Bacteremia Due to Viridans Group Streptococci with Diminished Susceptibility to Levofloxacin among Neutropenic Patients Receiving Levofloxacin Prophylaxis

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Despite the use of levofloxacin prophylaxis during the neutropenic period after autologous peripheral blood stem cell transplantation, viridans group (VG) streptococcal bacteremia developed in 6 (16.2%) of 37 patients who underwent transplantation between 1 January and 25 February 2001 at the Mayo Clinic in Rochester, Minnesota. All 6 patients presented with fever and mucositis after a mean of 4.5 days of neutropenia, and 3 developed septic shock. All 6 VG streptococcal isolates from these patients exhibited distinct patterns on pulsed-field gel electrophoresis. All isolates had diminished susceptibility to levofloxacin, 5 to gatifloxacin, and 4 to moxifloxacin. Quinolone resistance was associated with mutations in the quinolone resistance-determining region of GyrA and (for 1 isolate) of ParC. The use of levofloxacin may select VG streptococci with diminished susceptibility to levofloxacin and other quinolones with enhanced activity against gram-positive organisms and, therefore, may not be optimal for preventing VG streptococcal bacteremia in neutropenic patients.

Viridans group (VG) streptococci are a common cause of endocarditis, bacteremia, and abscesses. In neutropenic patients, VG streptococci can translocate across damaged gastrointestinal mucosa and cause bloodstream infection that may be associated with septic shock, adult respiratory distress syndrome, or both [1–3].

Since 1990, the use of quinolones for antibacterial prophylaxis during neutropenia has become widespread [4–6]. The efficacy of quinolone prophylaxis in preventing bacteremia due to gram-negative bacteria is well documented [4, 6]. However, prophylaxis with “older” quinolones (e.g., norfloxacin) has been associated with the emergence of infections with VG streptococci that are resistant to these agents [7, 8]. In contrast, levofloxacin, gatifloxacin, and moxifloxacin have enhanced activity against gram-positive organisms, rendering these agents potentially more effective for prophylaxis during periods of neutropenia [9–11]. Since March 1998, levofloxacin has been used in our institution as antibacterial prophylaxis during the neutropenic period that is consequent to autologous peripheral blood stem cell transplantation (APBSCT).

Testing of VG streptococci for quinolone susceptibility had not been done routinely in our clinical microbiology laboratory. In 2001, an apparent increase in the prevalence of VG streptococcal bacteremia among APBSCT patients receiving levofloxacin prophylaxis prompted quinolone-susceptibility testing of bloodstream VG streptococcal isolates from these patients.
This study describes the emergence of quinolone-resistant VG streptococci in connection with the use of levofloxacin prophylaxis during APBSCT-associated neutropenia, details the microbiologic and molecular characteristics of the VG streptococcal isolates, and discusses the clinical implications.

PATIENTS AND METHODS

Clinical Methods

Case identification. The clinical microbiology database and the blood and marrow transplant database at the Mayo Clinic (Rochester, MN) were reviewed to identify all cases of VG streptococcal bacteremia in adults who underwent APBSCT between 1 January and 31 March 2001. The medical records of patients from whose blood VG streptococci were isolated were reviewed. The study was conducted in accordance with the guidelines for human experimentation of and was approved by the Institutional Review Board of the Mayo Clinic.

Definitions. “Neutropenia” was defined as an absolute neutrophil count of \( \leq 500 \text{cells/\muL} \). “Duration of neutropenia” was defined as the number of days during which the absolute neutrophil count was \( \leq 500 \text{cells/\muL} \). “Neutrophil engraftment” was defined as recovery of the neutrophil count to levels persistently \( \geq 1000 \text{cells/\muL} \).

Conditioning chemotherapy. Patients received standard conditioning chemotherapy consisting of carmustine, etoposide, cytarabine, and melphalan or cyclophosphamide (for patients with lymphoma) or high-dose melphalan (for patients with multiple myeloma or amyloidosis). Stem cells were collected from patients who had multiple myeloma or amyloidosis before transplantation, after treatment of the patients with high-dose cyclophosphamide and administration of a hematopoietic growth factor as a mobilizing regimen.

Antimicrobial prophylaxis. Levofloxacin (500 mg orally daily) was administered to all patients, beginning on the first day of conditioning chemotherapy before APBSCT and continuing throughout the duration of neutropenia. Levofloxacin (500 mg orally daily for 7–10 days) was also administered to patients during the period of stem cell collection, unless the patient was not expected to become neutropenic. Antifungal and antiviral prophylaxis, consisting of fluconazole (400 mg orally daily) and acyclovir (400 mg orally 3 times daily), respectively, was administered to all patients until day 28 after APBSCT. Trimethoprim-sulfamethoxazole (800 mg of the trimethoprim component given twice daily on Mondays and Thursdays) was administered for the prevention of Pneumocystis carinii infection during the first 3 months after APBSCT.

Microbiologic Testing

Bacterial identification and determination of clonality. VG streptococci were identified by accepted morphological and biochemical characteristics [12]. VG streptococci were further identified by 16S ribosomal DNA sequence analysis. The Applied Biosystems MicroSeq 16S rDNA Bacterial Sequencing Kit was used in conjunction with data analysis with MicroSeq software and 500 library, version 1.40, and GenBank. Pulsed-field gel electrophoresis was done as described elsewhere [13].

Antimicrobial susceptibility. Antimicrobial susceptibility was determined by broth microtiter dilution (for levofloxacin, gatifloxacin, moxifloxacin, and garenoxacin [Bristol-Myers Squibb]) and agar dilution (for all other antimicrobial agents), as described elsewhere [14]. Quinolone MICs for VG streptococci were interpreted using criteria for pneumococci [14].

Mechanism of quinolone resistance. Mutations in the quinolone resistance–determining region (QRDR) of gyrA, gyrB, and parC were determined by PCR amplification, followed by amplicon sequencing, as described elsewhere [15–17]. Multiple attempts at amplifying parE were unsuccessful. Sequence data were analyzed with Sequencher 3.1.1 (GenCodes), compared with the previously published QRDR of VG streptococci (GenBank accession numbers AF079198–AF079208 for gyrA, AF07925–AF079220 for gyrB, and AF079187–AF079197 for parC) [17], and deposited in GenBank (accession numbers AF393759–AF393779).

RESULTS

Clinical data. VG streptococcal bacteremia occurred in 6 (16.2%) of 37 patients who underwent APBSCT procedures during an 8-week period between 1 January and 25 February 2001 (table 1). The 6 patients (ratio of male to female patients, 2; mean age, 51 years) underwent APBSCT for treatment of multiple myeloma (2), amyloidosis (1), or lymphoma (n = 1). The APBSCT procedures were done a median of 7 months (range, 5–30 months) after the diagnosis of the underlying disorders. Four patients received the stem cell infusion as an outpatient procedure.

The 6 cases of VG streptococcal bacteremia occurred after the patients had been neutropenic for a mean of 4.5 days (range, 2–11 days). Neutrophil engraftment occurred after a mean of 10 days (range, 7–16 days) of neutropenia. At the onset of VG streptococcal bacteremia, all 6 patients had fever (temperature, \( \geq 38.3^\circ \text{C} \)) and mucositis; 3 patients subsequently developed septic shock that required aggressive hemodynamic support, including the use of vasopressors and respiratory support devices (continuous positive airway pressure [n = 2] and mechanical ventilation [n = 1]). All patients recovered after 10–14 days of treatment with intravenous vancomycin (n = 3), ceftazidime (n = 4), or ceftriaxone (n = 1), alone or in combination.

Microbiologic data. The 6 VG streptococcal isolates were members of the Streptococcus mitis species group (n = 5) or...
Quinolone Resistance in Viridans Streptococci

CID 2002:34 (1 June) • 1471

Mechanism of quinolone resistance. The mutations identified in the QRDR are shown in table 1. No mutation in GyrB was identified. Two mutations have not been reported previously in VG streptococci: in GyrA (Ser81Leu) and in ParC (Ser79Ala).

All isolates with mutations in GyrA had levofloxacin MICs of \( \geq 16 \mu g/mL \), moxifloxacin MICs of \( \geq 2 \mu g/mL \), and gatifloxacin MICs of \( \geq 4 \mu g/mL \), regardless of whether a concomitant ParC mutation was present. The isolate with the highest gatifloxacin MIC had mutations in both GyrA and ParC. No mutation in GyrA, GyrB, or ParC was identified in the isolate (from patient 6) that was intermediately resistant to levofloxacin and susceptible to gatifloxacin and moxifloxacin.

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Why an apparent increase in the incidence of VG streptococcal bacteremia was observed early in 2001 is not clear. In reviewing the data for 526 patients who underwent APBSCT procedures between 1 January 1997 and 31 March 2001, we identified 34 patients (6.5%) with cases of VG strep-

### Table 1. Characteristics of patients with levofloxacin (Levo)–nonsusceptible viridans group streptococcal bacteremia during the neutropenic period following autologous peripheral blood stem cell transplantation and of isolates recovered from those patients.

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<th>Patient</th>
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<th>Neutropenic days(^a)</th>
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<td>1</td>
<td>66, M</td>
<td>Multiple myeloma</td>
<td>2/10</td>
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NOTE. All patients recovered from bacteremia; gyrB did not amplify in isolates from patients 2 and 5; no GyrB mutation was found in isolates from the other patients. Garen, garenoxacin; Gati, gatifloxacin; Moxi, moxifloxacin; NA, did not amplify; sp., species.

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tococcal bacteremia that followed the procedure; 3 (4.0%) of 75 APBSCT patients who underwent the procedure in 1997 (when ciprofloxacin and penicillin VK were used as antibacterial prophylaxis) had VG streptococcal bacteremia, and 31 (7.5%) of 416 patients who underwent APBSCT between March 1998 and March 2001 (when levofloxacin was used as antibacterial prophylaxis) had VG streptococcal bacteremia. The last 6 of these cases of VG streptococcal bacteremia, which are the subject of this report, occurred among 37 patients (6 of 37 patients; 16.2%) who received APBSCT in 2001. Whether the VG streptococcal bacteremia cases observed before 2001 were caused by quinolone-resistant organisms is not known, because our clinical microbiology laboratory did not routinely perform quinolone susceptibility testing of VG streptococci before 2001. Nevertheless, our observation of clinically significant bacteremia caused by VG streptococci suggests that quinolone resistance may be documented in VG streptococci isolated from other patients receiving quinolones. Although only 13 (2.0%) of 637 VG streptococcal isolates from clinical samples collected between 1997 and 1999 for which data are available in the SENTRY database were resistant to levofloxacin [10], a recent study revealed the presence of quinolone-resistant VG streptococci in as many as 10% of healthy persons [18].

The selection of quinolone-resistant VG streptococci most likely resulted from the use of levofloxacin prophylaxis in our patient population. Recent animal experimentation data suggest that the in vivo susceptibility of VG streptococci to levofloxacin (and trovafloxacin) may be suboptimal [19–21]. The levofloxacin MIC90 for VG streptococci is at the susceptibility breakpoint concentration [10], which may facilitate selection of quinolone-resistant VG streptococci in as many as 10% of healthy persons [18].

Phenotypic quinolone resistance in VG streptococci has been associated with mutations in the QRDRs, as well as with active quinolone efflux [9, 10, 17, 18, 22, 23]. The predominance of the GyrA mutation among our isolates suggests that DNA gyrase may be a preferential target of levofloxacin in VG streptococci. This illustrates a similarity between levofloxacin and other quinolones that have enhanced activity against gram-positive organisms and contrasts with the association that exists between the use of ciprofloxacin and a first-step mutation in the topoisomerase IV parC gene [23]. Accordingly, we infer that, because of this similarity in the primary enzyme target in VG streptococci among the other quinolones that have enhanced activity against gram-positive organisms, the resistance to levofloxacin that developed during the neutropenic period of APBSCT may have contributed significantly to the diminished susceptibility of VG streptococci to gatifloxacin and moxifloxacin. We recognize that other resistance mechanisms, such as the presence of the less commonly encountered ParE mutation, quinolone efflux, mutations in regions outside of the QRDR, or a combination of these, may play a role. Mechanisms other than the first-step GyrA mutations demonstrated in this study could account for the high-level resistance seen in some of our isolates. Active quinolone efflux might account for the genotypic differences in isolates from patients 3 and 5, which have similar levofloxacin MICs (table 1), and for the absence of GyrA, GyrB, and ParC QRDR mutations in the isolate from patient 6, which was intermediately resistant to levofloxacin.

Regardless of which mechanism is involved in quinolone resistance, this study underscores the emerging problem of resistance among VG streptococci to quinolones that have enhanced activity against gram-positive organisms and highlights potential clinical consequences (e.g., septic shock and adult respiratory distress syndrome) in neutropenic hosts receiving levofloxacin prophylaxis. An increasing incidence and severity of VG streptococcal bacteremia in neutropenic hosts has been observed elsewhere [24, 25], but the exact mechanism has not been elucidated. Whether this is the result of the changing characteristics of the host (e.g., degree of neutropenia and/or mucositis) or increasing bacterial virulence (or both) is unknown. It has been suggested that the use of quinolones influences bacterial virulence, at least in Escherichia coli; in an animal model, the use of ciprofloxacin enhanced bacterial virulence by inducing production of Shiga toxin—encoding bacteriophages in E. coli O157:H7 [26].

Because of the 6 cases of bacteremia due to levofloxacin-nonsusceptible VG streptococci described here, in March 2001, penicillin was added to levofloxacin in the regimen for antibacterial prophylaxis during APBSCT-associated neutropenia at the Mayo Clinic. Six weeks later, 1 episode of bacteremia with a levofloxacin-resistant VG streptococcus exhibiting diminished susceptibility to penicillin was noted (data not shown). The potential emergence of quinolone- and penicillin-resistant VG streptococci is of concern, because it may lead to increased use of vancomycin for the empirical treatment of neutropenic fever. The consequences of emergence of multiply drug-resistant organisms, including vancomycin-resistant enterococci, Staphylococcus aureus that are immediately susceptible to vancomycin, and even vancomycin-resistant VG streptococci, must be considered. Vancomycin tolerance has already been described in Streptococcus pneumoniae [27]; given the close genetic relationship between S. mitis group members and S. pneumoniae and the ability of these groups to exchange DNA by transformation [16, 18], the emergence of vancomycin tolerance in VG streptococci is anticipated.

The proximity of the VG streptococcal bacteremia episodes described herein raised concern that a common-source outbreak was occurring. However, the isolates in this study were not clonal. Concern about an outbreak may be more important with regard to pneumococcal isolates and other organisms that
are spread by person-to-person contact. Our findings of VG streptococci with potential cross-resistance to levofloxacin and the other quinolones that have enhanced activity against gram-positive organisms may foreshadow what will emerge among pneumococcal isolates, especially with the widespread use of quinolones in the general population. It is of further concern that the close homology of the QRDR between \textit{S. mitis} group members and \textit{S. pneumoniae} may facilitate horizontal interspecies transfer of quinolone resistance, a phenomenon that has been demonstrated in vitro [16] but, reassuringly, is uncommon among clinical \textit{S. pneumoniae} isolates in Canada [28].

In summary, our study suggests that levofloxacin use is associated with the selection of VG streptococci that are resistant to quinolones with enhanced activity against gram-positive organisms. The optimal regimen for antibacterial prophylaxis in patients during periods of neutropenia, if any, is not known. The clinical implications of the emerging problem of quinolone resistance are of particular concern with regard to neutropenic hosts but also apply to the general population because of the widespread use of quinolones in the community. Thus, the prudent use of quinolones in clinical practice is strongly advocated, to minimize the emergence of quinolone-resistant VG streptococci and other bacteria.

Acknowledgments

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