penicillin-resistant strains of *S. pneumoniae* [3, 4]. However, to my knowledge, results of specific controlled clinical trials involving patients with CAP treated with oral doxycycline in an ambulatory manner nor pharmacodynamic studies of the efficacy of doxycycline against *S. pneumoniae* infection have not been published to date.

Third, recommendations on antimicrobial treatment for treating adults with CAP are highly influenced by the severity of illness, and the presence of bacteremia is seldom taken into account when selecting the primary drug [3–5]. This fact, together with results of clinical trials that demonstrated the overall efficacy of certain drugs, probably led some authorities to recommend that certain therapies be given orally for the treatment of low-risk CAP, even though some of these drugs (i.e., azithromycin and doxycycline) may reach poor serum levels or display only inhibitory activity [2, 6]. However, caution should be exerted for patients receiving treatment for pneumococcal bacteremia, because delay in achieving bactericidal serum levels could play a crucial role in allowing development of breakthrough pneumococcal bacteremia during the course of oral therapy in those at low risk for breakthrough infection, as observed with doxycycline in an earlier study [7] and with azithromycin in a more recent study [8].

Although the overall incidence of pneumococcal bacteremia among patients with CAP is low (i.e., 10%–20%), several of these patients may belong to a low-risk class. Bantar et al. [5] assessed the distribution of the severity of illness index (as defined by the Pneumonia Outcomes Research Team [PORT] index) for 101 patients with bactereemic pneumonia enrolled in a number of clinical trials performed in Argentina, Chile, and Uruguay. Overall, 61 patients (60.3%) had a low-risk index (i.e., PORT I–III). It should be noted that, according to some guidelines, all of these patients would have been candidates for doxycycline therapy [3, 4].

Furthermore, results of a comparative ex vivo pharmacodynamic study demonstrated that, even against a tetracycline-susceptible pneumococcus strain, a single dose of oral doxycycline was only inhibitory during the first 8-h incubation period and was unable to inhibit bacterial growth after a 24-h incubation period in time-kill studies performed using serum samples obtained at 2, 4, and 6 h after dose administration (Bantar et al., unpublished data). Therefore, I strongly concur with Cunha [1] and recommend that a loading dose be used to initiate treatment if doxycycline is going to be administered, and I urge consideration of the fact that, although intravenous doxycycline has been suggested by some researchers to be a cost-effective option for treating hospitalized patients with CAP [9], this suggestion might be not applicable when using standard oral therapy to treat patients with low-risk CAP, especially those with suspected pneumococcal bacteremia. There is no doubt that comparative clinical trials assessing the efficacy of doxycycline administered in the manner proposed by Cunha [1] will be useful to definitively establish the cost-effectiveness of this drug in the treatment of patients with low-risk CAP.

References

Table 1. Relative eosinophil counts in and results of statistical analysis for 171 patients with or without bacteremia.

<table>
<thead>
<tr>
<th>Eosinophil level, % of WBCs</th>
<th>Positive</th>
<th>Negative</th>
<th>$P$</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Positive predictive value, %</th>
<th>Negative predictive value, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\geq 1$</td>
<td>75</td>
<td>91</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>0</td>
<td>96</td>
<td>83</td>
<td>.12</td>
<td>44</td>
<td>48</td>
<td>45</td>
<td>46</td>
</tr>
</tbody>
</table>

The potential utility of eosinophil counts as predictors of bacteremia was investigated by Lipkin [7] in a study of 75 adult inpatients with positive results of blood cultures that showed that, as the number of positive blood culture results per patient increased, the percentage of eosinophil counts decreased to as low as 0 in subjects who developed acute bacterial infection. Peripheral blood eosinopenia is well described in adult and pediatric patients with typhoid fever [5] and has been observed in association with other agents of sepsis [6].

The potential utility of eosinophil counts as predictors of bacteremia was investigated by Lipkin [7] in a study of 75 adult inpatients with positive results of blood cultures that showed that, as the number of positive blood culture results per patient increased, the percentage of eosinophil counts in the peripheral blood smear decreased [7]. No patient with $\geq 2$ positive blood culture results had a peripheral blood smear with $>1\%$ eosinophils, demonstrating a possible correlation between eosinopenia and bacteremia. We sought to confirm this relationship between decreased eosinophil count and bacteremia.

We reviewed the inpatient medical records of 171 patients with blood cultures positive for gram-negative bacilli, Staphylococcus aureus, and Streptococcus species during a 6-month period at the University of North Dakota School of Medicine and Health Sciences (Fargo). Immunosuppressed patients with bacteremia were excluded from analysis, as were patients with neutropenia (i.e., those with $<1000$ WBCs per high-power field). Case patients were age- and sex-matched with control patients with negative results of blood cultures during the same study period. Total leucocyte count and relative and absolute eosinophil counts were determined for both case and control patients, and $\chi^2$ analysis was used to compare results (table 1). Sensitivity, specificity, and positive and negative predictive values were calculated in the usual manner. We found no utility associated with eosinopenia (defined as a relative eosinophil level of 0%) for predicting bacteremia and conclude that the absence of peripheral blood eosinophils cannot be used as a clinically reliable marker of bacteremic infection.

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References

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Clinical Infectious Diseases 2004; 38:460–1 © 2004 by the Infectious Diseases Society of America. All rights reserved. 1058-4838/2004/3803-0030$15.00

Pyomyositis and Cutaneous Abscesses Due to Mycobacterium avium: An Immune Reconstitution Manifestation in a Patient with AIDS

Sir—The immune reconstitution syndrome (IRS) comprises inflammatory responses to preexisting infections triggered by restoration of immune function in HIV-infected individuals receiving HAART [1, 2]. Although IRS associated with Mycobacterium avium complex (MAC) is reported to cause focal lymphadenitis in the early weeks of HAART [3, 4], herein we describe an unusual case in a patient who presented with pyomyositis and skin abscesses.

A 45-year-old Ugandan female residing in the United Kingdom presented with cryptococcal meningitis and HIV-1 infection with a CD4 lymphocyte count of $84 \times 10^3$ cells/L and a plasma virus load of $\geq 5 \times 10^5$ RNA copies/mL. She received amphotericin and flucytosine for 2 weeks,

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