Overview of the Management Of Clostridium difficile Infections

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Clostridium difficile infection (CDI), a common cause of infectious diarrhea, has become increasingly prevalent in the acute care setting. CDI is associated with increased morbidity and more recently with increased mortality, and it has surpassed methicillin-resistant Staphylococcus aureus (MRSA) as the leading cause of hospital-acquired infections (HAIs). CDI also increases hospital length of stay (LOS) and care costs. A well-known cause of antibiotic-associated diarrhea, it is estimated to account for 15% to 25% of all diarrheal episodes. No longer only associated with health care facilities, C. difficile infections are now an emerging threat in the community.

Epidemiology

C. difficile is responsible for 12% of all HAIs in 10 geographically diverse states (Figure 1). This translates to an estimated 80,400 cases of hospital-onset infections. The Centers for Disease Control and Prevention (CDC) national and state HAI progress report estimated that there were 107,700 hospital-onset CDIs nationwide in 2011 (the most recently reported data from 2012 showed a 2% decline in reported cases). Once thought to have a low attributable mortality rate, recent data has estimated CDI mortality to be 6.9% at 30 days after diagnosis and 16.7% at 1 year. The infection accounts for approximately 14,000 deaths annually, and there was a 400% increase in CDI-related deaths from 2000 to 2007, with most deaths occurring in older individuals.

It is estimated that half of all CDIs occur in people younger than age 65 years. However, 90% of CDI-related deaths occur in those who are 65 and older.
Furthermore, about 25% show initial symptoms in the hospital versus 75% in nursing homes, doctors’ offices, and clinics; hence, 94% of all CDIs are linked to medical care. Not only is this a concern for patient safety, it is also a concern for health care costs nationwide, which indirectly affect patient care. Scott demonstrated an average attributable per-patient cost of $9,124 for CDI, higher than catheter-associated urinary tract infections, which occurred at a higher rate at the time of the study. This translates to approximately $1 billion in extra health care costs annually. Yet, others have estimated the cost for CDI treatment to be as high as $4.9 billion in the acute care setting.

Although once thought to be strictly an HAI, there is an increasing number of community-acquired C. difficile infections (CaCDI). Some reports estimate that 30% to 40% of all CDI cases are CaCDI. Of note, Khanna et al demonstrated that 22% of patients had no antibiotic exposure in the 90 days before the onset of CaCDI.

**Pathogenesis of Hypervirulent Strains**

As the rates of CDI increased in 2000, the North American Pulsed Field type 1 strain (NAP1), or PCR ribotype 027 emerged; this strain was responsible for the Pittsburgh, Atlanta, and Montreal CDI outbreaks. This strain has increased production of the classic A (enterotoxin; 16-fold) and B (cytotoxin; 23-fold) toxins, and also an additional binary toxin currently under study; the latter is associated with a more severe diarrheal illness. It is also inherently resistant to fluoroquinolone (FQ) antibiotics, likely secondary to their increasing and widespread use.

Although FQs are not recommended for the treatment of CDI, their use is an important epidemiologic risk factor for the spread within health care facilities. Metronidazole (various) is the current recommended choice for mild to moderate disease and those with NAP1 infections see high failure rates, thought to be secondary to the severity of the disease, low concentration levels in the fecal material, and poor tolerance. The NAP1 or...
ribotype 027 strains were associated with an increase in recurrences and a more complicated clinical course, therefore higher morbidity and mortality rates. Another strain sharing hypervirulence is *C. difficile* PCR ribotype 078. Keel et al demonstrated that this was the most commonly isolated strain in swine and calves. Also frequently found in meat products, ribotype 078 is a possible risk factor for animal-to-human transmission, as well as a source for CaCDI. In the United States, ribotype 078 is reported to be the third most commonly isolated strain in CaCDI. It shares toxin A and B production as well as a binary toxin.

In general, CaCDI may present with a more severe infection; patients are less likely to receive antibiotics and more likely to be younger and have a greater proportion of PCR ribotype 078 than those with CDI acquired in a hospital setting. More vigilance is required to detect these cases in the community which may not present with the traditional predisposing factors.

**Risk Factors**

As the leading cause of HAIs, there is a need for understanding risk factors associated with CDI. The CDC has confirmed advanced age (≥65) and antibiotic exposure as risk factors for CDI and CaCDI primary and recurrent infections. Multiple meta-analyses have confirmed older age, continued antibiotic exposure, and concomitant use of H2 blockers and proton pump inhibitors (PPIs) as risk factors for recurrent CDI as well as comorbid conditions, previous CDI recurrence, CDI acquired in the hospital setting, and prolonged hospital LOS.

Although it is generally agreed that exposure to certain antibiotics (particularly FQs) increases the risk for CDIs, there has been some conflicting data as to what classes of drugs yield the greatest risk. Goorhuis et al, for example, found FQ treatment to be an independent risk factor for CDI due to ribotype 078. Ribotype 027 also had higher rates of infection in patients age 65 years and older who had been admitted to an inpatient hospital setting, had any underlying disorder, and had a history of exposure to antibiotic therapy.

However, although Brown et al found use of tetracyclines and penicillins related to lower risk for CDI, Keessen et al found that clindamycin (various) exposure was also a major risk factor, in addition to exposure to cephalosporins and FQs, specifically for CDI due to ribotype 078. Yet another study showed that in addition to the aforementioned risk factors, hospital LOS was a risk factor for colonization with *C. difficile* leading to CDI. Additional studies have highlighted treatment with PPIs as a novel risk factor for CaCDI in military active duty personnel (this study also revealed higher morbidity and mortality rates among older individuals plus those once considered low-risk groups for CaCDI, including community dwellers, pregnant women, and children).

**Treatment Approaches**

In general, strategies for treatment should be tailored according to the patient’s age and underlying comorbidities (Table 1).

**FDA-Approved Options**

**Metronidazole and Vancomycin**

Metronidazole is a nitroimidazole with broad activity against anaerobic bacteria, including *C. difficile*. It is currently recommended as the drug of choice for mild to moderate CDI. Vancomycin is a glycopeptide that is not absorbed when given orally. Vancomycin is currently recommended for the first episode of moderate to severe CDI or in cases of metronidazole therapy failure or potentially life-threatening CDI.

Although early studies demonstrated similar efficacy between the 2 agents, studies since 2004 have shown...
an increased rate of treatment failures associated with metronidazole (16%-38%), whereas vancomycin failures remained the same (1%-6%). A study by Zar et al was the first to compare the drugs directly, in a prospective manner, in the treatment of *C. difficile*-associated diarrhea (CDAD). Among the patients with mild CDAD, treatment with metronidazole or vancomycin resulted in clinical cure in 90% and 98%, respectively (*P*=0.36). The critical results from this study were that among the patients with severe CDAD, clinical cure was 76% for metronidazole and 97% for vancomycin (*P*=0.02). Recurrence rates were similar (15% and 14%) between the 2 groups.

Oral metronidazole is completely absorbed in the gastrointestinal tract but fecal penetration is poor, leading to low luminal concentrations (range 0.8-24 mcg/g; the susceptible range is 0.2-2.0 mcg/mL). Additionally, IV metronidazole has been shown inferior (*P*<0.001) to both oral metronidazole and oral vancomycin.

**Fidaxomicin**

Fidaxomicin (FDX; Dificid, Cubist) is the most recent CDI treatment to receive FDA approval. It is a macrocyclic antibiotic that is highly active against *C. difficile* (MIC90, 0.25 mcg/mL), including the epidemic strain.

Results from 8 in vitro studies comprising 1,323 *C. difficile* isolates showed the minimum inhibitory concentration (MIC) range of FDX to be greater than 0.001 to 1 mcg/mL, with a MIC90 of 0.5 mcg/mL. No resistant isolate has been reported, although a single strain was recovered from a cured patient who had an elevated MIC of 16 mcg/mL at the time of recurrence.

In the pivotal trial of FDX versus vancomycin, clinical cure rates were similar and FDX was noninferior to vancomycin (92.1% and 89.8%, respectively). However, patients treated with FDX had lower recurrence (13.3% vs 24%; *P*=0.004). Additionally, data from the 2 Phase III trials showed that FDX, when administered concomitantly with other antibiotics, has a higher cure rate (46 of 51 [90.2%]) than vancomycin (33 of 45 [73.3%]; *P*=0.031) and that overall treatment with FDX compared with vancomycin was associated with lower recurrence rates (16.9% vs 29.2%; *P*=0.048). The lower recurrence rates associated with FDX may be due to the drug’s ability to preserve the normal gut microbiome and completely resolve the underlying CDI pathogen, or both. A randomized clinical trial assessed the microflora-sparing properties of FDX by examining fecal samples for quantitative cultures for *C. difficile* and cytotoxin B fecal filtrate concentrations against normal microbiota. FDX and vancomycin rapidly killed *C. difficile* and neutralized toxin; however, FDX preserved the microbiome during and after CDI treatment.

**Other Options**

Because results with currently available treatments have been suboptimal—with high rates of recurrence—new modalities and treatments have been pursued.

**Rifaximin**

Rifaximin (Xifaxan, Salix) is a semisynthetic derivative of rifamycin approved for the treatment of travelers’ diarrhea; it is also used off-label for irritable bowel syndrome and hepatic encephalopathy. It has in vitro activity against aerobic and anaerobic gram-positive and gram-negative bacteria. After 3 days of therapy, the fecal level of the drug reaches 8,000 mcg/g.

*C. difficile* resistance to rifampin (a surrogate for rifaximin) has been observed in several studies. The prevalence of rifampin resistance among 470 *C. difficile* isolates from a large teaching hospital was analyzed and was observed in 173 patients (36.8%), including 167 of 205 (81.5%) with epidemic clone (BI/NAP1) isolates (*P*<0.001). Of 8 patients who were exposed to rifamycin, 7 had rifampin-resistant *C. difficile* compared with 166 of 462 unexposed patients (relative risk, 2.4). In an open-label trial, 8 of 13 enrolled patients received rifaximin; all patients reported symptom resolution; 7 had no relapse at follow-up (median 162 days).

Overall, more attention has been given to use of rifaximin as a “chaser” rather than as first-line therapy. In one study, for example, patients were given rifaximin or placebo immediately after finishing standard anti-CDI antibiotics. CDI recurrence was lower in the rifaximin arm than in the placebo group (15% vs 31%; *P*=0.11). A randomized placebo-controlled trial testing the hypothesis that rifaximin given in a decreasing dose over 4 weeks after successful CDI treatment will reduce relapse is ongoing.

**Nitazoxanide**

Nitazoxanide (NTZ) is a synthetic nitrothiazole benzamide approved for the treatment of Cryptosporidium and *Giardia* species. It has excellent in vitro activity against *C. difficile* with an MIC90 of 0.125 mcg/mL. A prospective, randomized, double-blind study compared NTZ (7 and 10 days) with metronidazole (10 days) in hospitalized patients with *C. difficile* colitis. Response rate at 1 month for metronidazole was 57.6% compared with 65.8% (7 days) and 74.3% (10 days; *P*=0.34) for NTZ.

In another study, patients who had failed metronidazole treatment were given NTZ; 74% responded, although 7 later had recurrent disease (54% cure rate). Three who initially failed and 1 who had recurrent disease were retreated with NTZ and responded, yielding an aggregate cure rate of 66% in this difficult-to-treat patient population. No clinical trials are currently ongoing.

**Tigecycline**

Tigecycline (Tygacil, Pfizer) has activity against a broad spectrum of gram-positive and gram-negative aerobes and anaerobes, including *C. difficile* (MIC90 of 0.06-0.25 mcg/mL). Multiple case reports and small case series using IV tigecycline as adjunctive therapy to other treatment options for severe, refractory CDI in
critically ill patients have reported some success. A prospective clinical trial assessing the safety of tigecycline added to standard oral therapy (vancomycin or metronidazole) was completed recently and results are pending.

New Drugs in Development

LFF571

LFF571 (Novartis) is a novel semisynthetic thiopепtide antibiotic with potent activity against a variety of gram-positive pathogens, including *C. difficile*. In a hamster model, LFF571 was more efficacious and had fewer recurrences than vancomycin. A study investigating the safety and pharmacokinetics of single- and multiple-ascending oral doses in healthy individuals reported that the drug was generally safe and well tolerated. A Phase II study of the safety and efficacy of multiple daily dosing of oral LFF571 in patients with moderate CDIs was completed recently and results are pending.

Surotomycin

Surotomycin (CB-183,315, Cubist) is an orally available lipopeptide antibiotic that is structurally related to daptomycin. Surotomycin has shown good potency against *C. difficile* isolates (including O27/NAP1/BI isolates) as well as those with high MICs to metronidazole, moxifloxacin, and vancomycin. It lacks activity against Enterobacteriaceae and species of the *Bacteroides* group (MIC90 >8,192 mcg/mL); this suggests that this compound will minimize disruption and lead to rapid recovery of the normal gut flora.

Surotomycin has successfully completed a Phase II trial in patients with CDI. It also showed better sustained cure rates than vancomycin as well as reduction and delay in recurrence (17% for surotomycin vs 36% vancomycin) of CDAD episodes. Phase III trials are ongoing.

SMT 19969

SMT 19969 (Summit) is a bis-benzimidazole tetrahydrate compound that has demonstrated potent activity against *C. difficile* isolates with MIC90 values 2-, 8-, and 16-fold lower than FDX, metronidazole, and vancomycin, respectively. SMT 19969 has shown limited activity against gram-positive and gram-negative anaerobes, including *Bacteroides* species, *Bifidobacterium* species, and others (with the exception of Clostridia). This suggests that SMT 19969 would have minimal disruption in the gut flora and preservation of the normal gut microbiome. SMT 19969 was safe and well tolerated at all dosages in the recent Phase I trial. A Phase II trial is ongoing.

Cadazolid

Cadazolid (CDZ; ACT-179811, Actelion) is a new quinolonyl-oxazolidinone with structural elements of the oxazolidinone as well as the quinolone class. It is a strong inhibitor of *C. difficile* protein synthesis that leads to the suppression of toxin and spore formation. A recent study showed CDZ was active against all *C. difficile* strains (MIC90 0.125, range 0.03-0.25 mg/L). The CDZ geometric mean MIC was 152-, 16-, 9-, and 7-fold lower than those of moxifloxacin, linezolid, metronidazole, and vancomycin, respectively. CDZ levels persisted at 50- to 100-fold supra MIC for 14 days after dosing. Inhibition of gut microflora was limited with the exception of bifidobacteria; *Bacteroides fragilis* group and *Lactobacillus* species counts were not affected.

In Phase I trials, CDZ was well tolerated and systemic exposure was low. Most of the compound was recovered unchanged in the feces, resulting in high concentrations in the colon. A Phase II study evaluated the efficacy, safety, and tolerability of CDZ in patients with CDAD. The results of this study indicate that the cure rates for all twice-daily doses of CDZ (76.5% [250 mg]; 80% [500 mg]; 68.4% [1,000 mg]) were similar to or better than those for vancomycin (68.2%). Recurrence rates were lower for all twice-daily doses of CDZ (18.2% [250 mg]; 25% [500 mg]; 22.2% [1,000 mg]) compared with vancomycin (50%). Phase III clinical trials are underway.

Oritavancin

Oritavancin (ORI; LY333328, The Medicines Company) is a lipoglycopeptid with activity against *C. difficile*. In vitro, it was found to be at least 4-fold more potent than vancomycin against *C. difficile* strains tested. When tested for the treatment of PCR ribotype 027 in a human gut model, it was found that both ORI and vancomycin were effective in treating CDI, but only ORI appeared active against spore forms of *C. difficile*. Overall, ORI therapy may be more effective in treating CDI than vancomycin because it may prevent recrudescence of *C. difficile* spores.

In a simulated CDI human gut model, Chilton et al demonstrated that ORI short-course therapy (4-day) might be an effective CDI treatment. More recently this same group showed that ORI might adhere to spores, potentially causing early inhibition of germinated cells and preventing subsequent vegetative outgrowth and spore recovery. Again, this may prevent some recurrences of CDI that are due to germination of residual spores after antibiotic therapy. Despite all the information thus far available, no clinical trials are ongoing.

CamSA

Cholate meta-benzene sulfonyc derivative (CamSA) is a bile salt analog that inhibits *C. difficile* spore germination in vitro. Howerton et al infected mice with massive inocula of *C. difficile* spores and treated them with different concentrations of CamSA. A single 50-mg/kg dose of CamSA prevented CDI without any toxicity. This is a novel approach and would add to the treatment of CDI without compromising the microbiota in these patients. CamSA’s in vitro stability, distribution, and cytotoxicity are currently being characterized.
Monoclonal Antibodies

MK-3415A (Merck) is a combination of monoclonal antibodies (mAbs) to C. difficile toxin A (MK-3415) and toxin B (MK-6072). A Phase II study showed favorable results when C. difficile human mAbs were administered to patients with C. difficile infection after being treated with metronidazole or vancomycin. This clinical trial showed significant reduction in the rate of recurrence of C. difficile among patients treated with the mAbs (7% vs 25%; \( P<0.001 \)). The recurrence rates among patients with the epidemic BI/NAP1/027 strain were 8% for the antibody group and 32% for the placebo group (\( P=0.06 \); among patients with more than one previous episode of C. difficile infection, recurrence rates were 7% and 38%, respectively (\( P=0.006 \)).51 Phase III trials are ongoing.

Biotherapeutics

Fecal Microbiota Transplantation

There has been a lot of attention surrounding the success of fecal microbiota transplantation (FMT) in the treatment of recurrent CDI. To date, numerous studies have shown superior efficacy of FMT over traditional antibiotics.

The landmark study published by van Nood et al randomized patients with recurrent CDI to FMT via nasoduodenal infusion, vancomycin, and vancomycin with bowel lavage. The study was halted at interim analysis because the FMT arm showed a superior success rate (81%) compared with the vancomycin (31%) and vancomycin with bowel lavage arms (23%). Two of the 3 treatment failures in the FMT arm resolved with a second infusion from a different donor, bringing the overall success rate to 93.75%.52 This is consistent with meta-analyses of the success rate of FMT for CDI worldwide, which is 91%, regardless of the route of administration.53 Additionally, after the donor-feces infusion, patients showed an increased fecal bacterial diversity very much similar to the donors (Figure 2). In 8 patients from whom samples were available, the diversity of fecal microbiota could not be distinguished from that of the donors during the follow-up period.52

Although concerns have been raised regarding the safety of FMT, numerous literature reviews have reported no serious adverse events (AEs) or infectious transmissions directly attributable to FMT.54 There are, however, legitimate concerns regarding the safety of FMT in patients with compromised immune systems. Immunosuppressed patients seem to be at increased risk for developing recurrent CDI due to repeated antibiotic treatment, prolonged hospital LOS, and decreased ability to eradicate the infection. A multicenter retrospective study of FMT in 75 immunocompromised adults found similar efficacy (89%) to other studies and no infectious complications directly attributable to FMT, with follow-up to 11 months. Patients included were solid organ transplants, HIV/AIDS, patients undergoing chemotherapy, and those receiving immunosuppressive treatment for inflammatory bowel disease.55

Cost is also an issue with FMT. An analysis of FMT versus vancomycin for recurrent CDI found that FMT had an incremental cost-effectiveness ratio of $17,016 relative to vancomycin. More specifically, FMT via colonoscopy was felt to be the most cost-effective route of administration compared with duodenal infusion or enema.56

FMT has proven to be safe and efficacious, but it remains a time-consuming and nonstandard process. Although the major gastrointestinal societies and the Infectious Diseases Society of America released a joint statement on donor screening guidelines in July 2013, the recommendations are not evidence-based.57

Finding and screening a donor can be a time-consuming, expensive, and embarrassing process for the patient. In the inpatient setting with a critically ill patient, there is not always time to properly identify and screen a donor. Multiple techniques have been developed to try to work around these inherent difficulties in an attempt to standardize and speed up treatment, including frozen stool protocols and open-access stool banks.

In frozen stool protocols, donor stool is blended, filtered, and then processed with glycerol before freezing at \(-80^\circ\text{C}\) for later usage. Before use in FMT, the frozen slurry is thawed in an ice bath. A series of 43 patients treated with the frozen protocol showed an 86% treatment success rate, but it should be noted that 30% of the patients had underlying inflammatory bowel disease.58 More recently, Youngster et al conducted an open-label, randomized controlled pilot study using...
frozen inoculum from unrelated donors. Overall cure rate was 90% at 8 weeks.

North York General Hospital in Toronto, Canada, has begun offering patients the option to bank their own stool before hospital admission in the event they become infected with hospital-acquired CDI. This approach offers the advantages of not requiring a donor or screening testing. This program is a pilot study currently underway to publish safety and efficacy data. There is concern from the FDA regarding oversight and regulation of “stool banks,” although Open Biome operates under an institutional review board.

The goal is to remove the “fecal” from FMT, and this may be accomplished via stool substitute transplant therapy. Queen’s University in Canada has successfully reproduced 33 purified intestinal bacterial cultures under anaerobic conditions into a synthetic mixture, which was then instilled into the colons of 2 patients with recurrent CDI due to a hypervirulent ribotype 078 strain. Both patients had resumption of normal bowel habits within 3 days with durability of cure at 6 months.

The “holy grail” of FMT is to develop a pill that would reconstitute the colonic microbiome and eradicate C. difficile. Louie presented a pilot series of 31 patients treated with 24 to 34 pills of fecally derived bacteria covered in gelatin to survive gastric acid and deliver the contents to the colon; 30 of 31 patients enrolled were cured with no significant AEs noted.

### Table 2. C. difficile Vaccines and Immunologics

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**VP20621**

VP20621 (ViroPharma), spores of nontoxigenic C. difficile (NTCD) strain M3, have been shown to be protective against challenge with toxigenic strains in hamsters. Human administration and colonization by VP20621 may prevent primary CDI or recurrent CDI.

Phase I clinical safety testing was completed in 2010. Healthy adults received single or multiple doses of an oral suspension of VP20621 or placebo. All doses were well-tolerated, and no serious AEs were reported and no discontinuation due to AEs occurred. Participants did not experience diarrhea or change in bowel habits. Persistent colonization with VP20621 was detected in stools on days 21 to 28 in 44% of participants. VP20621 was able to colonize the gastrointestinal tracts of those pretreated with vancomycin. A Phase II clinical trial in recurrent CDI is underway.

**Probiotics**

A Cochrane meta-analysis of 31 randomized studies and 4,492 participants concluded that taking probiotics with antibiotics reduced the risk for developing CDAD by 64%. The use of probiotics appeared to be safe and effective in patients who were not immunocompromised. There are a number of clinical trials currently ongoing to determine the role of probiotics in the prevention of CDI and/or CDI recurrence.

**Vaccines**

The only currently available antibody treatment for CDI is pooled intravenous immunoglobulin (IVIG); IVIG preparations contain neutralizing levels of IgG antibody to toxin A and B. To date, no studies have provided conclusive evidence for any clinical benefit of IVIG. Active immunization rather than passive is appealing, as this would confer durable protection against CDI. Vaccines for CDI have been in development for more than 2 decades. Torres et al showed that a formalin-inactivated C. difficile vaccine (Intercell IC84) protected hamsters against toxigenic challenge and induced long-term immunity in protective antibody levels. The vaccine was well tolerated and induced no side effects.

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C. difficile culture filtrate protected hamsters when given by nasal, intraperitoneal, and subcutaneous routes.66

Currently there are 3 vaccines in clinical development. ACAM-CDIFF (Sanofi-Pasteur) is a mixture of formalin-inactivated toxin A and B that is given 3 times IM. The vaccine has been shown to be safe, well tolerated, and immunogenic in healthy adults. Phase II trials have been completed in the therapeutic setting and additional trials in the prophylactic setting are ongoing. Due to the fact that the vaccine addresses an important unmet medical need, ACAM-CDIFF has been fast-tracked by the FDA.67

A second injectable vaccine, IC84, is a subunit recombinant protein vaccine consisting of 2 truncated toxins A and B from C. difficile. IC84 has undergone Phase I safety and immunogenicity testing in volunteer subjects and also has been shown to be highly immunogenic in elderly subjects.68 In addition, a vaccine derived from molecularly and chemically inactivated toxins A and B is currently undergoing Phase I clinical trials.

Conclusion

The incidence of CDI has increased dramatically over the past 2 decades and we have seen the emergence of epidemic strains with new resistance patterns, which have resulted in high morbidity and mortality.

Despite the treatment advances in recent years, several challenges are still present: appropriate treatment of severe complicated/fulminant CDI; the management of CDI recurrence; proper management of repeat episodes and the BI/NAP1/027 strain; and, lastly, the role of vaccines, immunologics, and other biotherapeutics. The use of biotherapeutics to restore normal flora seems a novel and successful approach.

There is a great need to continue to explore and develop new agents in the antimicrobial arena that spare the normal flora and perhaps most of all, avoid using antimicrobials altogether, whenever possible.

References


