Guidelines for Vancomycin Use

To the Editor—In the new guidelines for vancomycin monitoring published in August 2009 in Clinical Infectious Diseases, Rybak et al [1] state that “continuous infusion regimens are unlikely to substantially improve patient outcome when compared to intermittent dosing” (p 326). In the original text [2] accompanying these guidelines, the authors cite 4 studies by James et al (1996) [3], Lacy et al (2000) [4], and Wysocki et al (1995 [5] and 2001 [6]) to support their claim. The first study, of which Dr Rybak is final author, was pharmacologic in nature and did not assess clinical outcome. It concluded that continuous infusion and conventional dosing vancomycin therapy “demonstrated equivalent pharmacodynamic activities” [3, p 696], although the serum bactericidal titer in the continuous-dosing group remained >1:8 for 100% of the time and that in the conventional-dosing group remained >1:8 for only 60% of the time. This study was very small, comprising only 10 patients, and had a cross-over period of only 2 days.

To our surprise, we found that the second study in question has been flatly misrepresented. Rybak and colleagues assert that Lacy et al “found virtually no difference in activity as measured by bactericidal titers between continuous and intermittent infusions” [2, p 87]. In fact, the study of Lacy and colleagues did not investigate continuous infusion of vancomycin—it only compared vancomycin given as 1 g once a day with vancomycin given as 1 g twice a day.

Furthermore, the authors cite 2 studies by Wysocki et al. In the first (1995) [5], 13 patients were prospectively treated with vancomycin by continuous infusion and matched with historical control subjects. Infection-related mortality was 23% lower in the continuous-infusion group, although the small number of patients as well as confounding factors ultimately precluded the drawing of “definitive conclusions” (p 354). The authors followed this pilot study with a randomized prospective trial in 2001 [6] that compared continuous to intermittent vancomycin infusion among 119 patients with severe staphylococcal infections. Indeed, microbiologic outcomes, clinical outcomes, and safety were similar in both groups. This study was limited, however, by its small sample size and short period of follow-up (10 days).

On a theoretical and pharmacologic level, as demonstrated in Dr Rybak’s study [3], the time-dependent nature of vancomycin supports its administration by continuous infusion. On a clinical level, there is currently not enough evidence to claim that treatment with continuous-infusion vancomycin produces a superior outcome; additionally, larger trials are needed. However, there is clearly not enough evidence to suggest the opposite—absence of evidence is not evidence of absence.

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Angela Huttner and Stephan Harbarth
Division of Infectious Diseases, University of Geneva Hospitals and Faculty of Medicine, Geneva, Switzerland

References


Olympics in the Tropics and Infectious Diseases

To the Editor—The International Olympic Committee has chosen the Brazilian city of Rio de Janeiro to host the 2016 Olympic Games, making it the first South American venue in Olympic history. The Olympic Games are a very popular but also vulnerable global event and thus intrinsically raise the expectations of the international community on all aspects of preparedness, including public health. Communicable diseases have not been a significant cause of health events during recent mass gatherings for major international sporting events. Despite this,
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 bothrops 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.

Brazilians 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

References


Reprints or correspondence: Dr Ricardo P Igreja, Cives (Travel Clinic), Rua Professor Rodolpho Paulo Rocco, Rio de Janeiro/RJ, Brazil, CEP:21941-617 (ipigreja@cives.sufh.br).

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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 protocoted 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-