

SOCIETY OF INFECTIOUS DISEASES PHARMACISTS



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PRESIDENT'S COLUMN

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Wow! As my term as President of SIDP comes to a close, I've reflected on the many events that have happened within the Society over the past year. Many have happened behind the scenes; most reflect the dynamic process of maintaining a relatively small organization with volunteer officers and committee members, as well as with limited full-time staff. The year was "culminated" by the postponement of ICAAC due to the devastation caused by Hurricane Katrina, which required drastic alterations in our Annual Meeting format. However, overall it has been a great year, and I look forward to working with the Board members as Past-President for another year.

The past year was highlighted by a number of successes. We were able to offer an additional SIDP-sponsored residency this year; in addition to an SIDP Infectious Diseases Pharmacotherapy residency (awarded to Doug Slain, Pharm.D.), we received funding for an HIV Pharmacotherapy Residency (awarded to Mike Postelnik, MS). In the upcoming year, we hope to acquire funding for **three** residencies.

We were able to increase our number of funded SIDP Research Awards this year to **four**, and increased the total amount awarded to \$20,000 per proposal. See the Announcements section of this newsletter for the Award recipients. We also had two SIDP members complete SIDP-sponsored "minisabbaticals"- Dave Burgess, PharmD and Vincent Tam, PharmD. We anticipate equal or greater funding next year.

Under the guidance of Tom Hardin, President-Elect, the Board moved to transfer a large portion of the Society's assets from a money market account to a balanced investment portfolio. This will allow us to substantially increase our investment income. In addition, we have implemented an online means of dues payment that avoids excessive paperwork, snail mail and check writing. Finally, as you can see, our newsletter has been converted to an electronic format, which allows us to increase the scientific content of the newsletter.

SIDP is actively collaborating with the Centers for Disease Control and Prevention to create a three-part online continuing

education program for hospital pharmacists. This program will assist pharmacists who wish to improve antimicrobial prescribing within their institutions to prevent and/or combat resistance. SIDP members have formed three committees and drafted presentations. Committee chairs are Mike Klepser, PharmD, Roger White, PharmD, and Mike Rybak, PharmD. The draft presentations were presented to a focus group of pharmacists at ASHP's Midyear Clinical Meeting in Las Vegas. We hope to finalize the program soon, and offer it to pharmacists beginning this summer.

Unfortunately, we have experienced some challenges this year as well. Our Membership Committee has continued to be frustrated with the delays in processing new member applications and renewing existing memberships. We have successfully merged the member databases used by the SIDP website and by SIDP's management company, AAMS. We are working to streamline the application process and convert it to an online format. Finally, we are considering a bylaws change that would simplify the application process by requiring fewer application materials.

Recently, I was informed by Chilton Roberts, Executive Director of AAMS, that he will be closing his company. This means that SIDP must find a new management company as soon as possible. Tom Hardin, President-Elect, is actively working on this and we hope to make an announcement on a new management company soon.

Finally, no outgoing President's letter would be complete without many sincere Thank You's. Space does not permit me to include everyone, but let me try. First, Thanks go to the SIDP Board Members- Doug Fish, Alice Pau, Peggy McKinnon, Dave Nix, and Tom Hardin- who were always available, willing to offer assistance, and were essential in their roles as committee liaisons. Thanks also to the Committee Chairs- Erik Sahloff (Publications), Jim Scott (Annual Report), Patrick Clay (Internet), Rob Owens (Newsletter), Ronda Akins (Elections), Melinda Neuhauser (Government Affairs), Rose Jung (Membership), Marianne Billeter (Program), Dave Bearden (Recognition), and Paul Gubbins (Research Awards). All of them worked incredibly hard and were invaluable in their contributions. In addition, a special thanks to Glenn Crocker, SIDP "webmaster", who REALLY knows how to get things done.

Funding, funding, funding- where would we be without the generous support of our pharmaceutical company partners? I hope you will join me in thanking them for their contributions to SIDP's ongoing successes: Pfizer Pharmaceuticals (Bill Jochimsen- Research Awards); Wyeth Pharmaceuticals (Craig Engesser and Laura Telepun- Research Award and Annual

Meeting); Janssen-Ortho-McNeil (Kim Evanyo- Residency and Annual Meeting); Abbott Virology (Roula Qaquish- Residency); Elan Pharmaceuticals (Rolf Wagenaar- Annual Meeting); Bio Merieux (Kevin Rivers- Minisabbaticals); Oscient Pharmaceuticals (Julie DeAngelis- Annual Meeting); Cubist Pharmaceuticals (Todd Krueger- Annual Meeting); and Vicuron Pharmaceuticals (Todd Lewis- Annual Meeting). We hope to continue to partner with these companies, as well as create new relationships with others.

Finally, I wish to thank YOU, SIDP's membership- for your support, your passion, your expertise, and- sometimes- your patience. Please support Tom Hardin as he assumes the role of President, and feel free to call on me if I can ever be of assistance.

Fall/Winter Member Achievements December 2005

Daryl D. DePestel, Pharm.D., Clinical Assistant Professor of Pharmacy at the University of Michigan Health System was elected as the Chair-Elect of the ACCP ID-PRN.

Marnie Jones, PharmD., Clinical Pharmacist in HIV at the Brody School of Medicine at East Carolina University was among 7 pharmacists recognized nationally with an HIV Leadership Award by TheBody.com Organization.

Sharon M. Erdman, Pharm.D., Clinical Associate Professor of Pharmacy Practice at Purdue University, was awarded Teacher of the Year - Second Year Basic Science, Class of 2007, at the Loyola Stritch School of Medicine.

Bob Rapp, Craig Martin and colleagues from the University of Kentucky were among those given American Society of Health System Pharmacists "Best Practice Award for 2004" for their submission: "Improving Antimicrobial Use at a University Hospital: Results of the First Five Years of a Multidisciplinary Antimicrobial Management Program."

Douglas Slain, Pharm.D., BCPS was promoted to Associate Professor with tenure at West Virginia University.

Congratulations to the following recipients of the 2005 SIDP Recognition Awards:

Young Investigator

Scott Penzak, Pharm.D.
National Institutes of Health

Practitioner of the Year

Craig A. Martin, Pharm.D.
Infectious Diseases Pharmacy Specialist
Assistant Professor
University of Kentucky Chandler Medical Center

Impact Paper of the Year

Angela D.M. Kashuba, Pharm.D.
Associate Professor, School of Pharmacy
University of North Carolina at Chapel Hill
"Combining fosamprenavir with lopinavir/ritonavir substantially reduces fosamprenavir and lopinavir exposure: ACTG protocol A5143 results." AIDS 2005;19(2):145-52.

2005-2006 SIDP Research Awards

Sarah Robertson, Pharm.D.
National Institutes of Health
"Association of efavirenz metabolism and CYP2B6 genotype".

George P. Allen, Pharm.D.
Oregon State University
"In Vitro Evaluation of Resistance Induction in Community-Associated Methicillin-Resistant *Staphylococcus aureus*".

Manjunath (Amit) Pai, Pharm.D.
University of New Mexico
"Pharmacodynamic evaluation of flucytosine, voriconazole, and micafungin in an in vivo model of *Candida albicans* infective endocarditis".

Rose Jung, Pharm.D.
University of Colorado HSC
School of Pharmacy
"Evaluation of efflux pumps in multidrug-resistant *Pseudomonas aeruginosa*".

Clostridium difficile-Associated Disease:

An Emerging Threat to Patient Safety

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Key Words.

Clostridium difficile, antimicrobial stewardship, adverse events

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Abstract. A formerly infrequently isolated strain of *Clostridium difficile* known as "BI/NAP1" has resulted in geographically diverse outbreaks of *C. difficile*-associated disease. Such a rapid dissemination and distribution of an outbreak strain of *C. difficile* is unprecedented with many regions across North America being affected, as well as several countries in Europe, all in such a short period of time. Also of note is that non-traditional hosts have been reported with severe disease (e.g., otherwise healthy, non-institutionalized persons residing in the community, some without antimicrobial exposure). Data suggest that certain virulence characteristics may be responsible for more severe clinical presentations and poor outcomes. These factors (e.g., hypertoxin production, hypersporulation, antimicrobial resistance) possessed by a previously uncommon strain of *C. difficile*, in conjunction with particular host factors (impaired immune response to certain

C. difficile toxins) and environmental factors (popularity of alcohol hand rubs, use of non-sporocidal hospital cleaning agents) may have precipitated the now widespread establishment of this pathogen. Antimicrobial intervention has traditionally been a mainstay of combating *C. difficile*-associated disease. Efforts to combat BI/NAP1 should include good antimicrobial stewardship in addition to effective infection control and environmental intervention. **Introduction**

The organism first termed *Bacillus difficilis* in the mid-1930s, and now known as *Clostridium difficile*, continues to evolve into a formidable pathogen. *C. difficile*-associated disease (CDAD) has traditionally ranged in presentation from self-limiting diarrhea to fulminant life-threatening disease. Of considerable interest is the observation that CDAD appears to be increasing worldwide in both incidence and severity of disease.^{1,2} Reasons for this are not entirely clear, are most likely very complex and interwoven, and may be due in part to the emergence of a previously uncommon strain of *C. difficile*.³ To better understand the implications of recent findings, it is fundamental to appreciate the fact that the risks for CDAD are complex and consist of exposure to toxigenic strains of the organism,⁴ prior use of any antimicrobial agent,⁵ perhaps compounded by the prior use of antimicrobials that are specifically inactive or have borderline activity against *C. difficile*,⁶ exposure to gastric acid suppressants,⁷ poor host serum immunoglobulin levels,⁸ advanced age,⁹ and severity of underlying illness of the host.⁹ The sequence of these events is important for acquiring CDAD: 1) exposure to antimicrobials, 2) exposure to toxigenic strains of *C. difficile*, and 3) the presence of additional factors mentioned above.⁹

The organism responsible for the recently reported outbreaks in North America and Europe has been labeled BI/NAP1 and is distinguishable from previously identified outbreak (J-type) strains from the late 1980s and early 1990s.¹⁰ The BI/NAP1 strains of *C. difficile* produce greater amounts of toxins A (TcdA) and B (TcdB),¹¹ carry an additional clostridial toxin termed a binary toxin,³ belong to toxinotype III,³ have an increased sporulation capacity,¹² and are fluoroquinolone resistant.³ These characteristics differentiate BI/NAP1 from traditional *C. difficile* strains.

In addition to the identified changes in the pathogen, certain augmenting host and environmental factors may also be to blame. These include the fact that traditional hand washing with soap and water in hospitals has shifted to the preferential use of alcohol-based hand hygiene products in many institutional settings over the last five to ten years (alcohol is ineffective against *C. difficile* spores),¹³ and our traditional hospital cleaning agents (quaternary ammonium based products) do not kill *C. difficile* spores. In fact, quaternary ammonium-based cleaning agents have been shown to substantially increase the sporulation capacity of *C. difficile*.¹² The greater severity of disease attributable to BI/NAP1 in combination with these environmental risk factors may be contributing to a cycle that has led to *C. difficile* outbreaks on at least two continents.

Both clinicians and health care administrators alike are concerned with the changes in the *C. difficile* landscape. In addition to the notable consequences of CDAD, this disease is burdening already taxed health care resources. For example, patients with CDAD have been shown to incur 54% greater costs and remain hospitalized for an average of 3.6 days longer than patients who do not develop CDAD during hospitalization.¹⁴ And because of changes in environmental cleaning policies required during outbreak scenarios, additional expenditures to equip environmental services departments to prepare and handle 10%

sodium hypochlorite (bleach) solutions or to purchase expensive commercially pre-prepared hypochlorite-based products are required. Moreover, patients in acute care facilities with CDAD need to be isolated or cohorted which may cause significant financial challenges related to bed management. This was exemplified best by ministry officials in Quebec directing 20 million dollars into hospital infection control resources and infrastructure changes to contain CDAD after more than 100 people died over a short period of time.¹⁵ The purpose of this review is to provide an update regarding what has been learned about the emerging epidemic strain of *C. difficile*, followed by a practical review of one institution's challenges related to its presence.

The Changing Epidemiology of CDAD

Incidence. The National Nosocomial Infections Surveillance (NNIS) system has reported an increasing trend in CDAD rates over the last two decades.² In addition, McDonald and colleagues¹⁶ reported a 26% relative increase in 2001 over 1998-2000 in the annual proportion of discharges from non-federal United States (U.S.) hospitals with CDAD listed as any discharge diagnosis. Although a recent study performed at Prevention Epicenter Hospitals suggested no increase in CDAD rates between 2000 and 2003,¹⁷ their mean hospital-wide rates of 12.1 cases per 10,000 patient-days or 7.4 per 1,000 hospital admissions was 2-6 times greater than that reported from the NNIS system hospitals from 1987-2001² and teaching hospitals during the same period.¹⁸ Regardless of national rates that appear to be increasing, it is of utmost importance to monitor rates locally.

Severity. In 2000, reports from the University of Pittsburg noted increased CDAD incidence and severity as indicated by a doubling of disease rates along with an increased number of colectomies and deaths.^{19,20,21} In Canada, most notably the Sherbrooke region within Quebec, a CDAD outbreak attributable to BI/NAP1 has resulted in excess mortality. Pepin and colleagues²² reported that 30-day mortality rates were 3-fold higher if CDAD complicated a patient's admission in a matched case-control study. Additionally, prolonged hospitalizations, relapses, and readmissions also characterized infection with *C. difficile* during this outbreak. Recently, reports of severe CDAD have surfaced in previously low risk populations (otherwise healthy persons living in the community) in a four-state region.²³

The Pathogen (BI/NAP1)

BI/NAP1 has contributed to outbreaks in several regions of North America, the United Kingdom, and the Netherlands. It is identified and referred to as ribotype 27 (CD027), by pulse field gel electrophoresis (PFGE) as North American pulse field type 1 (NAP1), by restriction enzyme analysis (REA) as group BI, and by toxinotyping studies as toxinotype III.³ Because various publications may refer to the strain by different terms (e.g., NAP1/027, BI/NAP1), it is important to note that they are referring to the same strain. This current outbreak strain is distinct from those causing previous outbreaks in the late 1980s/early 1990s, known as the J strain (REA type J7/9).¹⁰ As previously mentioned, notable virulence characteristics associated with the BI/NAP1 strains include increased toxin production (TcdA and TcdB),¹¹ the presence of a binary toxin,³ altered antimicrobial resistance patterns (fluoroquinolone resistance),³ and increased sporulation capacity.¹²

Increased Toxin Production. TcdA has been termed "the enterotoxin" (responsible for the expression of diarrhea and colonic inflammation), and TcdB "the cytotoxin" (responsible for actinomorphic changes in tissue culture cells).²⁴ In all but rare cases,

both toxins are expressed in patients with clinical disease; however, TcdA-negative, TcdB-positive strains have been identified.²⁵ TcdA (308 kDa) and TcdB (270 kDa) are amongst the largest toxins to be harbored by bacteria and are encoded on a chromosome within the pathogenicity locus (PaLoc) of the organism. Also located within the PaLoc are regulatory genes such as *tcdC*, which is a downstream negative regulatory gene that controls the expression of TcdA and TcdB. All identified BI/NAP1 strains contain an 18 base pair *tcdC* gene deletion³ that is thought to be responsible for the accelerated kinetics of toxin production recently as described by Warny and colleagues.¹¹ Traditionally, TcdA and TcdB are produced most efficiently when the organism is in stationary growth phase.²⁶ In contrast, BI/NAP1 strains produce 16-times more TcdA and 23-times more TcdB and studies indicate that the majority of this production occurs in logarithmic growth phase (**Figures 1A and 1B**).¹¹

Binary Toxin. In addition to the well-characterized TcdA and TcdB, a formerly uncommon binary toxin has been identified in all of the BI/NAP1 isolates (previously found in approximately 6% of clinical isolates).³ The structure and function of this toxin is similar to that of other binary toxins, such as iota toxin found in *C. perfringens*. Though patients infected with binary toxin positive strains of *C. difficile* trended towards having greater disease severity,²⁷ TcdA and TcdB negative but binary toxin positive strains of *C. difficile* have been shown to be non-pathogenic in classic non-clinical models of infection.²⁸ Thus, the pathogenic role of binary toxin in BI/NAP1 is currently unknown.

Toxinotyping. *C. difficile* strains can also be classied by toxinotyping studies. Subtle sequence variations within the PaLoc accounts for the various toxinotypes of *C. difficile*, of which there have been reported to be at least 22 different types.²⁶ Toxinotype III, to which BI/NAP1 belongs, was previously rare, accounting for only 2-3% of clinical isolates.¹¹ Whether toxinotyping can be used to distinguish virulence potential among strains has yet to be demonstrated.

Sporulation Capacity. It has been shown that genotypically distinct strains of *C. difficile* demonstrate a propensity to hypersporulate and have been reported to be responsible for previous outbreaks.²⁹ BI/NAP1, like other outbreak strains, has demonstrated the capacity to hypersporulate compared with other non-outbreak strains (**Figure 2**).¹² This putative virulence characteristic may be, at least in part, responsible for its rapid establishment in many institutions where outbreaks have been reported. As with the other recently identified characteristics of this organism, future studies are required to elucidate the exact role of hypersporulation in the transmission or pathology of *C. difficile*.

The Environment

It has been pointed out by experts that blaming antimicrobial agents alone is too simplistic and that people often forget about the source of the bacterium.³⁰ Both symptomatic and asymptomatic patients with *C. difficile* shed vegetative forms of the organism and spores into the environment.⁴ *C. difficile* spores may persist on surfaces for years and remain a problematic source of environmental contamination and infection.³¹ Although intuitive, it has been demonstrated that as levels of environmental contamination increase, so does the prevalence *C. difficile* found on the hands of health care workers.³² Thus, susceptible patients may acquire the organism either directly from the hands of health care workers or circuitously from the environment.

Disease Severity. Among the factors that may be contributing to outbreaks of CDAD is the increased severity of disease associated with BI/NAP1. Greater frequency of diarrhea, surgery requirements, and recurrences would at least theoretically lead to an advantageous scenario for the establishment of the organism into the environment. In concert with hypersporulation characteristics, BI/NAP1 appears to be ideally suited for widespread dissemination and survival.

Alcohol-Based Hand Hygiene Products. The use of alcohol-based hand hygiene products in place of hand washing with soap and water in health care settings has become common and may be playing a role in seeding *C. difficile* in the environment. Alcohol is not sporicidal and is not efficient in removing *C. difficile* from ones hands. In fact, it was reported that an average 36% (range 18-60%) of the initial inoculation of *C. difficile* spores on a contaminated hand could be transferred by handshake after using commercially available alcohol gels.³³ In contrast, the mechanical action of hand washing in a sink with soap and water for a specified period of time has proven to be effective in removing *C. difficile* from the hands of health care workers.^{13,34} To be clear, hand washing is defined as a scrub with chlorhexidine soap and water in an effort to remove skin oil (which harbors spores), followed by proper hand-drying with a disposable paper towel.³⁵ The time period for handwashing is at least thirty seconds, although the exact period of time required for optimal efficacy of this procedure is not clear. The CDC recommends substitution of alcohol-based hand rubs with hand washing using soap and water during outbreak situations.³⁶ Alcohol-based products do remain highly effective against non-spore forming organisms, are a vital part of increasing hand hygiene compliance in health care settings and should not be abandoned for these reasons.

Hospital Cleaning Agents. As common detergents used in hospitals to clean patient rooms are not sporicidal, the intervention of using a 10% sodium hypochlorite solution has resulted in significant reductions in CDAD cases as well as environmental spore burden.^{37,38} This same solution can be used to clean areas in the patient's home to kill *C. difficile* spores and should be used to minimize the potential for reinfection. One part of containing the spread of *C. difficile* during an outbreak is proper environmental disinfection. Replacing standard hospital cleaning agents such as quaternary ammonium-based products with 10% sodium hypochlorite solutions in the affected units (or universally) appears to be an effective intervention.³⁸ While manually prepared and diluted standard 1:10 sodium hypochlorite solutions are relatively inexpensive, they have the potential to be more noxious to environmental services employees, nursing staff, and patients, and require additional labor resources for daily preparation. Commercially available pre-prepared hypochlorite-based cleaning agents, such as the disinfecting agent Dispatch® (Caltech Industries, Inc., Midland, MI), are easier to prepare and administer to surfaces in a less noxious manner, but are significantly more expensive to purchase. In addition, their impact on the sporulation of *C. difficile* may be in question.¹²

The Host

A variety of host-related variables influence the development of symptomatic CDAD that include immunity, age, exposure to antimicrobials, and possibly gastric acid suppression. Like environmental risk factors, these variables may provide opportunities for intervention for reducing the risk of *C. difficile* infection.

Immunity. Patients in whom an immune response (circulation of antitoxin A IgG antibodies) cannot be properly mounted are more susceptible to recurrent CDAD.³⁹ In fact, patients that develop serum anti-toxin A IgG titers in response to colonization with *C. difficile* have been shown to be 48-times less likely to develop diarrhea than those who do not mount a response.²⁴ As a corollary, older age has been associated with CDAD and is a plausible risk owing to the senescence of immunity.⁴⁰ However, Pepin and colleagues⁴¹ also noted that age was confounded by other variables. For instance, older patients tended to have more comorbid conditions that led to longer hospitalizations. Because of the strong association between poor immune response and developing clinical disease, immune-based therapies including both active and passive immunization strategies are among the most promising treatment and prevention modalities for the future.²⁴

Antimicrobial Use. All antimicrobials (including certain chemotherapeutic agents) are viewed as inciting agents of CDAD; however, some agents may pose greater risks than others. Proposed variables that may augment risk include extended durations of antimicrobial use, use of antimicrobials with anti-anaerobic activity, as well as exposure to agents lacking in-vitro activity against the infecting strain of *C. difficile*. Prolonged exposure to antimicrobials further increases the risk for developing CDAD;⁴¹ thus, shorter durations of treatment should be employed where data exist (e.g., urinary tract infections, ventilator-associated pneumonia, intra-abdominal infections) as well as being vigilant about stopping therapy when the infection has been adequately treated or infection has been ruled out. One should remember that even single-dose administration of prophylactic antimicrobials has also been implicated in inciting CDAD.⁴¹ It has been proposed that antimicrobials with activity against anaerobes may result in greater risks for CDAD than those drugs lacking anaerobic activity;⁴² however, this theory has not been supported by quality evidence.^{43,44} For example, antimicrobials with potent activity against anaerobes such as piperacillin/tazobactam have been suggested to be protective against CDAD or at least minimally offensive,⁴⁵ while fluoroquinolones lacking activity against anaerobes (e.g., levofloxacin, ciprofloxacin) have been strongly implicated in well-conducted studies.^{20,41, 46, 47}

A case-control study at our institution conducted over a two-year period during the beginning of our outbreak attributed to BI/NAP1 evaluated risk factors for CDAD.⁴⁸ We matched each consecutive symptomatic CDAD case patient with two control patients based on date of hospital admission, admission unit, age, and gender with all other variables (e.g., days at risk, previous gastrointestinal surgery, exposure to gastric acid suppressants, presence of feeding tube, and severity of illness assessments using the Charlson Comorbidity Index and the Horn Index) being controlled for using multivariable analysis. The following risk factors were identified (relative risk, *p* value), cephalosporins (14, 0.007), macrolides (5.51, 0.035), vancomycin (4.18, 0.009), and fluoroquinolones (3.19, 0.006) as independent antimicrobial exposure risk factors for CDAD on multivariable analysis. Proton pump inhibitor use (2.89, 0.006) and the presence of a feeding tube (10.6, 0.002) were found to be non-antimicrobial risk factors for developing CDAD. Interestingly, cephalosporins were associated with the greatest risk (relative risk = 14, *p*<0.007), clindamycin was not identified as a risk factor (similar to the findings of Loo and colleagues⁴⁷, the majority of our strains were clindamycin susceptible), and differences in risks between fluoroquinolones based on in vitro potency against anaerobes or primary route of elimination (e.g.,

renal versus hepatobiliary/gastrointestinal) could not be distinguished. Furthermore, an evaluation of comparative clinical studies (phase II-IV) of more than 21,000 patients, including hospitalized patients enrolled in the U.S. and Canada, did not reveal differences in CDAD between the anti-anaerobic fluoroquinolone, moxifloxacin, and comparators.^{49,50} A recently published double-blind, randomized controlled trial evaluating the safety of moxifloxacin versus levofloxacin in hospitalized elderly patients with community-acquired pneumonia also revealed no differences in CDAD rates between moxifloxacin (1/195, 0.5%) and levofloxacin (6/199, 3.0%).⁵¹

Finally, and more plausibly, exposure to antimicrobials that lack activity against *C. difficile* has been shown to be a risk factor for CDAD.⁶ This is thought to occur secondary to the selective survival advantage provided by the antimicrobial, resulting in intestinal overgrowth of *C. difficile*. Based on this, one of the few proven formulary interventions to curb CDAD rates in hospitals was accomplished by restricting clindamycin use during an outbreak of clindamycin-resistant *C. difficile* strains.⁵² Because clindamycin seems to have a unique, prolonged effect on intestinal flora resulting in an extended susceptibility window for CDAD acquisition, perhaps the success of this formulary intervention cannot be extrapolated to other antimicrobials. The implications of BI/NAP1 being fluoroquinolone-resistant may mean that the use of this entire class of antimicrobials should be reserved or perhaps restricted during outbreak settings.³ Indeed, because BI/NAP1 resistance is uniform to all fluoroquinolone class members tested, no advantage can be gained by using one preferentially over another. For many common respiratory tract infections, the abolishment of fluoroquinolone use seems impractical as it would only lead to the increased use of other *C. difficile* precipitants such as the cephalosporins.

Ultimately, evaluating risk factors for CDAD has been inherently difficult due to the numerous and complex relationships between variables. In fact, most studies have failed to adequately address important confounding variables resulting in serious threats to the validity of their findings.⁵³ Since the published critique of past CDAD risk factor ascertainment studies,⁵³ several studies have been presented or published that are better designed to assess risk.^{20,41,48} However, one of the chief difficulties in risk factor ascertainment studies for CDAD that remains is the fact that many patients have received multiple antimicrobials in the past 6-8 weeks prior to developing CDAD, further complicating the ability to assign blame to a particular agent. Also, due to the retrospective nature of their study design, it is difficult to obtain a completely accurate outpatient antimicrobial history. And the more commonly used antimicrobials can be more commonly implicated in CDAD, as highlighted by the case of the fluoroquinolones. Thought of previously as "low-to-moderate" risk antimicrobials, these agents are now used with greater frequency in many geographies and have been more commonly identified as risk factors for CDAD.^{20,41} Thus, the issues related to assigning risks to antimicrobials for precipitating CDAD are complex. It is therefore difficult to support a single unifying theory that describes an antimicrobial's comparative risk for causing CDAD (e.g., possessing or lacking anti-anaerobic activity) based on the current published evidence. More research is needed to properly delineate the complex interrelationship between antimicrobial use and the other risk factors that contribute to CDAD.

Although practical considerations prevent us from knowing susceptibility data for *C. difficile* strains to a broad range of antimicrobials at our institutions, and whether or not antianaerobic activity deserves further attention or not, it is clear that interventions directed toward optimizing antimicrobial use are beneficial for reducing CDAD rates. This was demonstrated by the findings from a recent systematic review performed by the Cochrane group on interventions to improve antibiotic prescribing practices among hospital inpatients.⁵⁴ Accordingly, it is imperative that antimicrobials be used in a more discriminating manner as patients may develop life-threatening CDAD as a side effect of your treatment decisions.⁵⁵

Gastric Acid Suppression. It is well known that the suppression of gastric acid can increase host susceptibility to infection and has been documented as a risk factor for a variety of infections that include travellers' diarrhea, salmonellosis, cholera, as well as ventilator-associated pneumonia.⁷ Dial and colleagues⁷ used cohort and case-control study designs to determine whether or not exposure to proton pump inhibitors (PPIs) was an independent risk factor for CDAD. Multivariable analyses revealed statistically significant adjusted odds ratios (95% confidence interval) of 2.1 (1.2-3.5) and 2.7 (1.4-5.2) in the two studies identifying PPI use as a risk factor for CDAD. The use of gastric acid suppressants has also been associated with the development of community-acquired CDAD.⁵⁶ Others have also implicated the use of PPIs as an independent risk factor for CDAD,^{57,58} while one study did not find an association.⁴¹ In our institutional outbreak attributed to BI/NAP1, PPI exposure was determined to be an independent risk factor for CDAD after correcting for confounders.⁴⁸ Future prospective studies of this association are warranted; however, given the current evidence, it seems logical to increase our vigilance regarding the stewardship of PPI use.

Our Experience

The previous sections described what has been learned about the epidemic strain of *C. difficile* known as BI/NAP1. In the following sections, various challenges we faced related to the discovery and management of BI/NAP1 at our 600-bed community teaching hospital will be discussed. Although some of the issues discussed below may be common sense to the erudite reader, we were (and continue to be) surprised by our observations in the clinic. In 2002 as a part of our Antimicrobial Stewardship Program's daily review of antimicrobial therapy, we began to notice an enormous variability in the treatment of CDAD along with the introduction of non-evidence based practices in the treatment of CDAD at our institution (oral vancomycin plus oral metronidazole, extended durations of therapy beyond 10-14 days, "prophylaxis" with metronidazole for patients receiving antibiotics, donor stool transplantation, formulary requests for probiotics, cholestyramine use). Unaware of a simultaneous investigation by the CDC at other hospitals in the U.S., we requested that our laboratory culture clinical isolates of *C. difficile* for the purposes of susceptibility testing by a notable expert in this field. The chief reason for doing this was that the previous outbreaks caused by "J-type" strains had been controlled by restricting clindamycin; the caveat being that the J-type strains were uniformly clindamycin resistant. To our disappointment, our isolates were clindamycin susceptible thus removing a simple formulary change from our quiver of countermeasures; furthermore, the organisms tested were of a previously uncommon type. Serendipitously, we found ourselves in the midst of an outbreak due to BI/NAP1.³ Combined efforts between the CDC, Dr. Gerding's laboratory, and others established newly identified characteristics of this

previously uncommon strain of *C. difficile*.³ We continued our antimicrobial stewardship efforts and worked with our colleagues in infection control, environmental services, and hospital administration to address environmental issues. Realizing that CDAD management guidelines had not been updated in nearly a decade, we collaborated with the departments of gastroenterology, surgery, pharmacy and infectious diseases to establish evidence-based treatment guidelines to address our current situation in the new era of BI/NAP1. We developed local guidelines in part because of the rash of non-evidence based strategies being employed. We reviewed the literature and consulted with experts in the field which resulted in our final product. (Figure 3A, 3B) Through this process, we have corralled what we termed "the wild west" approach to CDAD management while reintroducing a more evidenced-based mentality. Subsequently, standardized order sets mimicking our treatment guidelines were incorporated into our computerized physician order entry system.

As eluded to, we routed a variety of alleged "panaceas" for *C. difficile* along the way that lacked evidence of effectiveness and/or presented potential harm to patients. Realizing that the treatment modalities for refractory CDAD lack double-blind, randomized controlled trial data, we were careful not to exclude potentially beneficial options. First, a regimen consisting of oral vancomycin along with oral metronidazole for the initial episodes of CDAD had become near routine practice. We learned that the primary reason for prescribing both drugs was that if clinicians felt that the patient was not responding to one of the two drugs early into therapy (e.g., day 2), hence the second drug was added. Previous guidelines recommend reevaluation of therapy at days 4-6 and that diarrhea should decrease but not resolve within this time frame. If symptoms do not improve or are worsening on therapy, then switching from oral metronidazole to oral vancomycin is recommended (not adding one to an already failing regimen). This is important because data suggest that the very drugs used to treat *C. difficile* may also predispose patients to future episodes of CDAD.⁵ Thus, if the goal is to allow for the recovery of the protective commensal organisms in gastrointestinal tract, the combination of the two drugs cannot be conducive to this goal.⁵⁹ Some have recently described that patients treated for CDAD have not responded as well to metronidazole as first line therapy,⁶⁰ but quality evidence to support this are lacking.^{61,62} Resistance to metronidazole and vancomycin among clinical isolates of *C. difficile* (both outbreak and non-outbreak strains) in the U.S. and elsewhere does not seem to be contributing to clinical failures since resistance is almost universally non-existent.⁶³ One possible explanation for the observations of poor response to metronidazole or vancomycin in the clinic is that patients are experiencing greater disease severity due to hypertoxin production and lasting disease due to increased sporulation of BI/NAP1.

Second, we received considerable pressure to add probiotic formulations to our hospital formulary for the management of CDAD. Thus, we conducted a Medline search for studies evaluating probiotic therapy of CDAD. We could find little if any quality evidence supporting their efficacy⁶⁴ but did find unexpected evidence to support their harm, chiefly in the form of numerous reports of fungemias due to *Saccharomyces boulardii* and bacteremias due to *Lactobacillus species* following probiotic administration to both immunocompetent and immunocompromised hosts.^{65,66,67,68} A recent review of the literature emphasized the potential harm associated with *Saccharomyces boulardii*.⁶⁹ To this end, probiotics at this juncture are not recommended at our institution.

Third, the use of anion binding resins or adsorbants (cholestyramine, colestipol) had also increased. Although theoretically beneficial as binders of select *C. difficile* toxins, colestipol has been shown to be equivalent to placebo for its ability to impact the fecal excretion of toxins.⁷⁰ Current evidence suggests that these drugs bind to a variety of medications, including vancomycin, in the gastrointestinal tract thereby rendering known effective agents potentially ineffective. Based on their unproven efficacy and potential to neutralize the efficacy of proven therapies, experts have recommended against their use.^{71,72} Unfortunately, the literature is replete with numerous review articles recommending the use of anion binding resins without supportive clinical efficacy data. Experimental toxin-binding polymers such as tolevamer are in development and may be useful if proven effective.⁷²

Fourth, we found some practitioners using “prophylactic” regimens of either metronidazole or vancomycin in patients (without diarrhea and with no suspicion of CDAD) who were receiving antimicrobial therapy for the treatment of an underlying infection was occurring reportedly in an effort to prevent a future episode of CDAD. This “prophylactic” approach had been gaining in popularity prior to the introduction of our guidelines. We know that exposing patients to antimicrobials (including oral vancomycin and metronidazole) increases the probability of infection with *C. difficile* as well as to future relapses in those with documented infection.⁵ We also know that the treatments (oral vancomycin and metronidazole) are not effective in eradicating *C. difficile* spores.⁷² Therefore administering oral vancomycin or metronidazole for “prophylactic” purposes is illogical, non-evidence-based, and potentially harmful in that it may increase the patient's risk for CDAD.

Fifth, we noticed that oral vancomycin doses varied widely for the initial therapy of first episode cases of CDAD and that treatment for extended durations beyond 10 days (often weeks) was becoming increasingly common. Our guidelines promote metronidazole as first line therapy unless multiple episodes are documented, intolerance existed, or the patient is pregnant. When oral vancomycin is used, evidence dictates that 125 mg administered every six hours is equivalent to 500 mg every six hours in terms of efficacy,⁷³ but costs significantly less. Higher doses of vancomycin (e.g., 2 grams/day) employed to treat refractory CDAD have been shown to be effective in descriptive studies.⁷²

For refractory disease, multiple relapses, or patients with a poorly functioning gastrointestinal tract, we realize that high quality evidence-based options are lacking. For patients with refractory disease (not responding at the day 4-6 evaluation point, we switch from oral metronidazole to oral vancomycin (but do not use them in combination). Rifampin can be added if the patient continues not to respond⁷⁴ and surgical consultation is suggested if markers for severe disease are present (high white blood cell count, ascites, obstruction, toxic megacolon). We also reserve oral vancomycin at higher doses, such as 2 grams/day, for patients with multiple relapses or are failing to respond to therapy. Pulse-dosed or tapered vancomycin regimens are suggested for patients with multiple relapses as described by McFarland.⁷² In addition, though not supported by quality data but because there are no better solutions, intravenous metronidazole is recommended in patients with suspected toxic megacolon or ileus, with or without the use of intracolonic vancomycin.

Summary

A previously uncommon strain of *C. difficile* termed “BI/NAP1” has been implicated as a cause of geographically diverse outbreaks of CDAD. It appears that certain virulence characteristics may be responsible for more severe clinical presentations and poor outcomes. Putative virulence factors (e.g., hypertoxin production, hypersporulation) possessed by a previously uncommon strain of *C. difficile*, in conjunction with particular host and environmental factors just may have resulted in the “perfect storm”. While it is too simplistic to assume that a basic change in an antimicrobial formulary as a single intervention strategy will be successful in reducing CDAD rates where BI/NAP1 is endemic, policies that incorporate good antimicrobial stewardship along with infection control and environmental interventions are likely to be necessary to combat CDAD. While awaiting updated national guidelines for the management of CDAD, we have developed local guidelines to reestablish evidence-based treatment and provide direction in the wake of BI/NAP1. Though BI/NAP1 is still present, our treatment variability has been dramatically reduced and is the subject of a current and ongoing evaluation. Finally, the reasons for suboptimal infection control and antimicrobial use in modern times are similar: derisory resources both human and financial, apathy, and ignorance. It is therefore up to clinicians and administrators alike to work on all three of these elements that stand in the way of curbing the growing epidemic of CDAD.

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Figure 1 A. BI/NAP1 Toxin A (TcdA) Production.¹¹

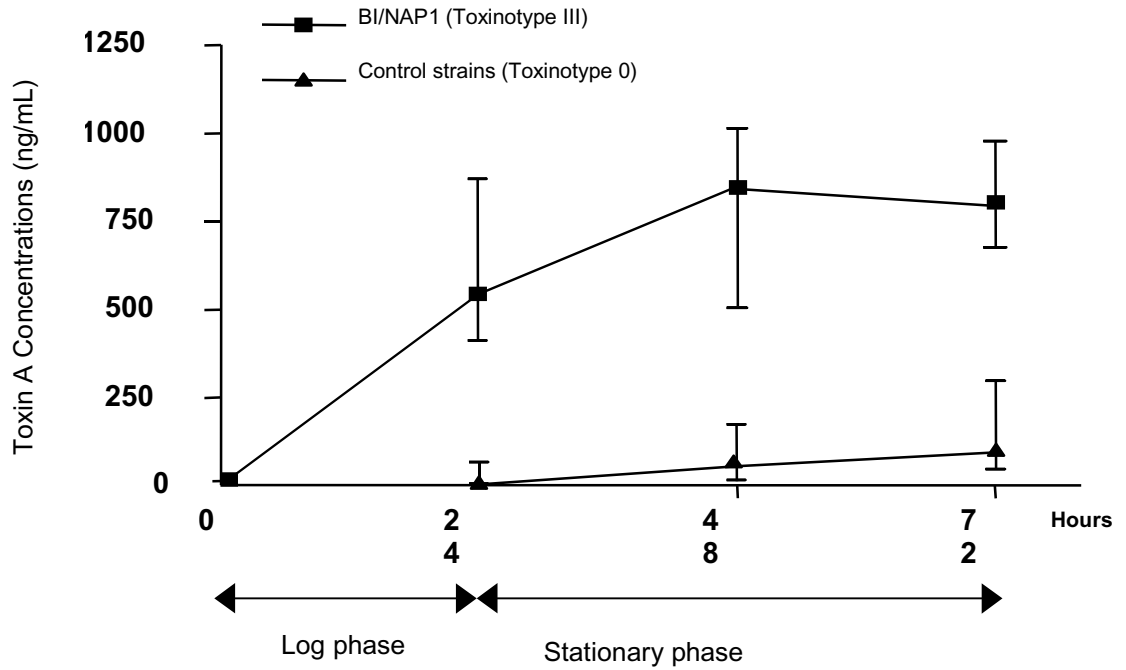


Figure 1B. BI/NAP1 Toxin B (TcdB) Production.¹¹

Toxin B Concentration (ng/mL)

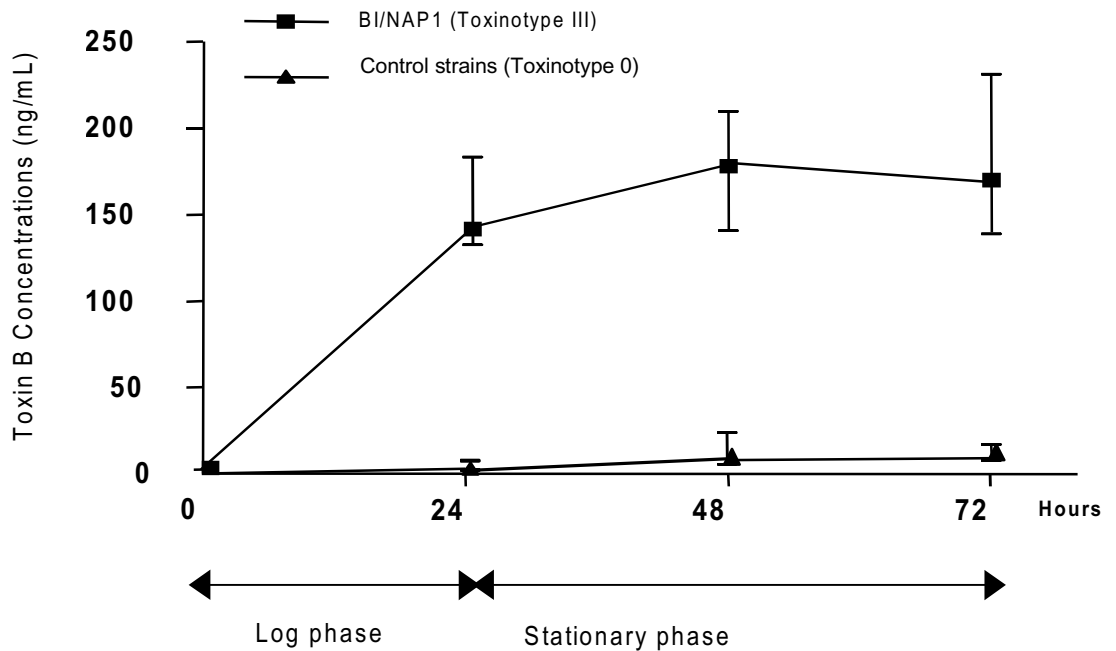
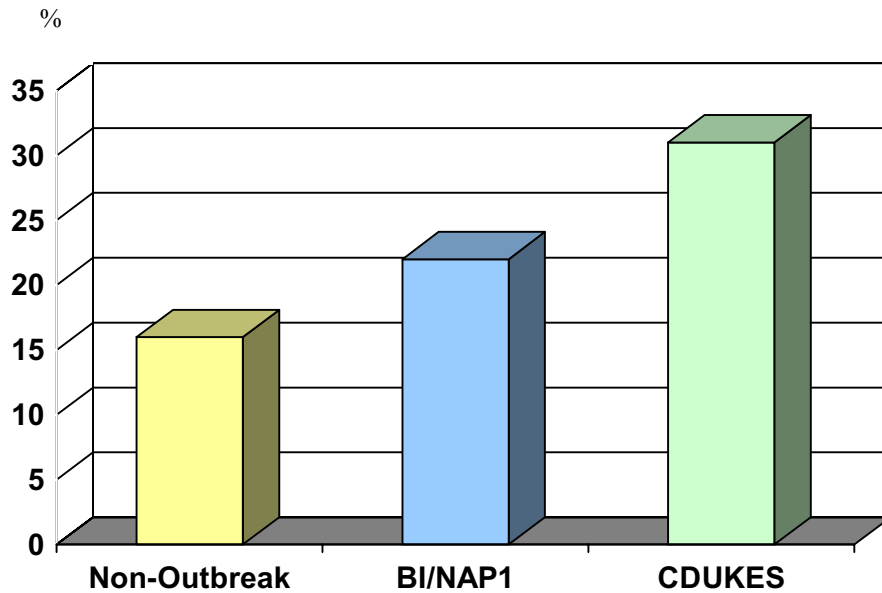


Figure 2. Sporulation capacity of *C. difficile* outbreak (BI/NAP1, CDUKES) vs. non-outbreak strains.¹²



BI/NAP1 vs. non-outbreak ($p < 0.05$)
 CDUKES vs. non-outbreak ($p < 0.05$)

Figure 3A. Treatment of first and second episodes of CDAD.

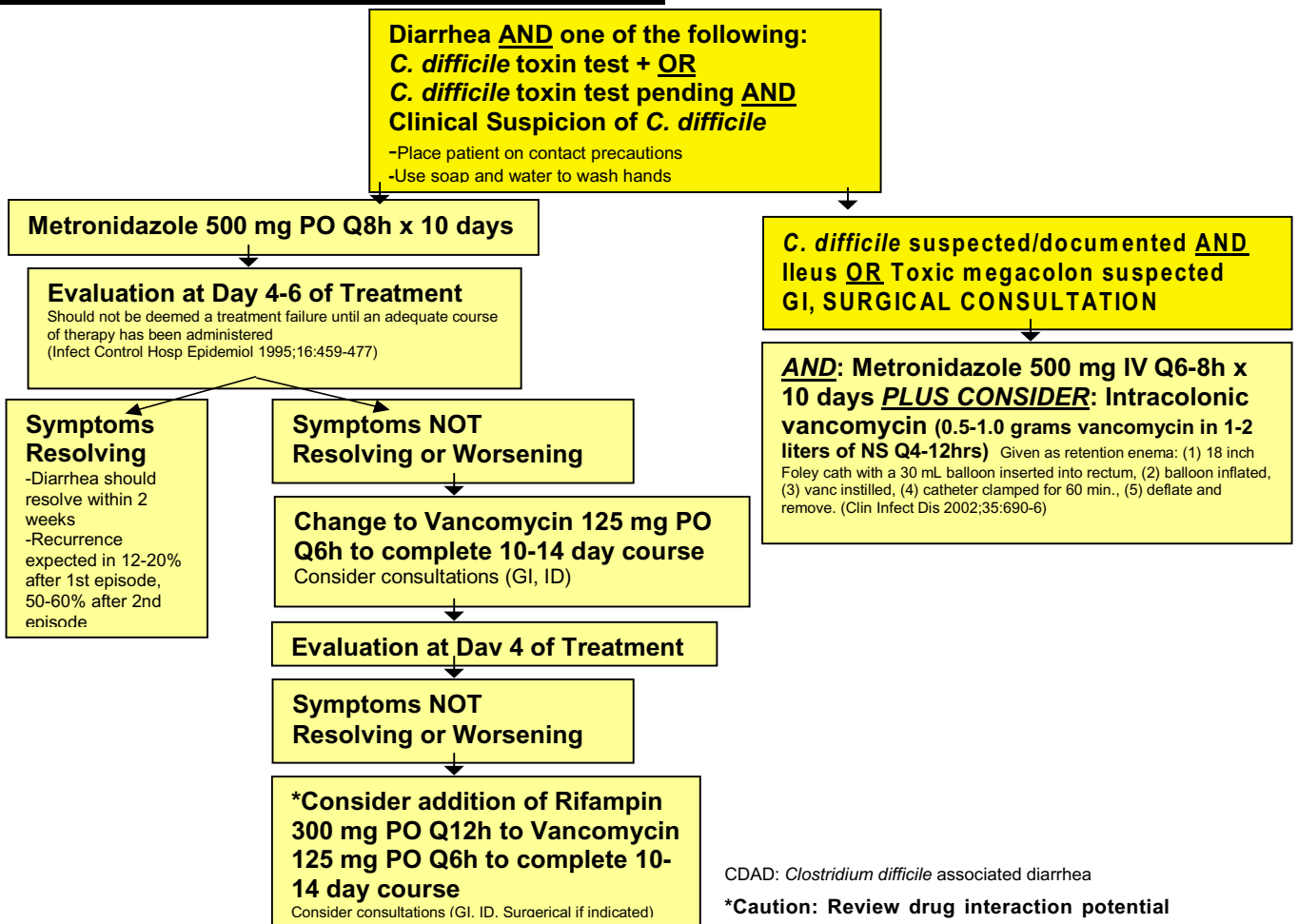
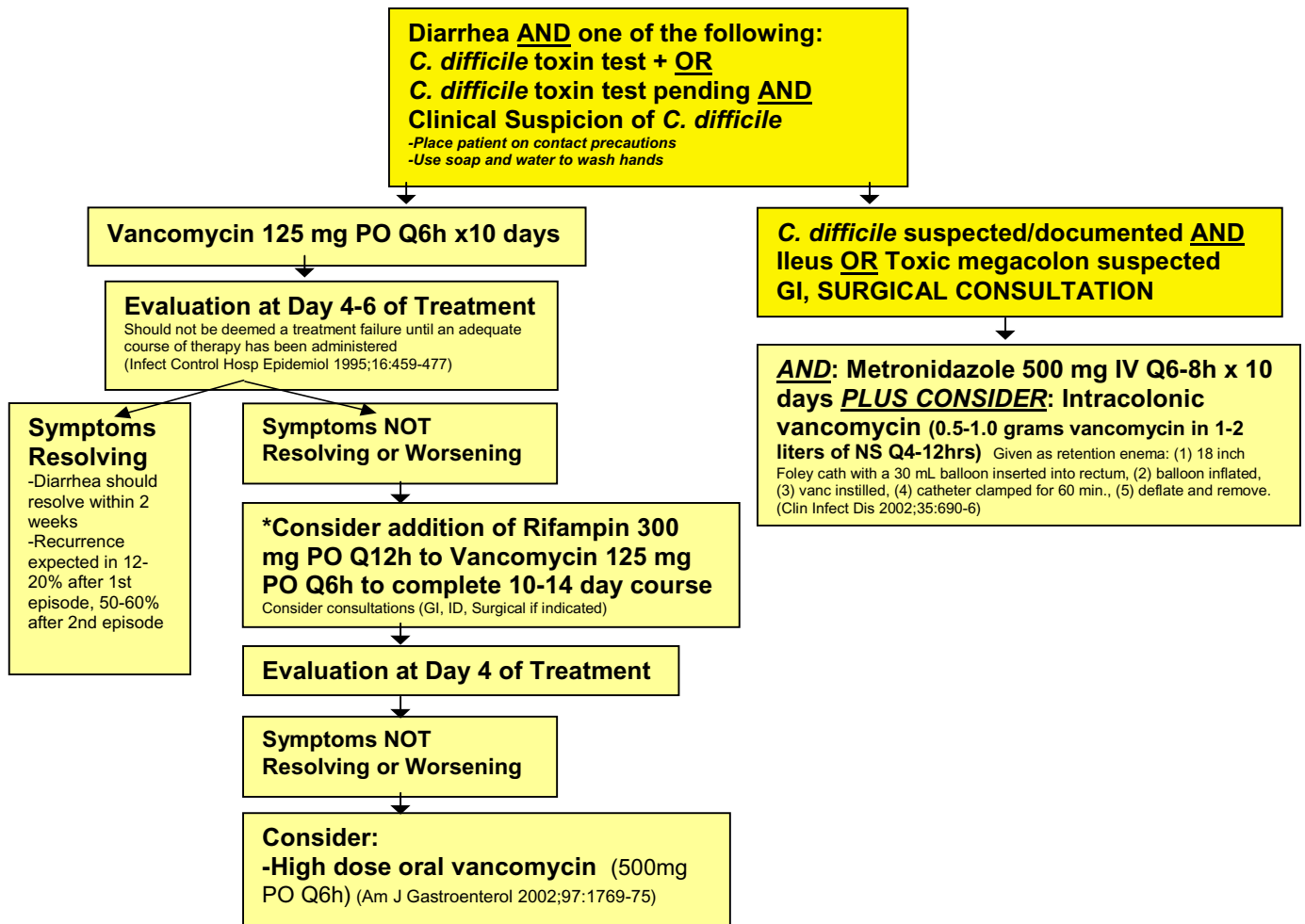


Figure 3B. Treatment of $\geq 3^{\text{rd}}$ episode of CDAD or initially Severe Disease.



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