Gastrointestinal Colonization with a Cephalosporinase-Producing Bacteroides Species Preserves Colonization Resistance against Vancomycin-Resistant Enterococcus and Clostridium difficile in Cephalosporin-Treated Mice

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Antibiotics that are excreted into the intestinal tract may disrupt the indigenous intestinal microbiota and promote colonization by health care-associated pathogens. β-Lactam, or penicillin-type, antibiotics are among the most widely utilized antibiotics worldwide and may also adversely affect the microbiota. Many bacteria are capable, however, of producing β-lactamase enzymes that inactivate β-lactam antibiotics. We hypothesized that prior establishment of intestinal colonization with a β-lactamase-producing anaerobe might prevent these adverse effects of β-lactam antibiotics, by inactivating the portion of antibiotic that is excreted into the intestinal tract. Here, mice with a previously abolished microbiota received either oral normal saline or an oral cephalosporinase-producing strain of Bacteroides thetaiotaomicron for 3 days. Mice then received 3 days of subcutaneous ceftriaxone, followed by either oral administration of vancomycin-resistant Enterococcus (VRE) or sacrifice and assessment of in vitro growth of epidemic and nonepidemic strains of Clostridium difficile in murine cecal contents. Stool concentrations of VRE and ceftriaxone were measured,ecal levels of C. difficile 24 h after incubation were quantified, and denaturing gradient gel electrophoresis (DGGE) of microbial 16S rRNA genes was performed to evaluate the antibiotic effect on the microbiota. The results demonstrated that establishment of prior colonization with a β-lactamase-producing intestinal anaerobe inactivated intraintestinal ceftriaxone during treatment with this antibiotic, allowed recovery of the normal microbiota despite systemic ceftriaxone, and prevented overgrowth with VRE and epidemic and nonepidemic strains of C. difficile in mice. These findings describe a novel probiotic strategy to potentially prevent pathogen colonization in hospitalized patients.

Infections with antimicrobial-resistant pathogens are a significant and increasing cause of morbidity, mortality, increased cost, and longer stay among hospitalized patients (1–6). Intestinal colonization is often a precursor to the development of clinical infection (7, 8), and patients who are at risk are often co-colonized with multiple pathogens concomitantly (9–11). Significant hospital-acquired pathogens expressing a clinically relevant antibiotic resistance phenotype in the modern antibiotic era include methicillin-resistant Staphylococcus aureus, multiresistant Gram-negative bacilli, vancomycin-resistant Enterococci (VRE), and Clostridium difficile, among others. Infections with the latter three pathogens are particularly associated with intestinal colonization or disease (12–19).

Our most important host defense against colonization with exogenous, potentially pathogenic microorganisms is the indigenous, predominantly anaerobic microbiota of the lower intestinal tract. This defense mechanism is termed colonization resistance, and the term refers both to prevention of colonization by exogenous pathogens and to inhibition of pathogen overgrowth (20–22). Colonization resistance may be markedly diminished or even abrogated entirely by the administration of systemic antibiotics, as antibiotics that are excreted into the intestinal tract may annihilate the native microbiota and thus render the host susceptible to colonization with hospital-acquired, antibiotic-resistant pathogens. β-Lactam, or penicillin-type, antibiotics are among the most commonly used antibiotics worldwide; like other antibiotics, many of these drugs have the potential to adversely affect colonization resistance. Many bacteria are capable, however, of producing enzymes that inactivate β-lactam antibiotics. While this phenomenon often renders the management of clinical bacterial infections problematic, the elaboration of β-lactamase enzymes by members of the indigenous microbiota may actually serve a constructive purpose, by degrading intraintestinal β-lactam antibiotics, conserving the microbiome, and preserving colonization resistance against nosocomial pathogens. With this end in mind, we showed previously that oral administration of recombinant, proteolysis-resistant β-lactamase enzymes that inactivate β-lactam antibiotics was able to protect the indigenous intestinal microflora and preserve colonization resistance against vancomycin-resistant enterococci (VRE) in mice treated with parenteral β-lactam antibiotics (23, 24). In subsequent work, we were able to demonstrate that administration of such an enzyme was also able to limit overgrowth of and toxin production by C. difficile in cecal contents of antibiotic-treated mice (25). The mechanism by which these phenomena occur is presumably via intraintestinal degradation of secreted antibiotic within the lumen of the intestinal tract. Another research group has also demonstrated successful delivery
of protective β-lactamase enzymes to the rodent colon, using a system that involves a pectin bead vehicle and that does not affect systemic amoxicillin pharmacokinetics (26).

In the present study, we hypothesized that mice that are intestinally colonized with a cephalosporin-producing anaerobe (Bacteroides thetaiotaomicron) might display increased colonization resistance on exposure to nosocomial pathogens, including VRE and C. difficile, despite systemic cephalosporin therapy. Characterization of such a phenomenon could provide insights into endogenous mechanisms of colonization resistance in hospitalized patients, as well as informing future research into novel probiotic strategies to prevent colonization in patients receiving antibiotics. (Portions of this study were previously presented in abstract form at the 109th General Meeting of the American Society for Microbiology, Philadelphia, PA.)

**MATERIALS AND METHODS**

**Bacterial strains.** A clinical strain of a highly cephalosporin-resistant, β-lactamase-producing Bacteroides fragilis group microorganism (Bacteroides thetaiotaomicron, a kind gift from D. W. Hecht, Maywood, IL) was used to colonize the lower intestinal tracts of piperacillin-tazobactam-treated mice. The MIC of ceftriaxone for this microorganism was >500 mg/liter. B. thetaiotaomicron was prepared for esophageal instillation into piperacillin-tazobactam-treated mice by growing the isolate anaerobically in sterile preduced brain heart infusion (BHI) broth (Becton, Dickinson, Sparks, MD) for 24 h.

The strain of VRE utilized to test colonization resistance in the experiments was strain C68, a well-characterized vanA-type vancomycin-resistant Enterococcus faecium clinical strain utilized previously in experimental murine models of colonization resistance by our laboratory (23, 24). Strains were prepared for inoculation into mouse cecal contents by serially diluting 24-hour broth cultures in sterile phosphate-buffered saline (PBS).

Two clinical isolates of Clostridium difficile from Cleveland were also used in the experiments to test colonization resistance. Strain 11 is a non-epidemic strain typed as J29 or J30 by restriction endonuclease analysis (REA; performed in the laboratory of Dale Gerding, Chicago, IL), and strain 17 is an epidemic strain typed as BI9. Both strains produce toxins A and B; strain 17 additionally is moxifloxacin resistant and had a positive PCR for the binary toxin gene cdtB. Both strains had been used by our laboratory in a previous experimental mouse model of colonization resistance to β-lactam antibiotic therapy (25). C. difficile strains were prepared for inoculation into mouse cecal contents by serially diluting 24-hour broth cultures in sterile phosphate-buffered saline (PBS).

**Drugs and dosing.** Subcutaneous (SQ) β-lactam antibiotic doses were equivalent to the usual human doses administered over a 24-hour period (milligrams of antibiotic/gram of body weight) and were as follows: piperacillin-tazobactam, 10.7 mg/0.2-ml dose; ceftriaxone, 1.6 mg/0.2-ml dose. SQ pantoprazole was given at 0.4 mg/0.2 ml (27).

**Mouse model of colonization resistance to VRE and C. difficile.** Female CF-1 mice weighing 25 to 30 g (Harlan Sprague-Dawley) were housed in individual cages with plastic filter tops, to prevent cross-contamination among animals. Mouse cages were changed daily to minimize coprophagy. The study protocols were approved by the Louis Stokes Cleveland Department of Veterans Affairs Medical Center’s Animal Research Committee.

An experimental timeline is shown in Fig. 1. Baseline stool collections were performed on all mice to exclude the presence of detectable cephalosporin-producing organisms at baseline. To abolish their native intestinal microbiota and create an ecological niche for establishment of colonization with a cephalosporin-producing Bacteroides sp., the mice received subcutaneous piperacillin-tazobactam injections once daily for 2 days. Piperacillin-tazobactam is a broad-spectrum β-lactam antibiotic/β-lactamase inhibitor combination in current clinical use, is secreted to a high degree into the mammalian intestinal tract, and has activity against a broad range of microorganisms, including anaerobes. On the second day, mice also received an injection of SQ pantoprazole, a proton pump inhibitor that decreases gastric acid secretion, to facilitate colonization with orally introduced bacteria. Subsequent to this, mice were randomized into 6 groups of 6 mice each. Groups 1 to 3 were utilized to test colonization resistance to VRE, and groups 4 to 6 were used in a separate model testing colonization resistance to C. difficile.

We used a well-established murine model (23–25, 27–33) to test intestinal colonization resistance to VRE. Mouse groups 1 and 3 received oral gavage with 0.5 ml of normal saline (NS) alone once/day for 3 days, delivered via a stainless-steel feeding tube (Perfektum; Popper and Sons), as their microbiota was recovering from the piperacillin-tazobactam. Group 2 was similarly gavaged but instead of normal saline received a 3-day oral course of an overnight culture (0.5 ml of a 10⁶ CFU/ml) of a cephalosporin-producing strain of Bacteroides thetaiotaomicron, in an attempt to establish this microorganism securely within the colon of the mice in this group. Establishment of colonization was confirmed by serially diluting, processing, and plating stool for β-lactam-resistant Bacteroides species on bacte-rides-bile-esculin (BBE) agar (Becton, Dickinson, Cockeysville, MD) containing 64 μg/ml ceftriaxone. After a 1-day hiatus, mice from groups 1 and 2 were initiated on once-daily SQ ceftriaxone injections for 3 days. Mice in group 3 did not receive any ceftriaxone, and their microbiota was thus allowed to continue to recover for a further 3 days. After another 1-day hiatus to ensure elimination of any antibiotic from within the intestinal tract, mice received 10⁶ CFU VRE, again by esophageal gavage. Fresh stool pellets were collected 1 day, 3 days, and 6 days after oral exposure to VRE, serially diluted, and processed for quantitative cultures for this pathogen on selective media according to previously described methods (23, 24).

Our C. difficile murine model is adapted from one utilized in hamsters by Borriello et al (34). The C. difficile murine model yields similar results in clindamycin- and aztreonam-treated mice and hamsters (34, 35) and has been used previously by ourselves to evaluate the effects of fluoroquinolone administration on C. difficile growth and toxin production in murine cecal contents (36). We have also utilized this model to substantiate the hypothesis that oral administration of exogenous β-lactamase enzymes can preserve colonization resistance against C. difficile in piperacillin-treated mice (25). In the current experiments, mouse group 4 and 6 received oral gavage with 0.5 ml of normal saline alone once/day for 3 days. Like group 3, group 5 was similarly gavaged but instead of normal saline received a 3-day oral course of an overnight culture (0.5 ml of a 10⁶ CFU/ml) of the Bacteroides thetaiotaomicron. Establishment of colonization was again confirmed by serially diluting and plating stool for β-lactam-resistant Bacteroides species as described earlier. After a 1-day hiatus, mice from groups 4 and 5 were initiated on once-daily SQ ceftriaxone injections for 3 days, while mice in group 6 did not receive any ceftriaxone. Thus, up until this point, these mice received the same treatment as mice in groups 1 to 3. After a day, stool pellets were collected for DGGE analysis immediately prior to sacrifice, and the mice were sacrificed and cecal contents harvested. After harvest, cecal contents were removed immediately to an anaerobic chamber (Coy Laboratories, Grass Lake, MI), and inoculated under anaerobic conditions with 1 of the 2 strains of C. difficile, for a final concentration of 10⁶ CFU/ml. After anaerobic incubation for 24 h, the samples were diluted in sterile PBS and plated on preduced cefoxitin-cycloserine-fructose agar (Becton, Dickinson, Cockeysville, MD) containing 1% taurocholic acid sodium salt (Sigma, St. Louis, MO) to quantify C. difficile (25, 35, 36). Part of the cecal contents were also reserved for evaluation of β-lactamase activity (see below).

**Denaturing gradient gel electrophoresis (DGGE).** DGGE provides a “molecular fingerprint” of the colonic bacterial flora for a particular mouse, with a banding pattern that is reflective of the diversity of microbial species that are present. To assess differences between the microbiotas of ceftriaxone-treated mice that had prior exposure to the B. thetaiotaomicron and those that did not, DGGE of PCR-amplified bacte-
Fecal 16S rRNA genes was performed on fresh stool pellets collected from 5 mice that received oral normal saline prior to receiving ceftriaxone (randomly selected from groups 1 and 4), 6 mice that received oral Bacteroides prior to receiving ceftriaxone (randomly selected from groups 2 and 5), and 3 mice that received normal saline and no ceftriaxone (randomly selected from groups 3 and 6), according to our previously described methods (23–25). Specimens for DGGE were collected on the second day after ceftriaxone therapy ended (the same day that mice would either have received oral VRE or have been sacrificed and had cecal contents inoculated with C. difficile. D/T, piperacillin-tazobactam; NS, normal saline; CTX, ceftriaxone.

**Fecal ceftriaxone and β-lactamase levels.** Ceftriaxone levels in fresh fecal pellets collected on the third and final day of ceftriaxone administration were measured for groups 4 to 6 with an agar well diffusion assay using an indicator strain of Escherichia coli according to previously described methods (21, 32). β-Lactamase activity in the cecal contents of these mice was also measured on the day of cecal harvest. Such activity is most easily measured using the chromogenic cephalosporin substrate nitrocefin, which changes from pale yellow to deep orange or red within a minute of undergoing hydrolysis of the amide bond by β-lactamases (37). Cecal contents were homogenized, and 10 μl of each cecal content sample (without particulate material) was added to 100 μl of a 1 mM solution of nitrocefin and gently pipetted up and down. Reactions were photographed and recorded after 10 min, although color change was much more rapid than this in most cases.

**Statistical analysis.** One-way analysis of variance (ANOVA) was performed to compare VRE and C. difficile densities among the treatment groups. P values were adjusted for multiple comparisons using the Scheffe correction. Computations were performed with the use of Stata software (version 6.0; Stata, College Station, TX). A P value of <0.05 was considered significant. DGGE similarity indices were compared using Student’s t test.

**RESULTS**

**Preservation of colonization resistance.** Mice that were treated with parenteral ceftriaxone and subsequently exposed to oral VRE
developed massive overgrowth of VRE in their intestinal tract 1 day after exposure, which persisted to at least 6 days after VRE exposure. However, mice colonized with the \(\beta\)-lactamase-producing member of the microbiota (\(B.\) thetaiotaomicron) prior to parenteral ceftriaxone treatment were protected against such overgrowth despite VRE exposure (mean log\(_{10}\) VRE/g stool for \(Bacteroides\) group mice versus NS controls, 4.7 versus 10, \(P < 0.0001\)) (Fig. 2). Indeed, \(Bacteroides\)-treated mice showed levels of VRE in stool that were very similar to those in mice which had not received any ceftriaxone at all and which thus had a relatively recovered microbiota. Similarly, mice that were treated with parenteral ceftriaxone developed significant overgrowth of \(C.\) difficile in their harvested cecal contents 1 day after inoculation of this pathogen, while mice that had been colonized with a \(\beta\)-lactamase-producing member of the microbiota prior to parenteral ceftriaxone treatment did not (mean log\(_{10}\) CFU \(C.\) difficile/ml cecal contents for \(Bacteroides\)-treated mice versus NS controls, 3.3 versus 7.6, \(P < 0.0001\)) (Fig. 3).

**DGGE analysis of the microbiota.** Our previous work demonstrated that antibiotic-treated mice recover the diversity of their microbiota by 5 to 10 days after cessation of therapy (28). This is consistent with the findings exhibited here by the mice that did not receive any ceftriaxone (groups 3 and 6): 8 days after completing piperacillin-tazobactam, these mice demonstrated recovery of a diverse microbiome by DGGE. DGGE analysis further showed that ceftriaxone caused a significant disruption of the murine indigenous microbiota but that ceftriaxone treatment in mice that had previously received \(Bacteroides\) caused relatively minor disruption of the microbiota, with DGGE banding patterns similar to those seen with mice that had not received any ceftriaxone at all (mean similarity indices of mice treated with ceftriaxone plus oral NS and mice treated with ceftriaxone plus oral \(\beta\)-lactamase-producing \(Bacteroides\) in comparison to indices of mice treated with no ceftriaxone at all were 36.5% and 70.5%, respectively; \(P < 0.0001\) for differences between \(Bacteroides\)-treated mice and NS-treated mice and for differences between NS-treated mice and mice that did not receive any ceftriaxone) (Fig. 4).

**\(\beta\)-Lactamase and ceftriaxone activity in intestinal contents.** Cecal contents of individual mice were also reacted in wells with the chromogenic cephalosporin substrate nitrocefin to assess \(\beta\)-lactamase activity. Mice that received oral \(Bacteroides\) demonstrated cephalosporinase activity in their cecal contents, while mice that had received oral NS or no ceftriaxone at all did not, with the exception of one normal-saline-treated mouse (Fig. 5). Complementarily, mice treated with the cephalosporinase-producing \(Bacteroides\) strain maintained undetectable levels of ceftriaxone in stool by agar well diffusion assay (versus average of 250 mg/liter for NS treated mice), suggesting that preservation of the microbiota in these mice was due to intraintestinal degradation of ceftriaxone by a cephalosporinase.

**DISCUSSION**

Antibiotic-resistant microorganisms are increasingly common causes of hospital-acquired infections. Moreover, contrary to previous beliefs, there does not seem to be an especial fitness cost to carriage of many these resistance determinants, and many antibiotic-resistant microbes seem to exhibit unimpaired (or in some cases even augmented) virulence compared to their antibiotic-resistant counterparts.
susceptible counterparts. In particular, quinolone-resistant *C. difficile* and Gram-positive pathogens, including MRSA—both of which are endemic in health care settings—frequently cause infection in noncompromised, previously healthy hosts (38, 39). As a result, health care facilities are focusing more and more on mechanisms to prevent such infections *a priori*. Infection control programs, including those encompassing better stewardship of antimicrobial agents and those fostering an increased awareness of the role of the hospital environment as a source for pathogen transmission, have been widely endorsed by health care societies (40, 41); the latter have spawned successful hand hygiene and environmental decontamination interventions, among others, in many settings (41–43). Our study, which describes a mechanism by which the colonic microbiota may be preserved in the face of antibiotic pressure, represents yet another strategy by which the initial acquisition and spread of such organisms could be halted.

We have shown that murine intestinal colonization with a *Bacteroides thetaiotaomicron* /β-lactamase-producing strain was associated with preservation of the microbiota in the face of parenteral ceftriaxone and with preservation of colonization resistance against the pathogens VRE and *Clostridium difficile*, a finding that could have important implications for hospitalized patients receiving parenteral /β-lactam antibiotic therapy.

In previous work, we demonstrated that oral administration of recombinant, proteolysis-resistant class A /β-lactamases and Colonization Resistance

FIG 3 Oral pretreatment with a β-lactamase-producing strain of *Bacteroides thetaiotaomicron* prevented overgrowth of *C. difficile* in cecal contents of ceftriaxone-treated mice. The values are densities (log_{10} CFU/ml) of *C. difficile* 24 h after inoculation into cecal contents. Prior to inoculation, none of the mice had detectable levels of *C. difficile* in cecal contents (level of detection ~ 2 log_{10} CFU/ml). Treatment with subcutaneous ceftriaxone after prior receipt of only oral normal saline (NS) resulted in high-density *C. difficile* colonization, whereas treatment with subcutaneous ceftriaxone after receipt of oral *B. thetaiotaomicron* did not (mean log_{10} CFU *C. difficile*/ml cecal contents for *Bacteroides*-treated mice versus NS controls, 3.3 versus 7.6; *P* < 0.0001). Strains 11 and 17 are nonepidemic and epidemic strains of *C. difficile*, respectively. The error bars represent standard deviations.

FIG 4 Denaturing gradient gel electrophoresis analysis of stool microbiota. Each lane represents results from either a control bacterial strain or stool from an individual mouse. Mice that did not receive any CTX and mice precolonized with β-lactamase-producing *Bacteroides* prior to receiving CTX show many bands, each likely representing a different member of the indigenous microbiota; mice treated with CTX and oral NS (rather than *Bacteroides*) alone show loss of most bands, likely representing loss of many commensal bacterial species secondary to antimicrobial therapy. Lanes 1 to 3, controls (E. coli, *C. difficile*, and *B. thetaiotaomicron*, respectively); lanes 4 to 8, mice treated with CTX plus oral NS; lanes 9 to 14, mice treated with CTX plus oral *B. thetaiotaomicron*; lanes 15 to 17, mice that did not receive any CTX.
therapy—i.e., if β-lactamase is not present within the lumen of the colon when a β-lactam antibiotic is secreted, the antibiotic will adversely affect the microbiota, and colonization resistance will be abolished. This would be true for each scheduled dose of antibiotic and oral enzyme, and maintaining a regimen where not one single dose is delayed or missed might be challenging in a clinical setting. Moreover, factors such as delayed intestinal transit times, ileus, or other gastrointestinal pathologies in hospitalized patients could have the potential to interfere with the efficacy of an orally administered enzyme, even if this were engineered to be resistant to proteolysis in the stomach. Because of these concerns, we wished to explore the possibility of a more durable form of protection, i.e., one that would be less dependent on variations or deficits in individual dosing schedules. One such durable option would include precolonization of the colon with a β-lactamase-producing microorganism, preferably a constituent member of the indigenous microbiota, that is already well adapted to its ecological niche within the colon and would therefore be likely to survive there for a prolonged period of time, without a requirement for any further dosing. Finally, supporting the feasibility of such a strategy, Léonard and colleagues had demonstrated that administration of a β-lactamase-producing mixed-fecal flora cocktail from the intestinal tract of a human volunteer was able to preserve the microbiota, that is already well adapted to its ecological niche

FIG 5 Cecal contents of individual mice (one mouse per well) after reaction with the chromogenic cephalosporin substrate nitrocefin. Mice that received oral Bacteroides demonstrated β-lactamase activity in cecal contents (nitrocefin hydrolysis associated with change from yellow to red). Note that one mouse in the normal saline (NS) group had β-lactamase activity in its cecal contents, possibly representing upregulation of an endogenous bacterial source.

group organisms produce low levels of constitutive chromosomal cephalosporinase (45, 46), but up to 6% of strains have been shown to be hyperproducers of cephalosporinase (45). Based on these observations and on a recent review estimating that members of the genus Bacteroides probably comprise the largest single population of anaerobes in the human colon (25%) (48), we hypothesized that the colonic presence of subpopulations of Bacteroides species that produce (or hyperproduce) cephalosporinase could be one mechanism by which individuals are protected from adverse effects during cephalosporin antibiotic therapy. It is notable that one mouse in our experiments that did not receive oral Bacteroides nonetheless demonstrated significant β-lactamase activity in its cecal contents (Fig. 5), suggesting that in certain patients, endogenous expression or upregulation of enzyme by members of the native microbiota might take place under β-lactam antibiotic pressure.

There are several factors that could limit the extension or utility of the findings we have described above in clinical settings. First—and probably most importantly—antibiotics are overused, and many patients receive more than one class of antimicrobial agent while hospitalized. The strategy outlined in the present work would have to be accompanied by effective antimicrobial stewardship practices, as it would preserve the microbiota only in the face of parenteral β-lactam antibiotic therapy and obviously would have no effect in terms of inactivating other classes of antibiotics that are secreted into the gut. Second, we initially abolished the murine indigenous microbiota with piperacillin-tazobactam to create a niche for colonization with the protective Bacteroides; whether such colonization could be achieved without this conditioning regimen—or without administration of a proton pump inhibitor, for that matter—is unknown. Third, differential location of β-lactamase-producing bacteria throughout the colon could in theory lead to heterogeneity in terms of protection against pathogen colonization. Finally, the use of a probiotic colonizing agent with a broad-spectrum resistance determinant, regardless of the bacterium’s categorization as a member of the native microbiota, poses potential threats in terms of possible
infection of the host or possible resistance gene transfer within the colon. While the current study is intended as a proof of principle that advances our understanding of the ecology of endogenous colonization resistance, and Bacteroides species may or may not end up being a viable option for therapeutic studies in patients, future research in this area will need to judiciously manage these risks. It is worth noting, however, that with regard to the risk of resistance determinant dissemination, transfer of β-lactamase resistance determinants from B. fragilis group bacteria to other species of bacteria appears to be exceedingly rare; indeed, we are not aware of any reports of this occurring in nature. It is also important to be cognizant of the fact that in 2014, fecal microbiota transplantation—consisting of the transfer of an entire diverse microbial community and its largely uncharacterized resistome from one individual’s intestinal tract to another’s—is advocated as the preferred therapy for patients suffering from recurrent Clostridium difficile infection (49). Fecal microbiota transplantation is currently being used for treatment of disease, and its efficacy in the prevention of disease in humans remains to be characterized; however, given its clinical implementation, the eventual endorsement of probiotic strategies that are more specific and targeted—such as the one we describe above—does not seem farfetched and even seems comparatively safe.

In summary, we have demonstrated that establishment of intestinal colonization with a β-lactamase-producing anaerobe was able to protect the indigenous microbiota and preserve colonization resistance against the pathogens VRE and C. difficile in ceftriaxone-treated mice. If an analogous strategy could be utilized in patients, protection against colonization by a broad range of pathogens could potentially be conferred.

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REFERENCES


