Clindamycin Resistance in the Bacteroides fragilis Group: Association with Hospital-Acquired Infections

David Dalmau,* Maryse Cayouette, François Lamothe, Jean Vincelette, Nathalie Lachance, Anne-Marie Bourgault, Christiane Gaudreau, and Pierre L. Turgeon

A retrospective study was conducted to assess the relationships between clindamycin resistance in members of the Bacteroides fragilis group, previous antimicrobial therapy, and the context for the development of infection, whether in the community or during hospitalization. Eighty-five clindamycin-resistant clinical strains (one isolate per patient) isolated from January 1988 to October 1994 were matched (one to one) with clindamycin-susceptible isolates recovered during the same period, and the charts of the patients from whom the isolates were recovered were reviewed retrospectively. Of the clindamycin-resistant strains, 65% were recovered from patients with hospital-acquired infections compared with 40% of the clindamycin-susceptible strains (odds ratio [OR], 2.75; 95% confidence interval [CI], 1.41–5.38; P = .002). Prior antimicrobial therapy for ≥48 hours was also associated with clindamycin resistance (OR, 2.33; 95% CI, 1.16–4.70; P = .02). However, clindamycin resistance remained associated with hospital-acquired infections independent of prior antimicrobial therapy (Mantel-Haenszel weighted average OR, 2.22; 95% CI, 1.03–4.89; P = .04). Clinicians should consider the risks for clindamycin resistance when treating hospital-acquired infections caused by members of the B. fragilis group.

Clindamycin is a widely used antimicrobial agent that has activity against members of the Bacteroides fragilis group (the most common anaerobes isolated from human infections) [1]. Over the past 15 years, numerous investigators have shown that resistance in members of the B. fragilis group to most of the traditionally used antimicrobial agents is increasing [2–6], with a shift in the patterns of susceptibility even in the different species of the group [7–9]. In the United States and Europe, the rate of resistance to clindamycin varies from one center to another, reaching 20% in some hospitals [5, 10]. In Canada, the resistance rate varies between 2% and 10% [11, 12]. In our hospital (Hôpital Saint-Luc, Montreal), the rate of resistance to clindamycin is nearly 8% among members of the B. fragilis group [12, 13].

Clindamycin resistance is transferable and is mediated by resistance factors found on both plasmids and chromosomes by means of a transposon mechanism [14, 15]. Moreover, it has been demonstrated that genetic material can be exchanged between Bacteroides species and Escherichia coli [15].

The epidemiology of clindamycin resistance in the B. fragilis group has not been well studied, and it is unclear whether clindamycin resistance is more prevalent in hospital organisms than in community strains. In addition, prior antimicrobial therapy could be of importance in the emergence of clindamycin resistance. We performed a retrospective study to assess the relationships between clindamycin resistance, previous antimicrobial therapy, and the context for the development of infection, whether in the community or in the hospital.

Materials and Methods

Between January 1988 and October 1994, susceptibilities of clinically significant members of the B. fragilis group that were isolated in the diagnostic microbiology laboratory of Hôpital Saint-Luc, a tertiary referral center, were analyzed for clindamycin resistance. A total of 93 clindamycin-resistant isolates was found. A retrospective study in which clindamycin-resistant members of the B. fragilis group were matched with clindamycin-susceptible isolates was designed. Each isolate within the same species was from a different patient.

Eight strains were excluded from the study (Bacteroides eggerthii, 3; B. fragilis, 2; Bacteroides ovatus, 1; Bacteroides thetaiotaomicron, 1; and Bacteroides stercoris, 1) because the charts of the patients from whom they were isolated were unavailable. We matched the remaining 85 resistant strains with 85 susceptible isolates from infected patients according to species and the nearest isolation date (mean difference, 26 days; range, 1–210 days). All strains were recovered from blood, perioperative samples, and specimens from superficial or deep-seated postoperative infections.

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The isolates were identified by using standard methods [16]. The MIC of clindamycin was determined by the agar dilution method recommended by the National Committee for Clinical Laboratory Standards [17] with use of Wilkins-Chalgren agar (Difco Laboratories, Detroit). Strains for which the MIC of clindamycin was ≥8 mg/L were considered resistant. Clinical charts of the patients from whom the isolates were recovered were reviewed, and the following data were obtained when available: age, sex, type and site of infection, prior antimicrobial therapy, and duration of therapy. The duration of prior antimicrobial therapy could not be determined for two patients from whom clindamycin-susceptible isolates were recovered. Infections were classified as hospital- or community-acquired as well as superficial or deep-seated according to the definitions of the Centers for Disease Control and Prevention for nosocomial infections [18, 19].

Statistical Analysis

All data were stored, retrieved, and analyzed by using database management (Dbase III Plus, Borland International, Scotts Valley, CA) and statistical software (Epi-Info version 5.01b, Centers for Disease Control and Prevention). Odds ratios, Cornfield 95% confidence intervals, and Yates' corrections were calculated to evaluate the association between categorical variables. Mantel-Haenszel weighted average odds ratios and the summary \( \chi^2 \) distribution were used to control for the confounding variables.

Results

The overall rate of resistance to clindamycin among the 1,052 strains of \( B. \) fragilis group (excluding duplicates) that were isolated during the 7-year period was 8.8%. The resistance rates among each species in the group were as follows: 9.8% (4 of 41), \( B. \) caccae; 14.1% (11 of 78), \( B. \) distasonis; 6.2% (23 of 368), \( B. \) fragilis; 9.3% (17 of 182), \( B. \) ovatus; 11.7% (21 of 180), \( B. \) thetaiotaomicron; 7.3% (4 of 55), \( B. \) uniformis; 7.3% (9 of 123), \( B. \) vulgatus; 37.5% (3 of 8), \( B. \) eggerthii; and 5.9% (1 of 17), \( B. \) stercoris.

When the 85 patients from whom clindamycin-resistant isolates were recovered were compared with the 85 matched patients from whom clindamycin-susceptible strains were recovered, there was no significant difference in mean age (52 vs. 51 years, respectively), male sex (49% vs. 52%, respectively), or site of infection (superficial: 45% vs. 55%, respectively; and deep-seated: 55% vs. 45%, respectively).

Clindamycin resistance was correlated with the context for the development of infection (table 1). Of the 85 isolates resistant to clindamycin, 65% were recovered from patients with hospital-acquired infections compared with 40% of the clindamycin-susceptible strains (OR, 2.75; 95% CI, 1.41–5.38; \( P < .001 \)).

<table>
<thead>
<tr>
<th>Table 1. Clindamycin resistance in members of the ( B. ) fragilis group according to type of infection.</th>
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</thead>
<tbody>
<tr>
<td><strong>Strains</strong></td>
</tr>
<tr>
<td>Clindamycin-resistant</td>
</tr>
<tr>
<td>Clindamycin-susceptible</td>
</tr>
</tbody>
</table>

NOTE. OR, 2.75 (95% CI; 1.41–5.38); \( P = .002 \). There was no significant difference in the distribution of the species of the \( B. \) fragilis group among hospital- and community-acquired strains (\( P = .63 \)). Furthermore, the species of the DOT subgroup (\( B. \) distasonis, \( B. \) ovatus, and \( B. \) thetaiotaomicron), which are known to be more resistant to antimicrobials, were homogeneously distributed among hospital- and community-acquired strains (OR, 0.89; 95% CI, 0.46–1.71; \( P = .82 \)). However, of the species of the DOT subgroup, 30 (64%) of the 47 clindamycin-resistant strains and 18 (38%) of the 47 clindamycin-susceptible strains were isolated from patients with hospital-acquired infections (OR, 2.84; 95% CI, 1.14–7.19; \( P = .02 \)).

Overall, the percentages of clindamycin-resistant and clindamycin-susceptible strains recovered from patients who received prior antimicrobial therapy were 59% and 49%, respectively (a nonsignificant difference [OR, 1.46; 95% CI, 0.76–2.81; \( P = .28 \)]. However, when only prior antimicrobial therapy for ≥48 hours was considered (excluding two patients for whom the duration of treatment was unknown), these percentages became 45% and 26%, respectively (OR, 2.33; 95% CI, 1.16–4.70; \( P = .02 \)). No correlation could be established between clindamycin resistance and specific antimicrobial regimens. Fifteen patients had received prior clindamycin therapy for ≥48 hours, but even in isolates recovered from these patients, clindamycin resistance could not be associated with treatment (Mantel-Haenszel weighted average OR, 1.32; 95% CI, 0.36–5.00; \( P = .86 \)).

Sixty-six (74%) of the 89 patients with hospital-acquired infections and 26 (32%) of the 81 patients with community-acquired infections had received prior antimicrobial therapy (OR, 6.07; 95% CI, 2.97–12.52; \( P < .001 \)). Patients with hospital-acquired infections received prior antimicrobial therapy for ≥48 hours more frequently than did patients with community-acquired infections (51% vs. 7%, respectively) (OR, 12.78; 95% CI, 4.73–36.44; \( P < .001 \)). Because clindamycin resistance is associated with both hospital acquisition of infection and prior antimicrobial therapy for ≥48 hours and because these two variables are linked together, a Mantel-Haenszel test was performed to determine their respective importance (table 2). The weighted average odds ratio indicated that resistant strains remained associated with hospital acquisition after controlling for prior antimicrobial therapy for ≥48 hours and because these two variables are linked together, a Mantel-Haenszel test was performed to determine their respective importance (table 2).
Table 2. Clindamycin resistance in members of the *Bacteroides fragilis* group according to type of infection when controlling for prior antimicrobial therapy.

<table>
<thead>
<tr>
<th>Prior antimicrobial therapy, clindamycin resistance</th>
<th>Hospital-acquired</th>
<th>Community-acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12 (34)</td>
<td>23 (66)</td>
</tr>
<tr>
<td>No</td>
<td>11 (26)</td>
<td>32 (74)</td>
</tr>
<tr>
<td>Duration of &lt;48 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10 (67)</td>
<td>5 (33)</td>
</tr>
<tr>
<td>No</td>
<td>10 (42)</td>
<td>14 (58)</td>
</tr>
<tr>
<td>Duration of ≥48 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>33 (94)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>No</td>
<td>12 (75)</td>
<td>4 (25)</td>
</tr>
</tbody>
</table>

NOTE. Mantel-Haenszel weighted average OR, 2.22 (95% CI, 1.03–4.89; *P* = .04). Two of the 170 strains were excluded from this analysis because the duration of prior antimicrobial therapy for the patients from whom they were recovered was unknown.

Our data suggest that clindamycin resistance in members of the *B. fragilis* group is associated with hospital-acquired infections. To our knowledge, this study is the first to demonstrate such an association with use of clinically significant isolates. Reig et al. [5] found a high prevalence of clindamycin resistance in clinical and fecal isolates of *B. fragilis* from nontreated patients, whether or not they were hospitalized, and healthy volunteers. Elhag et al. [20] were unable to demonstrate any significant difference in antimicrobial susceptibility between 89 strains of *B. fragilis* causing community-acquired infections and 97 strains of *B. fragilis* causing hospital-acquired infections. However, these same investigators found that fecal isolates from patients hospitalized for >10 days were significantly more resistant to ampicillin, cefoxitin, and clindamycin than were those isolates from normal subjects in the community.

Our approach brings new perspectives to these studies. First, only clinically significant isolates were included in our analysis. Second, the same standardized antimicrobial susceptibility testing was used throughout the study. Finally, because of the retrospective design of the study, a large number of resistant strains could be included, which helped to control for confounding factors such as species and temporal variations in antimicrobial resistance.

The selection effect of previous antimicrobial use is often incriminated in the acquisition of resistance in the hospital setting [21]. Nevertheless, in our study, the association between clindamycin resistance and hospital acquisition of infection seemed to be independent of prior antimicrobial therapy.

To our knowledge, nosocomial transmission of members of the *B. fragilis* group has never been demonstrated. However, nosocomial acquisition of other anaerobes such as *Clostridium difficile* is well described [22]. Diarrhea and the sporulation of *C. difficile* facilitate its transmission as shown by cultures of specimens from the hands of health care workers and by its recovery from inanimate material. It has been shown that, with a high inoculum, *B. fragilis* can survive several minutes in the presence of oxygen [16]. We could then hypothesize that under appropriate conditions, the transmission of *B. fragilis* from person to person might occur in the hospital environment and eventually result in the acquisition of clindamycin-resistant strains of *B. fragilis* by hospitalized patients.

Another hypothesis to consider is the acquisition of clindamycin resistance by means of other microorganisms already circulating in the hospital. It is well known that *E. coli* can carry macrolide-lincosamide-streptogramin B resistance markers. Hence, it is conceivable that the hospital environment may serve as a reservoir for clindamycin resistance. In fact, transfer of clindamycin resistance has been shown to occur between members of the *B. fragilis* group and *E. coli* through plasmid or chromosomal mechanisms [14, 15, 23–25]. This reservoir may be more important than previously realized, especially since it may include *E. coli* and many other species with a potential for patient-to-patient transmission in the hospital environment.

Our results also suggest that, for a given patient, prior antimicrobial therapy is not the only factor to consider when evaluating for the risk of clindamycin resistance in the strain infecting that patient. Often, when facing a clinically suspected anaerobic infection, the physician must make a therapeutic decision without the results of antimicrobial susceptibility testing because they are either pending or, more commonly, unavailable. Our data suggest that when *B. fragilis* group infections occur in the hospital setting, clinicians should take into account the increased risk for clindamycin resistance whether or not the patient has received prior antimicrobial therapy, including clindamycin.

There are limitations to our study: the design is retrospective, and it was carried out in only one hospital. Clindamycin resistance in members of the *B. fragilis* group may vary according to geographic region [5, 26, 27] and from one hospital to another [28]. In six hospitals in the Chicago area, an interhospital variation similar to the geographic pattern documented in a national survey was observed, thereby suggesting the importance of local rather than regional factors [28, 29]. In Canada, interhospital variation of clindamycin resistance was also documented [12]. Therefore, one should be cautious about overgeneralization of our data.

In conclusion, our results extend the general concept that clinically significant nosocomial gram-negative organisms are more frequently resistant than are community isolates to members of the *B. fragilis* group. However, even this presumption remains controversial [30]. More studies, preferably prospec-
tive, multicenter investigations including molecular epidemiology, are needed to fully understand the epidemiology of clindamycin resistance in members of the _B. fragilis_ group. In the meanwhile, clinicians should consider the risks for clindamycin resistance when treating hospital-acquired infections caused by members of the _B. fragilis_ group.

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**References**