 10.1111/j.1469-0691.2004.01036.x

Surveillance of linezolid resistance in Germany, 2001–2002

J. Brauers[1], M. Kresken[1], D. Hafner[2] and P. M. Shah[3] on behalf of the German Linezolid Resistance Study Group

[1]Antiinfectives Intelligence GmbH, Bonn, [2]Institute of Pharmacology and Clinical Pharmacology, H. Heine-University, Düsseldorf and [3]J. W. Goethe University Hospital, Frankfurt, Germany

ABSTRACT

A surveillance study was performed throughout Germany from November 2001 to June 2002 to assess the prevalence of linezolid-resistant isolates among Gram-positive bacteria from routine susceptibility data and to compare the in-vitro activity of linezolid to that of other antibacterial agents. Each of 86 laboratories provided routine susceptibility data for 100 consecutive isolates. Most laboratories (*c.* 60%) used the disk diffusion test. Laboratories were also requested to send a representative sample of their isolates, as well as all isolates reported as intermediate or resistant to linezolid, to a reference laboratory for MIC determination. Susceptibility data for 8594 isolates were evaluated. Sites of infection were skin and soft tissue (29.9%), upper and lower respiratory tract (19.1%), foreign body or catheter (10.5%), or urinary tract (9.8%). Routine linezolid susceptibility data were reported for 6433 isolates. The prevalence of linezolid resistance, as reported to the clinician, was 0.4% in *Staphylococcus aureus*, 0.3% in *Staphylococcus epidermidis*, 2.9% in *Enterococcus faecalis*, 2.3% in *Enterococcus faecium*, 1.4% in *Streptococcus pyogenes* and 2.9% in *Streptococcus agalactiae*. Linezolid resistance was not detected in *Streptococcus pneumoniae* or in viridans group streptococci. Sixty-nine of 115 isolates reported as intermediate or resistant to linezolid were retested, but none was resistant to linezolid. Linezolid exhibited excellent in-vitro activity against representative isolates of the six most frequently encountered species (MIC_{90}, 1–2 mg/L). The prevalence of resistance to linezolid was very low in Germany. Organisms reported as linezolid-resistant should be retested, either in the same laboratory with an alternative method or in a reference laboratory.

Keywords Antibiotic resistance, *Enterococcus* spp., Germany, linezolid, *Staphylococcus* spp., *Streptococcus* spp.

Original Submission: 28 January 2004; **Revised Submission:** 23 August 2004; **Accepted:** 12 September 2004

Clin Microbiol Infect 2005; 11: 39–46

INTRODUCTION

The growing resistance to many antibiotics in Gram-positive pathogens, and the spread of resistant organisms in both the community and the hospital setting, means that antimicrobial therapy is becoming increasingly complicated. Therefore, a real need exists for new treatment options for Gram-positive infections, and for a reduction in the increasing selection pressure caused by the antibacterial agents being used currently [1–5].

Linezolid is the first representative of a new class of systemic antibacterial agents, the oxazolidinones, which have a unique mode of action whereby assembly of a functional initiation complex for bacterial protein biosynthesis is blocked [6]. As this mode of action differs from those of other protein synthesis inhibitors, linezolid shows no cross-resistance to other classes of antimicrobial agent with the same target [7]. Linezolid exhibits an antibacterial spectrum that includes all frequently encountered Gram-positive species, including multiresistant strains [8–13], and has shown considerable promise in the treatment of Gram-positive infections in phase III studies [14].

Linezolid was approved in 2001 by regulatory authorities in Europe and the USA. Shortly after the introduction of linezolid in Germany, a surveillance study was started by a network of

Corresponding author and reprint requests: J. Brauers, Antiinfectives Intelligence GmbH, Immenburgstraße 20, D-53121 Bonn, Germany
E-mail: johannes.brauers@antiinfectives-intelligence.de

clinical microbiology laboratories throughout Germany to assess the prevalence of linezolid resistance. Routine susceptibility testing results generated by the participating laboratories were requested, and the in-vitro activity of linezolid was compared to that of other antibacterial agents against a representative sample of isolates with a standardised method in a reference laboratory.

METHODS AND MATERIALS

Eighty-six laboratories participated in the study. Laboratories were either affiliated to university hospitals (n = 30), teaching hospitals (n = 22) or public health institutions (n = 2), or were private diagnostic laboratories (n = 32). Each laboratory was requested to collect and test 100 consecutive clinically significant Gram-positive isolates (one isolate/patient), comprising 35 *Staphylococcus aureus*, 30 coagulase-negative staphylococci (CNS) (blood culture isolates only), 20 enterococci (15 *Enterococcus faecalis* and five *Enterococcus faecium*), five *Streptococcus pneumoniae*, five *Streptococcus pyogenes* and five viridans group streptococci from hospitalised patients during an 8-month period. A case report form was completed for each isolate, giving the patient's age and gender, site and type of infection, type of specimen, the routine susceptibility testing method used and the susceptibility results obtained.

Methods for identification of bacteria and susceptibility testing (i.e., agar diffusion, broth microdilution or an automated system) were those performed routinely. Susceptibility results for antibacterial agents considered to be important for the treatment of Gram-positive infections (according to the investigator's opinion) were recorded. All participating laboratories were accredited by an annual quality assurance programme (http://www.instand-ev.de).

Laboratories were requested to send a representative sample of their isolates, as well as all isolates reported to the clinician as non-susceptible, i.e., reduced susceptibility to linezolid in routine susceptibility tests, defined as an MIC ≥4 mg/L or an inhibition zone diameter ≤22 mm (enterococci) or ≤20 mm (staphylococci, streptococci and pneumococci), respectively, to a reference laboratory (Antiinfectives Intelligence, Bonn, Germany) for retesting and confirmation.

The subset of representative isolates (every tenth consecutive isolate) was tested in the reference laboratory against linezolid in comparison to 11 other antimicrobial agents with the broth microdilution method according to German (DIN) guidelines [15]. Microdilution trays containing vacuum-dried antibacterial agents were purchased from Merlin Diagnostika (Bornheim-Hersel, Germany). The quality control strains used were *Strep. pneumoniae* ATCC 49619, *Staph. aureus* ATCC 25923 and ATCC 29213, and *E. faecalis* ATCC 29212.

Breakpoints (S ≤ /R >, in mg/L) for penicillin G (0.125/1 for pneumococci and streptococci, 0.125/0.125 for staphylococci), ampicillin (2/8), oxacillin (1/1), clindamycin (1/4), erythromycin (1/4), doxycycline (1/4) and vancomycin (4/8) were those recommended by DIN [16]. NCCLS breakpoints (S ≤ /R ≥, in mg/L) [17,18] were used for levofloxacin (2/8), rifampicin (1/4) and quinupristin–dalfopristin (1/4). Breakpoints for teicoplanin were those recommended by DIN for vancomycin (S ≤ 4/R > 8). Breakpoints for linezolid were those recommended by the manufacturer (Pharmacia GmbH, Erlangen, Germany) and stated in the Summary of Product Characteristics (SmPC) approved by the European Agency for the Evaluation of Medicinal Products, namely ≤2 mg/L (S), 4 mg/L (I) and ≥8 mg/L (R).

RESULTS

Bacterial isolates

During the period November 2001 to June 2002, the 86 participating laboratories provided susceptibility testing results for 8594 Gram-positive bacterial isolates, with an average number of 100 isolates/site (range 51–126). Staphylococci (n = 5155) comprised 3844 (44.7%) *Staph. aureus*, 1040 CNS (773 *Staph. epidermidis*, 267 other species) and 271 staphylococci with no species identification. Other organisms collected were *E. faecalis* (n = 1188; 13.8%), *E. faecium* (n = 524; 6.1%), unidentified enterococci (n = 254; 2.6%), *Strep. pneumoniae* (n = 480; 5.7%), *Strep. pyogenes* (n = 392; 4.7%), *Streptococcus agalactiae* (n = 105; 1.2%), viridans group streptococci (n = 223; 2.6%), and isolates of various other Gram-positive species (n = 273; 3.2%).

Patients and hospital wards

Bacteria were obtained from 4777 (55.6%) male and 3665 (42.6%) female patients. The gender was not specified for 152 patients (1.8%). The mean ages of the male and female patients were 53.4 (± 23.5) and 54.9 (± 25.6) years, respectively. Most (51.2%) isolates were obtained from patients on general wards, followed by patients on intensive care units (20.8%), paediatric wards (7.4%), haemato-oncology wards (3.7%) and organ transplantation wards (0.8%).

Sites of infection

The most frequent infections were complicated and uncomplicated skin/skin structure infections and post-operative wound infections (29.9%), upper and lower respiratory tract infections (19.1%), infections of unknown origin (18.5%), foreign body/catheter infections (10.5%) and urinary tract infections/urosepsis (9.8%). Specimens were recovered primarily from wounds (29.4%), blood (23.4%), urine (9.6%) and the lung/respiratory tract (8.0%).