

criteria, and exclusion criteria available from the author). The quality of these studies is quite variable, and quality is certainly more important than quantity. Most trials of the newer agents were designed and funded by industry. In general, ciprofloxacin and levofloxacin have been studied in patient populations with more severe illnesses, including nosocomial infections, than the newer quinolones. With the exception of a single moxifloxacin trial (8), the trials of the newer quinolones have enrolled patients with predominantly mild or moderate community-acquired infections and low overall mortality rates.

Scheld provides a table that lists case reports of clinical failures of levofloxacin for the treatment of pneumococcal infections. Some cases were associated with primary or secondary levofloxacin resistance. These case reports should not be surprising, since CAP trials regularly identify clinical failures regardless of the therapy chosen. The rate of clinical failure is best determined by data from prospective trials rather than case reports. Both levofloxacin and moxifloxacin have performed well in patients with severe pneumococcal infections, on the basis of the rates of therapeutic success and death (8–10).

Scheld's choice of ciprofloxacin as a component of combination therapy for suspected *P. aeruginosa* infections can be affirmed. Ciprofloxacin has pharmacodynamic potency against *P. aeruginosa*, a track record of safety in large populations, and a large published literature. Ciprofloxacin has demonstrated efficacy in patient populations with severe illnesses, including nosocomial infections.

Antimicrobial drug therapy decision-making for patients with CAP and other respiratory tract infections is much more complex. Individual patient factors should be considered, including the severity of illness, coexisting illnesses, risk factors for drug-resistant *S. pneumoniae*, and

risk factors for specific adverse effects. A respiratory quinolone will be an appropriate choice for some patients with CAP. Among the respiratory quinolones, a wholesale switch from levofloxacin to moxifloxacin, on the basis of pneumococcal potency alone, would be premature. Clinicians should use newer quinolones cautiously until their safety has been established in large patient populations.

#### Richard Frothingham\*

\*Veterans Affairs Medical Center and Duke University Medical Center, Durham, North Carolina, USA

#### References

- Scheld WM. Maintaining fluoroquinolone class efficacy: review of influencing factors. *Emerg Infect Dis* 2003;9:1–9.
- Frothingham R. Rates of torsades de pointes associated with ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, and moxifloxacin. *Pharmacotherapy* 2001;21:1468–72.
- Noel GJ, Natarajan J, Chien S, Hunt TL, Goodman DB, Abels R. Effects of three fluoroquinolones on QT interval in healthy adults after single doses. *Clin Pharmacol Ther* 2003;73:292–303.
- Lasser KE, Allen PD, Woolhandler SJ, Himmelstein DU, Wolfe SM, Bor DH. Timing of new black box warnings and withdrawals for prescription medications. *JAMA* 2002;287:2215–20.
- Shaffer DN, Singer SJ. Macrolide antibiotics and torsades de pointes postmarketing analysis, slide 42. Presented at the FDA Center for Drug Evaluation and Research Anti-Infective Drugs Advisory Committee, April 26, 2001. [cited 2003 April 24] Available from: URL: [http://www.fda.gov/ohrms/dockets/ac/01/slides/3746s\\_02\\_Shaffer/sld042.htm](http://www.fda.gov/ohrms/dockets/ac/01/slides/3746s_02_Shaffer/sld042.htm)
- Top 200 brand and generic drugs by units in 2001. *Drug Topics* 2002(5);38. Available from: <http://www.drugtopics.com>
- Top 200 brand and generic drugs sold in 2002 by units. *Drug Topics* 2003(6);60. Available from: <http://www.drugtopics.com>
- Finch R, Schurmann D, Collins O, Kubin R, McGivern J, Bobbaers H, et al. Randomized controlled trial of sequential intravenous (i.v.) and oral moxifloxacin compared with sequential i.v. and oral co-amoxiclav with or without clarithromycin in patients with community-acquired pneumonia requiring initial parenteral treatment. *Antimicrob Agents Chemother* 2002;46:1746–54.
- File TM Jr, Segreti J, Dunbar L, Player R, Kohler R, Williams RR, et al. A multicenter, randomized study comparing the efficacy and safety of intravenous and/or oral levofloxacin versus ceftriaxone and/or cefuroxime axetil in treatment of adults with community-acquired pneumonia. *Antimicrob Agents Chemother* 1997;41:1965–72.
- Norrby SR, Petermann W, Willcox PA, Vetter N, Salewski E. A comparative study of levofloxacin and ceftriaxone in the treatment of hospitalized patients with pneumonia. *Scand J Infect Dis* 1998;30:397–404.

Address for correspondence: Richard Frothingham, Durham VA Medical Center, 508 Fulton St, Building 4, Durham, NC 27705, USA; fax: 919 286 0264; email: richard.frothingham@duke.edu

## Vancomycin-resistant *Enterococcus faecalis* in Serbia

**To the Editor:** First isolated in France (1), vancomycin-resistant enterococci (VRE) have become pathogens of major importance, particularly in the United States (2). Infections due to VRE are still uncommon in most European countries (3). We report the first isolation of high-level vancomycin-resistant *Enterococcus faecalis* in Serbia.

A 55-year-old woman was admitted to the Clinic for Cardiovascular Diseases, Belgrade, on April 1, 2002, for aortobifemoral bypass surgery. Three weeks after she was admitted to the hospital, an infection developed in the surgical wound and treatment with trimethoprim-sulfamethoxazole (160/800 mg q 12 h) was empirically introduced. Bacteriologic analysis of the wound swab sample showed a methicillin-resistant strain of *Staphylococcus aureus*, a multiresistant strain of *Acinetobacter* sp., a commonly susceptible strain of *Enterococcus* sp., and a VRE strain.

According to the results of susceptibility testing, imipenem (1 g q 6 h) was added to the patient's treatment protocol. VRE were not isolated from subsequent wound samples or any other sample submitted for microbiologic analysis. The patient was discharged at the end of the 14-day treatment period.

The isolate was identified as *E. faecalis* by biochemical characterization, as recommended by Facklam and Collins (4) and confirmed by API 20 Strep (bioMérieux, Marcy-l'Etoile, France). Susceptibility testing, performed by the disk diffusion method, showed that the isolate was resistant to vancomycin, teicoplanin, gentamicin, streptomycin, tetracycline, and ciprofloxacin, while susceptible to ampicillin, amoxicillin, amoxicillin and clavulanic acid, and imipenem. Resistance to vancomycin, teicoplanin, gentamicin, and streptomycin was confirmed by the broth dilution method, according to the National Committee for Clinical Laboratory Standards (NCCLS) recommendations (5). The obtained MICs were 256 µg/mL for vancomycin, 64 µg/mL for teicoplanin, >4,000 µg/mL for gentamicin, and >2,000 µg/mL for streptomycin. This phenotype, with high-level resistance to vancomycin and teicoplanin, is typical for the *vanA* genotype (2). The strain was subsequently genotyped by pulsed-field gel electrophoresis, using previously described methods (6). The presence of the *vanA* gene was confirmed by polymerase chain reaction assay, according to a previously described procedure (7). *E. faecium* EF228 was used as the positive control.

The enterococci are among the most frequent causes of nosocomial infections, particularly in intensive care units, and present a major therapeutic challenge (2). While the emergence of VRE strains in the United States is probably associated with extensive use of vancomycin, the occurrence of VRE in Europe is possibly due to application of avoparcin

(glycopeptide analog) as a growth promoter in animal husbandry (3). However, avoparcin has not been used in Serbia, and vancomycin application has been restricted to hospitalized patients and quite limited due to its high cost. Thus, emergence of VRE strains in Serbia has not been likely.

The origin of this VRE isolate is unknown: the strain may have been imported or may have originated from the hospital environment. The first prospective pan-European VRE surveillance study (January–April 1997) showed VanA-VRE strains in only eight European countries, with isolates numbering from one to four per country (3). No epidemiologic relations were established among the VanA isolates, and only 2 out of 18 isolates (11%) were identified as *E. faecalis* (3). Since our patient-case had no history of travel outside Serbia, we assumed that the VRE isolate originated from the hospital environment. However, a study investigating the occurrence of VRE strains in Belgrade, the capital of Serbia, detected no such isolates in five different hospitals (8). Although the study did not analyze samples from the Clinic for Cardiovascular Diseases, it did include samples from the Clinic for General Surgery, which is located within the same building. The susceptibility of 191 isolates of enterococci to vancomycin was tested by agar dilution method according to NCCLS recommendations. Of the 191 isolates, 159 were classified as susceptible and 32 as intermediately susceptible.

This report of the first isolation of VRE in Serbia, as well as the previously shown presence of enterococci displaying intermediary susceptibility to vancomycin, provides the rationale for future active screening for VRE in hospital environments in the region.

**Branka Stošovic,\* Srdjan Stepanovic,† Susan Donabedian,‡ Tanja Tošic,\* and Milica Jovanovic\***

\*Institute of Infectious and Tropical Diseases "Dr Kosta Todorovic," Belgrade, Serbia; †University of Belgrade School of Medicine, Belgrade, Serbia; and ‡William Beaumont Hospital, Royal Oak, Michigan, USA

## References

1. Leclercq R, Derlot E, Duval J, Courvalin P. Plasmid-mediated resistance to vancomycin and teicoplanin in *Enterococcus faecium*. N Engl J Med 1988;319:157–61.
2. Cetinkaya Y, Falk P, Mayhall CG. Vancomycin-resistant enterococci. Clin Microbiol Rev 2000;13:686–707.
3. Schouten MA, Hoogkamp-Korstanje JA, Meis JF, Voss A. Prevalence of vancomycin-resistant enterococci in Europe. Eur J Clin Microbiol Infect Dis 2000;19:816–22.
4. Facklam RR, Collins MD. Identification of *Enterococcus* species isolated from human infections by a conventional test scheme. J Clin Microbiol 1989;27:731–4.
5. National Committee for Clinical Laboratory Standards. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Approved standard M7-A4. Wayne (PA): National Committee for Clinical Laboratory Standards; 1997.
6. Donabedian S, Chow JW, Shlaes DM, Green M, Zervos MJ. DNA hybridization and contour-clamped homogeneous electric field electrophoresis for identification of enterococci to the species level. J Clin Microbiol 1995;33:141–5.
7. Clark NC, Cooksey RC, Hill BC, Swenson JM, Tenover FC. Characterization of glycopeptide-resistant enterococci from U.S. hospitals. Antimicrob Agents Chemother 1993;37:2311–7.
8. Dakic I, Vukovic D, Stepanovic S, Kalezić I, Švabic-Vlahovic M. Enterococci isolated in Belgrade hospitals: the resistance to vancomycin. In: Abstract book of the 9th International Congress on Infectious Diseases, Buenos Aires, Argentina, 2000 April 10–13; p. 213.

Address for correspondence: Srdjan Stepanovic, Institute of Microbiology and Immunology, University of Belgrade School of Medicine, Dr Subotica 1, 11000 Belgrade, Serbia; fax: +381-11-656950; email: stepan@afrodita.rcub.bg.ac.yu