the nature of mass gatherings can pose ideal circumstances for the spread of infectious diseases, and infectious disease outbreaks with impacts of varying seriousness have occurred during previous mass gathering events (eg, the norovirus outbreak during the 2006 Football World Cup) [1]. Although Rio de Janeiro is a city located in the tropics, there is no malaria transmission here and tropical diseases are not a major problem, except for dengue. In 2008, there were >120,000 dengue cases and 157 related deaths [2]. Leishmaniasis (<100 cases/year) transmission occurs in rural areas. It is important that travelers take personal protective measures against mosquito bites. Accidents involving Bohtrops snakes may happen during ecotouristic activities.

There are no specific vaccinations required for travel to Rio de Janeiro; however, it is advisable that all travelers ensure that their routine immunizations are up-to-date. Although vaccine-preventable diseases such as polio and measles were eliminated in 1988 and 1999, respectively, in 2006 there was an outbreak of rubella that attacked people aged 20–34 years in the largest numbers [3].

Travelers to Rio de Janeiro are at significant risk of travelers' diarrhea. Therefore, all travelers are advised to ensure strict food and water hygiene. Hepatitis A vaccine is very important. Typhoid fever is actually quite uncommon in Rio de Janeiro.

The total number of people with AIDS in Rio de Janeiro is >30,000 [4]. Travel is associated with loosening of inhibitions, a sense of anonymity, and a splitting of fixed sexual partnerships. Sexually transmitted diseases such as human immunodeficiency virus (HIV) have been listed as potentially high-risk public health concerns at previous Olympic Games [5]. Travelers thus need to be advised about the significant risks associated with unprotected casual sexual relations. Hepatitis B vaccination is advised for those who could be at risk.

Brazil was heavily affected by pandemic H1N1 2009 influenza. Of 899 deaths reported in the country, 42 occurred in Rio de Janeiro [6].

Despite the precautions recommended in this letter, it is time to light the Olympic cauldron in a tropical country.

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Ricardo P. Igreja
Departamento de Medicina Preventiva, Faculdade de Medicina, Universidade Federal do Rio de Janeiro

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Should We Be Debating the Importance of Timely Adequate Antimicrobial Therapy?

TO THE EDITOR.—Ammerlaan et al [1] found that inadequate empiric therapy of Staphylococcus aureus bacteremia (SAB) was not associated with increased 30-day mortality in their multicenter study. However, they defined adequate empiric therapy as the intravenous administration of at least 1 antibiotic to which the isolate expressed in vitro susceptibility that started within 2 days after the positive index blood culture had been obtained or within 1 day if the patient had severe sepsis or septic shock. The investigators acknowledged several important limitations to their study design, but they should also have included the definition of adequate therapy as a limitation. Patients were classified as receiving adequate therapy despite treatment delays of up to 48 h (24 h in severe sepsis and septic shock) after the onset of SAB.

Several investigators have demonstrated important associations between the timing of adequate antimicrobial therapy and outcome, especially for patients with severe sepsis and septic shock. Kumar et al [2] evaluated 2154 patients with septic shock who received effective antimicrobial therapy only after the onset of persistent hypotension. Administration of adequate antimicrobial therapy within the first hour of hypotension was associated with a survival rate of 79.9%. Each hour of delay in antimicrobial administration over the ensuing 6 h was associated with an average decrease in survival of 7.6%. A recent meta-analysis from the National Institutes of Health examined studies comparing adults with septic shock who received protocolized care with those who received nonprotocolized care, and demonstrated that decreased time for the administration of antibiotics and increased use of adequate antibiotics were consistent findings associated with improved survival [3]. Assessment of other protocol components (fluid administration, vasopressors, inotropes, packed red blood cells, titration of fluids to hemodynamic goals, corticosteroids, and human recombinant activated protein C) were not consistently found to be associated with improvements in outcome.

Studies of specific pathogens have also shown the timing of adequate antimicrobial therapy to be strongly linked to patient outcome. Three studies of Candida bloodstream infection linked delayed ad-
ministration of adequate therapy with greater hospital mortality [4–6]. In a study of SAB, Lodise et al [7] found that delayed treatment was an independent predictor of infection-related mortality. Schramm et al [8] examined 549 patients with sterile site infections due to methicillin-resistant *Staphylococcus aureus* (474 with SAB) and also showed that not administering adequate antibiotic therapy within 24 h of developing infection increased the risk of hospital mortality, by both univariate and multivariate analyses.

Although, the current study of SAB failed to demonstrate an association between adequate therapy and outcome, physicians should be careful not to minimize the clinical importance of getting antibiotic therapy “right” as soon as possible. This would appear to be most important for the sickest patients, including those with septic shock and neutropenia [9, 10]. Therefore, it seems logical to develop local strategies aimed at optimizing treatment practices for patients with serious infections, including SAB. Such strategies should include the administration of adequate antibiotic therapy administered in a timely manner.

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Marin H. Kollef
Division of Pulmonary and Critical Care Medicine, Washington University School of Medicine, St Louis, Missouri

References


Reprints or correspondence: Dr Marin H. Kollef, Div of Pulmonary and Critical Care Medicine, Washington University School of Medicine, 660 S Euclid Ave, Campus Box 8052, St Louis, MO 63110 (mkollef@wummc.edu).

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Reply to Kollef

To the Editor.—Dr. Kollef [1] raises a concern related to the definition of adequate therapy as used in our study [2]. Patients were classified as receiving adequate therapy despite treatment delays of up to 2 days (1 day with severe sepsis and septic shock) after the onset of *Staphylococcus aureus* bacteremia, whereas several investigators have demonstrated, in retrospective studies, associations between the timing of adequate antimicrobial therapy and outcome.

In our study, delay of adequate antimicrobial therapy was not associated with increased mortality, which contradicts with some [3–6] but not all studies [7–9]. Data on hour of prescription were lacking in our database; however, the association between inadequate therapy and mortality was not stronger when taking 1 day as the cutoff for all cases of bacteremia.

The obvious intuitive association between inadequate treatment and mortality may be obscured by several factors. First, the definitions of inadequate therapy are inherently arbitrary and vary among studies [10, 11]. We used the recommendations provided by McGregor et al [10] to define appropriate treatment as validly as possible.

Second, because such studies are observational, removing confounding factors is a challenge. In observational studies, significant differences that exist between treatment groups may not be adjusted sufficiently using commonly used multivariable techniques. As an example, we consider a study of critically ill patients with bacteremia, in which therapy was defined as inadequate if administered antimicrobials were ineffective against the causative pathogen at the time of identification of the microorganism and its antibiotic susceptibility [12]. The estimated “adjusted” effect of inadequate antimicrobial treatment of bloodstream infection, compared to adequate therapy, on hospital mortality had an odds ratio of 6.9, after including the following factors: use of vasopressors, age, organ dysfunction, and severity of illness, in a multivariable logistic regression model.

A major limitation of such an analysis is that the model only includes confounders based on statistical significance with respect to mortality (determined by a stepwise variable selection approach, with a *P* value of .05 as the limit for acceptance or removal of terms), which may inappropriately exclude important confounding factors that adjust for differences between treatment groups, such as time in the hospital prior to bloodstream infection, prior use of antimicrobials, and serum albumin level. Presumably, these differences were factors that influenced the probability that treatment was inadequate, or they were proxies for such factors. Not including