A SPECIAL ARTICLE

Guidelines for Prevention, Surveillance, Diagnosis, and Treatment, in this New Era of More Virulent Strains of Antibiotic Associated Diarrhea (AAD), *Clostridium Difficile*-Associated Diseases/Diarrhea (CDAD) and *Clostridium Difficile* Colitis (CDAC)

by Perry Hookman and Jamie S. Barkin

In December, 2005 the NIH/Center for Disease Control's (CDC) newsletter MMWR reported that in the past *Clostridium difficile*-associated diseases which usually affected hospital patients, are now appearing in cases of relatively healthy adults, including some who have not even been exposed to a hospital. In the same month *The New England Journal of Medicine* printed an early edition with several reports suggesting that not only is the rate of disease associated with *C. difficile* increasing, but a previously uncommon strain of *C. difficile* has been found. The new found strain of *C. difficile* has variations in toxin genes and is more resistant to fluoroquinolones and has emerged as a cause of geographically dispersed outbreaks of Antibiotic Associated Diarrhea (AAD), specifically *C. difficile* diseases (CDD), and *Clostridium Difficile*-Associated Diarrhea (CDAD). Bacteria are constantly mutating to become resistant to antibiotics. These more virulent toxin producing *C. difficile* infections include CDAD, *C. difficile*-associated colitis or pseudomembranous colitis (CDAC). This latter can progress to toxic megacolon (TM). CDAC is increasing in frequency and severity. *C. difficile* also accounts for an unknown but increasing percentage of community acquired diarrhea. Fluoroquinolones, especially C-8-methoxy fluoroquinolones like moxifloxacin and gatifloxacin have been

(continued on page 68)

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A SPECIAL ARTICLE

(continued from page 65)

incriminated in CDAD epidemics in different health care facilities. This article describes the methods of prevention, early diagnosis and prompt aggressive treatment which are critical in managing CDAD/CDAC. A very important method of controlling outbreaks of *C. difficile*-associated disease must be interventions on the prevention and use of antimicrobial agents implicated as risk factors for the disease. These interventions have been shown to be cost effective and successful in improving antibiotic prescribing to hospital inpatients. These interventions have also been shown to reduce antimicrobial resistance or hospital acquired infections. Guidelines to prevent and curtail AAD, and CDAD epidemics are presented in this article for this new era of virulent nosocomial and community acquired bacterial resistant infections.

Health care professionals continue to misuse and overuse more and more powerful antibiotics to treat self limiting viral infections and even the mildest URI and UTI. Kallen, et al have reported that Quinolones have surpassed sulfas as the most common class of antibiotics prescribed for urinary tract infections (UTI) in women which raises concerns about increasing resistance to this class of antibiotics (1).

Thus, constantly mutating bacteria evolve to become resistant to these antibiotics. Drug Resistant bacteria ("Super bugs") were initially detected in long-term care and rehab facilities (LTCF), then were found in acute care facilities and now are infiltrating into communities. One very well known result of this phenomenon is Methicillin resistant Staphyloccus Aureus (MRSA) which has become hyper-virulent and is now incriminated in the death of 12,000 patients annually. Methicillin resistant staphylococcus (MRSA) which caused problems primarily in health care facilities can now be increasingly found in the community, with more than half of MRSA infections currently of the community acquired strain. Some MRSA species, according to the CDC, also have acquired a cytotoxic gene (2). The role of toxin-producing *S. aureus* in cases of AAD needs further investigation. Ackerman, et al found toxin-producing *S. aureus* in some diarrheal patients (3). Community acquired MRSA (CA-MRSA) strains have also increased in Denver over a period of 2 years (4). Even the lay press (1/20/06 *Wall St. Journal*) announced that "a Drug-resistant staph, officially known as community-associated methicillin-resistant *S. aureus*, or CA-MRSA, that cropped up a few years ago, now has health officials concerned about an epidemic. In the most severe cases, it kills up to a quarter of those infected, often with great rapidity."

Antibiotic resistance has been developed by Clarithromycin-resistant genotypes of *H. pylori*. Three (3) point mutations at A2143G, A2142G, and A2142C are now also being reported to cause a decrease in the eradication rates of triple therapy against *H. pylori* (5).

Two current papers by McDonald, et al (6) and Loo, et al (7) point out that toxin producing *C. difficile* are also becoming more virulent.

Similar to the above infections, *C. difficile* infections are also increasing in frequency and severity. From 2000 to 2001, the rate of a hospital discharge diagnosis of *C. difficile*-associated disease increased by 26% (8). *C. difficile* infections are of increasing concern to many medical and surgical specialties-from the internist, hospitalist, intensivist, family practice, to the geriatrician and the pediatrician. The gastroenterologist is often consulted in the evaluation and management of patients who may have the entire spectrum of these disorders. This spectrum includes AAD, CDAD, which may be benign and self limiting after discontinuation of the antibiotic; *C. difficile* associated colitis or pseudomembranous colitis (CDAC) which is more serious and requires intensive therapy to prevent progression to toxic megacolon (TM) which often requires surgery.

These disorders result from introduction of toxin producing *C. difficile* spores to patients usually located at skilled nursing facilities (SNF's), long-term care and rehab facilities (LTCF) and other (acute) Health Care Facilities. This occurs primarily as a nosocomial infection, where exposure to antimicrobial drugs (the major risk factor for CDAD) and environmental contamination by *C. difficile* spores are more common (9).

C. difficile is a gram-positive, anaerobic, spore-forming bacillus that is indirectly spread by the fecal-

(continued on page 73)

(continued from page 68)

oral route through spores left on surfaces, and produces two cyto-toxins, A and B. Toxin A loosens the junctions of the epithelial cells that line the colon allowing toxin B to penetrate between the epithelial cells (10,11). This begins a cascade of tissue damaging inflammatory processes involving destructive leukotrines and cytokine release.

More virulent strains of *C. difficile* are causing epidemic disease of greater frequency and severity. The latter is indicated by higher rates of toxic megacolon, leukemoid reaction, shock, requirement of colectomy, and death (12–15). Loo, et al found that the overall mean incidence of CDAD was 22.5 per 1000 admissions (range, 10.2 to 39.9) during their study period. CDAD was the attributable cause of death in 117 of the 1703 patients (6.9 percent). The attributable mortality rate increased with age.

Fluoroquinolones (16), especially C-8-methoxy fluoroquinolones like moxifloxacin has been incriminated as the cause of 1 epidemic and gatifloxacin, its C-8-methoxy fluoroquinolone molecular relative has been identified as the cause of at least 3 separate CDAD epidemics in 3 different health care facilities. These epidemics of CDAD related to C-8-methoxy fluoroquinolones were stopped (17) by switching back to the original quinolones. It is thought that the enhanced anaerobic spectrum of the newer quinolones such as gatifloxacin has a more disruptive effect on the fecal flora.

The fact that CDAD occurs when the normal microbial barrier is altered by antibiotics, or rarely by cancer chemotherapeutic agents, suggests that some organism (or group of organisms) in the normal flora prevents colonization by *C. difficile*. This may be the Gm+ anaerobe *Bacteroides* which account for over 90 percent of the total number of bacteria in feces. These species disappear in many patients with CDAD & CDAC.

According to Bristol Meyers Squibb Prescribing information (1999 Princeton) Gatifloxin has "enhanced activity over many more anaerobic bacteria than is covered by Ciprofloxacin" and it also has (4–8×) stronger activity against GRAM + BACTERIA than Ciprofloxacin (18–20).

The 2005 PDR states that "Gatifloxacin is an 8-methoxyfluoroquinolone with in vitro activity against a wide range of gram-negative and gram-positive microorganisms. The antibacterial action of gatifloxacin results from inhibition of DNA gyrase and topoisomerase IV. DNA gyrase is an essential enzyme that is involved in the replication, transcription and repair of bacterial DNA. Topoisomerase IV is an enzyme known to play a key role in the partitioning of the chromosomal DNA during bacterial cell division."

It thus appears that the C-8-methoxy moiety was utilized to enhanced activity because of its lower selection of resistant mutants of gram-positive bacteria compared to the non-methoxy C-8 moiety (21).

But this "attribute" may reduce more *C. difficile* competitors in the normal bacterial GI flora and thus presumably can foster a greater overgrowth of toxin producing *C. difficile* in the gut.

Resistance determining regions of the bacteria are found at the DNA gyrase position (GYRA) when an amino acid is substituted in the GYRA gene. Perhaps *C. difficile* bacteria have thus unlocked the key to their survival as increased clonality of *C. difficile* is found with Gatifloxin which may likely be more resistant to the fluoroquinolones.

Hospital formularies which are often sensitive to financial costs strive to keep only 1 or 2 of the same family of drugs such as quinolones in stock. Many second and third generation antibiotics like fluoroquinolones cost less per treatment day than the older drugs. Therefore use of these drugs like gatifloxacin which are now on the preferred list of many hospital formularies leads to overuse of a "cannon to hit a fly" and result in more virulent strains of *C. difficile*.

The emergence of a previously uncommon strain of *C. difficile* that is more resistant and potentially more virulent than other strains indicates a need for intensified surveillance for *C. difficile*-associated diseases at emergency rooms and inpatient health care facilities. This is especially true for LTCFs in which the rate of acquiring *C. difficile* approaches 50% (22).

All health care facilities must closely track the incidence of CDAD, especially if a spurt of increased rates is noted.

We also need to remember that iatrogenic CDAD may occur by bodily insertion of a toxic strain of *C. difficile* by invasive body procedures and disruptions in normal gut bacteria.

These iatrogenic associated events include-Intubations e.g. enemas (RR = 3.26); Gastrointestinal stimulants (RR = 2.4); Common rectal thermometers (23), and/or removing the natural (i.e. acid) barriers to bacteria found in the stomach which prevents ingested *C. difficile* spores from entering the intestine. Gastric acid-suppressing drugs are implicated as being a risk factor for community-acquired CDAC (e.g. antacids (RR = 1.80); H_2-blockers, and PPI's proton pump inhibitors adjusted (RR = 2.9).

This was confirmed by Dial, et al (24) who reported that the incidence of *C. difficile* and risk associated with gastric acid-suppressive agent use has increased. The authors found that the adjusted rate ratio of *C. difficile*-associated disease with current use of proton pump inhibitors was 2.9 (95% confidence interval (CI), 2.4–3.4) and with H_2-receptor antagonists the rate ratio was 2.0 (95% CI, 1.6–2.7). An elevated risk was also found with the use of nonsteroidal anti-inflammatory drugs (NSAIDS) (RR = 1.3; (95% CI, 1.2–1.5).

Bliss, et al documented that hospitalized, tube-fed patients, especially those receiving post-pyloric tube feeding, are at greater risk for the acquisition of *C. difficile* and the development of CDAD than are hospitalized, non-tube-fed patients. Thus clinicians must regularly test for *C. difficile* in tube-fed patients with diarrhea (25).

Other risk factors of CDAD in addition to age >60 years, is the presence of co-morbidities, inter- institutional transfers, especially from LTCF's and prolonged hospitalization of patients plus the presence of any invasive device (e.g. central venous catheters). Additional major risk factors for increased CDAD severity are co-existing diseases of the vascular system, the heart, the kidneys and the lungs (26), plus co-incident malignancy, chronic obstructive pulmonary disease, immunosuppressive therapy, renal failure, and/or exposure to antiperistaltic medications (27).

Toxic megacolon (TM) is the much feared complication of CDAD. Gan, et al (28) has reported the incidence of TM as 0.4%–3% in patients with CDAC. The author also predicts that the current mortality of 30%-80% of TM will increase in proportion to the rapidly increasing prevalence of CDAD-indeed. . . "a dramatic doubling of overall incidence likely related to broad spectrum antibiotics."

Major precipitating factors of TM include antimotility agents, opiates, anticholinergics, antidepressants; possibly barium enema, and colonoscopy which may cause distention that further impairs the blood supply to the colon wall. However, this theoretical use should not prevent their appropriate use.

The most widely used criteria for the clinical diagnosis of toxic megacolon are: Radiographic evidence of colonic distension >6 cm. in the transverse; or ascending colon, accompanied by small bowel and gastric distention plus at least three of the following: Fever >38.6°C (101.5°F) Heart rate >120 beats/min, neutrophilic leukocytosis >10,500/mm, or anemia; AND at least one of the following: Dehydration, altered sensorium, electrolyte disturbances and/or hypotension.

When TM is suspected, prior to verification of diagnosis, limited sigmoidoscopy with minimal air insufflation may best help differentiate between infective causes such as CMV or Pseudo-membranous colitis (PMC), rather than complete colonoscopy, since the extent of the disease should not affect management.

Infection-control measures, including strict monitoring and contact precautions should immediately be instituted for all patients with suspected *C. difficile*-associated disease especially in long term care and rehab facilities (LTCF).

It is generally not appreciated that free standing clinics, medical offices and medical treatment given in home health care settings should have the same standard of infection control either by trained professionals or contracting with hospitals for the service. All health care workers must now receive more effective training in nosocomial infection prevention and control.

Because of the increasing rate of community acquired infections, surveillance of nosocomial infections, which is currently almost exclusively an inpatient activity must also be extended to the outpatient setting.

The Center for Disease Control is also warning that the spores of *C. difficile* are spread into the mouth from feces and are difficult to kill even with most conventional household cleaners. Alcohol based sanitizers do not eliminate all the spores (29). Thus, strict infection-control and prevention measures, as recommended by

(continued on page 76)

A SPECIAL ARTICLE

(continued from page 74)

the CDC should be enforced along with wearing gloves and frequent hand washing with soap and water when caring for a patient with CDAC (30).

CDAD should be suspected in any patient exposed to systemic antibiotics within the previous 2-3 months who is experiencing at least 3 watery or unformed stools/day for 2 days and/or abdominal pain. A single cup size loose watery specimen should be submitted for *C. difficile* cytotoxin assay; and if positive, treatment should begin immediately first with Metronidazole-(Flagyl) 500 mg PO tid for 10–14 days. The common side effects of Flagyl include nausea, headache, dry mouth, metallic taste. Rare side effects include pseudomembranous colitis, and pancreatitis.

Fecal excretion of *C. difficile* is transient in most patients, and prophylaxis with metronidazole is not effective in asymptomatic patients. Although treatment with vancomycin is temporarily effective in eliminating the organisms, it is associated with a significantly higher rate of *C. difficile* carriage two months after treatment and therefore, is not recommended as initial treatment (31).

Another reason vancomycin should not be used as the initial drug is to reduce vancomycin resistance. However, in critically ill patients, including those with severe immune deficiency disorders, the very debilitated, elderly, with significant co-morbidities, (alb <2.5 g/l, intensive care stay, etc.) one could start with oral vancomycin (32,33) at a dose of 125–250 mg PO qid for 10–14 days. Clinical improvement is usually seen within 2–4 days of initial treatment, and remission is usually seen in 7–10 days. A high leukocyte count and an elevated creatinine level are strongly associated with adverse outcomes.

After adjustment for age and other confounding factors, patients initially given oral vancomycin therapy have a decreased risk of progression to complicated CDAD—79% lower than the risk among patients initially treated with metronidazole alone (adjusted odds ratio 0.2, 95% confidence interval 0.06–0.8, p = 0.02) (34). Therefore, the recommendations are to use vancomycin in severe disease. Another approach in severely ill patients with *C. difficile* infection is evaluation of a course of metronidazole at a dose of 250 mg intravenously every 6 hours combined with vancomycin 500 mg orally every 6 hours for 10 days. In severely ill patients monitoring should be similar to that in a patient with severe ulcerative colitis with daily flat and upright films and increased abdominal x-ray and multiple visits each day. Monitoring should be close and a prompt surgical evaluation should be performed if signs of peritonitis or megacolon develop (sometimes heralded by a sudden decrease in frequency of stools).

Approximately 10%–20% of individuals treated for *C. difficile* infection have a relapse of *C. difficile* disease (RCDD). This is usually due to failure of the initial course of treatment to eradicate the organism from the bowels or reinfection from the environment. The recommended treatment for a relapse is another course of either metronidazole or vancomycin—whichever formerly succeeded. Wilcox, et al (35) showed that extended tapered or pulsed dosing regimens of vancomycin may result in a significantly better cure of RCDD.

In treating patients with CDAD Bricker, et al (36) reminds us of our two goals of therapy. The first is obviously improvement of the patient's clinical condition; the second is prevention of spread of *C. difficile* infection to other patients. Bricker believes teicoplanin is the best therapeutic choice. This was shown in a Cochrane database meta-analysis which evaluated nine randomized, controlled trials of antibiotic treatment of patients with *C. difficile*-induced diarrhea. They found that metronidazole, bacitracin, and fusidic acid were as effective as vancomycin, while teicoplanin was slightly more effective with a relative risk of 1.21 (95% CI 1.00–1.46). Unfortunately Teicoplanin is not readily available in the United States, but Rifampin has also been used in recalcitrant cases of antibiotic associated colitis (37).

Non-antimicrobial treatment of CDAC by binding the toxin with cholestyramine may also be effective in CDAC patients. Other toxin binding compounds have also been studied (e.g., GT160-246—an experimental Toxin Binding Polymer) and found more effective than cholestyramine—at least in animals used as models (38).

Spellberg (39) recommends that the U.S. Congress should give pharmaceutical manufacturers an incentive, in the form of tax breaks and other financial car-

(continued on page 78)

(continued from page 76)

rots, to get back into an intensive antibiotic R&D, since for economic reasons there is an empty pipeline in Drug company antibiotic production. Similarly all appropriate World and U.S. organizations (WHO; NIH, CDC and others) should make a concerted effort to push for a vaccine against these lethal toxins(s). In addition, the FDA should look again at other agents not currently used in the U.S., especially the only antibiotic—-Teicoplanin that has been shown to be a good choice for eliminating *C. difficile* by the 2005 Cochrane Data Base (40).

The Johns Hopkins group (41) has reported important extra colonic features in CDAD patients. These include small bowel involvement in those patients with previous SB surgery, and visceral abscess mainly in the spleen, but also found less commonly in pancreatic abscesses, reactive polyarticular arthritis, cellulitis, necrotizing fascitis, osteomyelitis, and prosthetic device infections.

Intensified efforts must be made for early diagnosis and treatment (42) of *C. difficile*-associated disease which since 1990 has been the most common nosocomial infection in North America and Europe.

Increased (43) risks are that CDAC may progress to severe colitis and toxic megacolon necessitating surgery if diagnosis and treatment is delayed. Cleary (44) reports that a delay in diagnosis, and/or the length of time from onset to treatment was most associated with mortality. In addition he reported that mortality is increased in patients who are elderly, are receiving immuno-suppressive therapy, or with underlying malignancies. Thus, early diagnosis and prompt, aggressive treatment are critical in managing CDAD/CDAC. Delay in treatment as well as inappropriate drugs given during the advanced phase of CDAC (i.e. anti-peristaltics, narcotics, etc) increase the potential for complications (45). Therefore avoid those medications that decrease bowel motility especially in patients with severe disease.

As for probiotics—-Dendukuri N, et al (46) believe that studies conducted up to date provide insufficient evidence for the routine clinical use of probiotics to prevent or treat CDAD. However, McFarland (47) in a recent meta-analysis concluded that a variety of different types of probiotics show promise as effective therapies for AAD and CDD. McFarland reported that *Saccharomces boulardi*, *Lactobacillus rhamnsus* GG and probiotic mixtures significantly reduced the development of AAD, but only *S. boulardi* was effective for CDD treatment.

Vasa, et al (48), found that although many non-infected patients in their study received no benefit by empiric metronidazole, they still believe that empiric metronidazole should immediately be utilized in strongly presumptive CDAD patients—-especially older patients with comorbid conditions, who cannot hemodynamically or otherwise tolerate diarrhea. Used judiciously, the authors believe that empiric therapy may more rapidly resolve symptoms, and could conceivably prevent/abate severe complications and nosocomial spread.

If the initial stool cytotoxin test is negative and symptoms persist despite withdrawal of antibiotics an additional 2 stool specimens are again submitted for stat toxin assay. If stool persistently tests negative for *C. difficile* toxin in a patient with fever, abdominal pain and diarrhea, stool cultures should also be done for the most frequently recognized enteropathogens (i.e., *Jejuni*, *Salmonella*, *Shigella* species, *E. Coli* O157:H7) and also for *S. aureus* and *Klebsiella oxytoca*, especially if there is a cluster of LTCF patients with these symptoms (49–51).

The following 10 additional recommendations for all Health Care facilities have been merged from the Healthcare Infection Control Practices Advisory Committee, the HICPAC/SHEA/APIC/IDSA, the CDC and the Healthcare Infection Control Practices Advisory Committee (HICPAC) and the Association for Professionals in Infection Control and Epidemiology. These 10 merged recommendations are:

1. The CDAD patient should be quarantined either in a special area or placed in a room alone or with another patient with *C. difficile*-associated disease.
2. Strict antiseptic procedures should be followed by health care workers in contact with the patient utilizing disposable gloves, mask and gown. Because alcohol is ineffective in killing *C. difficile* spores, health care workers must frequently wash their hands with soap and water, rather than with alcohol-based waterless hand sanitizers, especially when caring for CDAD patients (52).

3. Patient-care equipment (such as blood-pressure cuffs, stethoscopes, thermometers etc.) should either be used only for the infected patient or cleaned well before it is used for another patient (53).
4. Enhanced environmental cleaning with dilute bleach should be used to eliminate *C. difficile* spores (54) from all patient contact surface areas on a regular schedule. These spores may remain on infected surface areas for months or even years (55).
5. A very important method of controlling outbreaks of *C. difficile*-associated disease should be restriction of the use of antimicrobial agents implicated as risk factors for the disease (56) Davey, et al (57) documented that interventions to improve antibiotic prescribing to hospital inpatients are successful, and they can reduce antimicrobial resistance or hospital acquired infections.
6. Because fluoroquinolones have become a mainstay in the treatment of several common infections, a large-scale restriction of the use of these drugs would be quite difficult. Perhaps the first focus should be on those 2nd and 3rd generation quinolones like gatifloxacin and moxifloxacin which should be removed from the pharmacy "preferred list of quinolones."

   At least one additional incentive to limit gatifloxacin use is the observation by Park-Wyllie L.Y, et al (58) that as compared with broad-spectrum oral antibiotics—including other fluoroquinolones—the use of gatifloxacin among outpatients is associated with an increased risk of in-hospital treatment for both hypoglycemia and hyperglycemia especially in older adults.
7. Effective surveillance for Antibiotic- Resistant Bacteria and CDAD must be intensified in every Health Care setting—-especially in LTCFs. All of these facilities must have easy lab access for prompt and active surveillance culturing plus *C. difficile* cyto-toxin testing—-both A and B—-at the earliest indication of an any infection or CDAD (59). In addition, Furuno, et al (60) advises that those patients at higher risk for carriage of Antibiotic-Resistant Bacteria should be identified early for active surveillance, targeting-culturing for MRSA and Vancomycin Resistant Enterococci (VRE); i.e. patients who have had (self reported) antibiotics or previous hospital admissions within the past year. The authors found that this was very cost effective and saved a projected $19,000–$26,000 compared with non-directed, hospital-wide screening for resistant organisms (of MRSA and VRE),during an 8 month study period in their tertiary care facility.
8. Though anaerobic culture of the *C. difficile* organism is the most sensitive test it takes 3–5 days and it cannot differentiate between toxigenic and non-toxigenic strains. The cytotoxicity assay for toxin B is the most specific test available (99%), and it has a high sensitivity as well (94%–100%). But, this too takes too long to perform (1–3 days), is expensive, and requires facilities equipped for tissue culture assays. So given the cost and complexity of culture and cytotoxicity assays, most laboratories rely on tests for toxin A detection only and also because Enzyme immunoassays are available at lower costs with more rapid results—4 hours—(sensitivity (60%–90%) or specificity (75%–100%).
9. While testing of a single diarrheal stool is generally sufficient to make the diagnosis of CDAD in most instances it can miss a substantial portion, therefore 3 stools should be submitted. Testing should be performed on loose stool specimens only. If CDAD is suspected despite negative initial testing, submission of multiple specimens and sigmoidoscopy should be considered; and check to verify that your lab is testing for both A and B toxins.
10. SHEA recommendations for the management and control of *C. difficile* in health care facilities and LTCFs include these above measures along with effective surveillance by regular and frequent testing of residents with antibiotic-associated diarrhea or acute diarrheal illnesses not explained by other causes and alerting other similar facilities in the area of any increased rates of detection.

These recommendations will serve as the foundation for attempting to decrease and control this iatrogenic disease.

SUMMARY AND CONCLUSIONS

Over 15 years ago Thibault, et al (61) suggested that control of nosocomial *C. difficile*-associated diarrhea would be attained by minimizing the administration of all antibiotics, avoidance of high-risk antibiotics, and having a high index of suspicion of CDAD in patients who develop diarrhea especially after gastrointestinal surgery.

As John Bartlett states (62), "Particularly important is antibiotic stewardship with restraint in the use of epidemiologically implicated antimicrobial agents, usually second- and third-generation cephalosporins, clindamycin, or fluoroquinolones, or a combination of the three."

Until we implement the above practices we can continue to expect outbreaks, if not epidemics, of bacterial resistant CDAD and other bacterial resistant infectious diseases. ■

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