



eLITERATURE
REVIEW

eInfections Review
Podcast Issue

Presented by
The Johns Hopkins University
School of Medicine

Supported by an Educational
Grant from AstraZeneca,
Cubist Pharmaceuticals and
ViroPharma, Inc.



HOME NEWSLETTER ARCHIVE CME INFORMATION PROGRAM DIRECTORS EDIT PROFILE RECOMMEND TO A COLLEAGUE

VOLUME 2 — ISSUE 4: TRANSCRIPT

Featured Cases: Infections—*C. difficile* infection (CDI): 2010 Update

Editor's Note:

We are happy to announce the launch of *eInfections Review Summary Monograph*. This new CME certified program contains a brief synopsis of all 12 issues in Volume 1, written by the top KOL's in infectious disease.

Our Guest Author is John Bartlett, Professor of Medicine at the Johns Hopkins University School of Medicine.

At the conclusion of this audio activity, participants should be able to:

- Describe the use of current testing methods for *C. difficile*
- Discuss how to manage cases of acute *C. difficile*
- Discuss how to manage cases of recurrent *C. difficile*

This discussion, offered as a downloadable audio file and companion transcript, covers the important issues related to Clostridium difficile infection (CDI) in the format of case-study scenarios for the clinical practice. This program is a follow up to the January 2010 Infections Review newsletter, *C. difficile* infection (CDI): 2010 Update

MEET THE AUTHOR



John G. Bartlett, MD

Professor of Medicine
Department of Medicine
The Johns Hopkins University
School of Medicine
Baltimore, Maryland

Guest Faculty Disclosures

John G. Bartlett, MD, has disclosed that he has served as a consultant for Salient.

Unlabeled/Unapproved Uses: The author has indicated that this presentation will include discussions of the off-label product use of metronidazole.

PROGRAM DIRECTORS

Paul G. Auwaerter, MD

Associate Professor of Medicine
Clinical Director, Division of
Infectious Diseases and General
Internal Medicine
The Johns Hopkins University
School of Medicine
Baltimore, MD

John G. Bartlett, MD

Professor of Medicine
Department of Medicine
The Johns Hopkins University
School of Medicine
Baltimore, MD

Sara E. Cosgrove, MD, MS

Associate Professor of Medicine
Division of Infectious Diseases
Director, Antibiotic Management
Program
Associate Hospital Epidemiologist
The Johns Hopkins University
School of Medicine
Baltimore, MD

ACCREDITATION STATEMENTS

The Johns Hopkins University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATIONS

Physicians

eNewsletter: The Johns Hopkins University School of Medicine designates this educational activity for a maximum of 1.0 *AMA PRA Category 1 Credit*[™]. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Podcast: The Johns Hopkins University School of Medicine designates this educational activity for a maximum of 0.5 *AMA PRA Category 1 Credit(s)*[™]. Physicians should only claim credit commensurate with the extent of their participation in the activity.

DISCLAIMER STATEMENT

The opinions and recommendations expressed by faculty and other experts whose input is included in this program are their own. Use of The Johns Hopkins University School of Medicine name implies review of educational format design and approach. Please review the complete prescribing information of specific drugs or combination of drugs, including indications, contraindications, warnings and adverse effects before administering pharmacologic therapy to patients.

SUCCESSFUL COMPLETION

To successfully complete this activity, participants must read the content, then link to [The Johns Hopkins University School of Medicine's CME website](#) to complete the post-test, and evaluation. Once you receive a passing grade, you can access and print your certificate of credit.

NOTE: If you have already registered for the Hopkins CME programs at the CME Website simply enter the requested information when prompted.

STATEMENT OF RESPONSIBILITY

The Johns Hopkins University School of Medicine takes responsibility for the content, quality, and scientific integrity of this CME activity.

INTENDED AUDIENCE

This activity has been developed for the Primary Care Physician, Internist, and Infectious Disease Specialist.

There are no prerequisites.

INTERNET CME/CNE/CPE POLICY

The Office of Continuing Medical Education (CME) at The Johns Hopkins University School of Medicine is committed to protect the privacy of its members and customers. The Johns Hopkins University SOM CME maintains its Internet site as an information resource and service for physicians, other health professionals and the public.

Continuing Medical Education at The Johns Hopkins University School of Medicine will keep your personal and credit information confidential when you participate in a CME Internet based program. Your information will never be given to anyone outside of The Johns Hopkins University School of Medicine's CME program. CME collects only the information necessary to provide you with the services that you request.

FACULTY DISCLOSURE

As a provider accredited by the Accreditation Council for Continuing Medical Education (ACCME), it is the policy of Johns Hopkins University School of Medicine to require the disclosure of the existence of any relevant financial interest or any other relationship a faculty member or a provider has with the manufacturer(s) of any commercial product(s) discussed in an educational presentation. The presenting faculty reported the following:

- Paul G. Auwaerter, MD – has disclosed that he has served as a consultant Adamas Pharmaceuticals, LifeCell, Schering-Plough, and Wyeth. He has disclosed that he is a stock shareholder of Johnson & Johnson, Merck and Pfizer
- John G. Bartlett, MD – has disclosed that he has served as a consultant for Salient.
- Sara E. Cosgrove, MD, MS – has disclosed that she has received grants or research support from Cubist, AdvanDX, and Astellas, and served as a consultant for Theravance/Astellas, Merck, and Forest.

Guest Author's Disclosures**HARDWARE & SOFTWARE REQUIREMENTS**

Pentium 800 processor or greater, Windows 98/NT/2000/XP or Mac OS 9/X, Microsoft Internet Explorer 5.5 or later, 56K Modem or better, Windows Media Player 9.0 or later, 128 MB of RAM, monitor settings: high color at 800 x 600 pixels, sound card and speakers, Adobe Acrobat Reader.

MR. BOB BUSKER: Welcome to this eInfections Review podcast.

eInfections Review[™] is presented by The Johns Hopkins University School of Medicine. This program is supported by an educational grant from AstraZeneca, Cubist Pharmaceuticals and ViroPharma.

Today's program is a follow-up to the January 2010 eInfections Review topic, *C. difficile* Infection: 2010 Update.

Our guest is Dr. John G. Bartlett from Johns Hopkins University.

This activity has been developed for primary care physicians, internists and infectious disease specialists caring for patients with infectious disease conditions. There are no fees or prerequisites for this activity.

The accreditation and credit designation statements can be found at the end of this podcast. For additional information about accreditation, Hopkins policies, expiration dates and to take the post-test to receive credit online, please go to our website newsletter archive, www.einfectionsreview.org, and click on the February 2010 podcast link.

At the conclusion of this audio activity, participants should be able to:

- Describe the use of current testing methods for *C. difficile*;
- Discuss how to manage cases of acute *C. difficile*; and
- Discuss how to manage cases of recurrent *C. difficile*.

I'm **BOB BUSKER**, Managing Editor of *eInfections Review*.

On the line with us we have this Newsletter's author. Dr. John Bartlett is a Professor of Medicine, at the Johns Hopkins University School of Medicine in Baltimore, Maryland

Dr. Bartlett has disclosed that his relevant relationships with commercial supporters are that he has served as a consultant to Salient Pharmaceuticals.

His presentation today will include discussions of the off-label product use of metronidazole.

MR. BUSKER: Dr. Bartlett, welcome to this eInfections Review podcast.

DR. JOHN BARTLETT: I'm glad to be hear and talk about *Clostridium difficile* infections

MR. BUSKER: To help expand our understanding of *C. difficile* infection, we've asked Dr. Bartlett to discuss some typical case scenarios. So if you would, Dr. Bartlett – please present our first case, to address the issue of *C. difficile* infection testing.

DR. BARTLETT: I'm going to use the same patient for all three cases, but illustrate different points in his case. So we'll start with a 60-year old man who is treated for community acquired pneumonia with ceftriaxone as an inpatient, and on the fourth day that patient reports that he has diarrhea with three to four watery stools per day. He has had this for two days, which is the time it usually takes for the physician to be aware of it. And at that point the physician orders a *Clostridium difficile* toxin test and the test returns positive.

MR. BUSKER: So the initial question would be: what do you do with those results?

DR. BARTLETT: The answer to that is pretty complicated right now, a lot more complicated now than it was before. It's turning out that 95 percent of hospitals in the United States use the EIA, the enzyme immunoassay, for detection of *Clostridium difficile*. The good news about that test is that it is rapid, we get the results back in 2 to 3 hours.

The other good property is that it is specific. So if this man had a positive test, we could say that he has *Clostridium difficile* infection. That, by the way, is the new term used for *Clostridium difficile* associated diarrhea or *Clostridium difficile* antibiotic associated colitis. What we are now using is *Clostridium difficile* infection, or CDI.

The bad news about that test is that it is not very sensitive, and that is a big problem. Various studies have shown that it is probably somewhere between 50 and 80 percent sensitive. In my hospital it turned out

to be 40 percent sensitive when compared to the cytotoxin assay.

MR. BUSKER: If sensitivity is an issue, why is the test used?

DR. BARTLETT: Laboratories like the test because it is rapid and therefore they can get the answer fast, it is cheap, and all of the reagents are commercially available. That accounts for the heavy usage.

So there are two parts to this question: what do you do in this specific case and what's going to happen with the testing? In terms of the first question you have to say you don't know whether this 60 year old man with community acquired pneumonia has *Clostridium difficile* infection or not, and therefore there are a couple of options.

One, you can try to sort out the clinical features of the case to see if there is enough clinical information to support a diagnosis of *Clostridium difficile* infection, and much of that is going to be driven by the severity of the illness. If this man has devastating diarrhea and other features of inflammation or colitis, and fever, it's attributed to this disease, this complication, an elevated white count attributed to this infection, or evidence of colitis by a CT scan or by endoscopy. And the reason that these signs of inflammation of colitis are important is that this distinguishes antibiotic associated diarrhea from antibiotic associated colitis due to *Clostridium difficile*.

If we take 1,000 tests in American hospitals for *C. difficile*, 75 to 80 percent of them are going to be negative. Most of those are going to be true negatives. What that means is that when a patient develops diarrhea in the context of antibiotic exposure, most of the time they have something else as the cause. We call it antibiotic associated diarrhea, but it is not well understood in terms of the pathophysiology. It tends to be dose related and stops immediately when you stop the drug. Many patients will tell you, Doctor, every time I take ampicillin I get diarrhea; that's what this is.

MR. BUSKER: So differentiate that for us, if you would, from CDI.

DR. BARTLETT: *Clostridium difficile* infection is a true infection caused by a toxin producing organism that can be lethal. It's very different. And the signs of

colitis distinguish this from antibiotic associated diarrhea that is really a benign, self-limited disease.

MR. BUSKER: So going back to the original question: What should the clinician do? What are the options?

DR. BARTLETT: One of the options you would have in this case that would make sense to me and would make sense to most of you is to simply repeat the test, because if 70 percent are positive then there is probably a good chance a second test is going to be positive if, in fact, this is the case. It turns out that's not the case. It turns out that those who have studied it have found out that if the first test is negative and the patient has *Clostridium difficile* infection by other markers, a second test is likely to be negative, a third test is likely to be negative, and a fourth test is likely to be negative.

So what we used to do was to order three tests on every patient. Our lab does not allow us to do that anymore and it's sage advice because we get no pickup with more tests. So this is really a point at which there is a clinical decision about whether this man needs to be managed as antibiotic associated diarrhea or antibiotic associated colitis due to *Clostridium difficile*. This could be diarrhea induced by ceftriaxone, or it could be *Clostridium difficile* infection and they are quite different.

MR. BUSKER: CDI testing options in the future – your thoughts on what we might be seeing.

DR. BARTLETT: People are well aware of the limitations of the current testing, which is the EIA that I mentioned. Most doctors don't know what the laboratory uses, they just send the stool off and they get an answer back. About 95 percent of hospitals in the United States use the EIA and, therefore. That is kind of the standard at the moment, but it's likely to change. And there are a couple of options that are coming up in the future. I don't want to talk too much about them because I'm not sure how rapidly they are going to be embraced by clinical practice, and how people are going to be making those decisions, but I'll mention a couple.

RTPCR is a new technique to detect the presence of the organism, *Clostridium difficile* that produces toxin. It has the advantage of being very sensitive and very rapid, and that is actually what doctors want. It can cause false positive tests, but most physicians

say you give me a test that's fast and sensitive and I'll use my clinical judgment about whether this is specific or not specific in this particular case. So that's how we're probably going to be doing much of the testing in the future.

There's a couple of other options that are also on the horizon that are also rapid and sensitive tests. One is GDH, the glutamine dehydrogenase test, which is very sensitive for detection of the organism, and sometimes combined with the EIA. So that is very specific when it's positive.

There are a number of hybrids that will combine different tests. I think the RTPCR is the one attracting the most attention at the moment, and your laboratory is likely to change. One thing physicians might do is urge their laboratory to give them a better test on the basis of what we have just discussed.

MR. BUSKER: Thank you, Dr. Bartlett. Let's move on now to our second objective and discuss management of acute *C. dif*.

DR. BARTLETT: So we'll take the same patient, a 60 year old man who has been treated for community acquired pneumonia with ceftriaxone. On the fourth day he complains of diarrhea with 3 to 4 watery stools a day for 2 days, and now we'll say we've decided that he has *Clostridium difficile* infection. In fact, you could say this is a man who now has a positive test, or had a negative test, and you decided that he needed to be treated for *Clostridium difficile* infection.

MR. BUSKER: What should the clinician do?

DR. BARTLETT: There are a couple of things that are standard. One is that you stop the inducing agent, and that means ceftriaxone has to go. In general, that's a problem because many of the patients are getting an antibiotic that cause the complication but they still have the infection for which they were originally treated.

The drugs to avoid in this situation are what I call the big three. The big three are those that seem to drive *Clostridium difficile* the most, the broad spectrum cephalosporins like ceftriaxone and cefotaxime, all of the fluoroquinolones, and, of course, the mother of *Clostridium difficile*, clindamycin. Those are the ones to avoid.

In this case you might be able to use a macrolide, you might be able to use tetracycline, you might be able to use a number of narrow spectrum betalactams. If he had pneumococcal pneumonia, you could, of course, use penicillin at the present time, or a narrow spectrum cephalosporin. So there are a number of options to sort of fill in that blank.

Now, in terms of the *Clostridium difficile* infection, there's two drugs that are used, and they have been used since 1978 — metronidazole, and oral vancomycin. And these are actually the only two drugs we have used with any frequency in the past 30 years. I mean it is pretty amazing, we just don't have any new drugs for this infection.

MR. BUSKER: So how do you decide between the two? Whether to use metronidazole or oral vancomycin?

DR. BARTLETT: The advantage of metronidazole is that it's cheap, it's been extensively used in the oral form, and it seems to work. The advantage of vancomycin is that it makes much more sense. The difference is in pharmacology. When you give vancomycin by mouth, all of it goes to the colon, and that's where the action is, that's where you want the antibiotic.

Metronidazole, when taken by mouth, is totally absorbed. Now you may get some in the colon as a result of going across an inflamed membrane, or in the presence of very flora diarrhea, some of it may slip through the small bowel. But by and large, metronidazole doesn't ever get to the colon, or it gets there very erratically. In fact, think of it this way, metronidazole is the strongest drug we have for anaerobic bacteria, the colon flora is full of anaerobes, 99.9 percent anaerobes. Metronidazole has no impact on the fecal flora, it just doesn't get there.

So for many of us, we were puzzled by the fact that metronidazole worked at all, but nevertheless, it turns out that it does seem to do pretty well in therapeutic trials in patients that are very sick with *Clostridium difficile* infection. However, if this patient is very sick you need to turn to the gold standard, and that's oral vancomycin. We usually give it at a dose of 125 milligrams 4 times a day, and all of it goes to the colon. When we give either one of these drugs, but the best studied is vancomycin, the diarrhea usually resolves in an average of 4 days. The response

is quite impressive. The signs of inflammation like fever and leukocytosis, also go pretty fast. So the response rates are pretty good for most patients.

MR. BUSKER: What about other drugs to avoid — aside from the Big 3 antibiotics — in these patients?

DR. BARTLETT: You want to avoid the antiperistaltic agents, like loperamide. You want to do that because ileus is a major complication of *Clostridium difficile* infection, and you don't want to give a drug that is going to promote ileus, which could lead to really catastrophic complications. I don't know how good the data are to support that. We have said that lomotil and loperamide and narcotics are contraindicated in the presence of diarrheal infections, in general, and by and large, almost all of the enteric pathogens are now freed of that admonition. *C. difficile* is probably still a good idea, but I must say the data right now on that point are soft.

Okay, so now we're going to decide whether this patient is sick, but not too sick, and can be treated with metronidazole or vancomycin. And favoring metronidazole in this case, if we decide that he is not very sick, is the fact that it's cheap and it is pretty well tolerated.

MR. BUSKER: What criteria should the clinician use to determine how sick the patient is?

DR. BARTLETT: The things that are probably most important are things that are pretty obvious, like if he has flora diarrhea with 10 to 20 liquid stools a day that is pretty bad diarrhea. If he has shock, then you know that it's severe. If he needs entry or transfer to the intensive care unit, then that is pretty bad. If the patient has renal failure as a result of *C. dif* infection, then that makes it a severe infection.

Now let's get to the things that are more subtle. More subtle is the white count. The white count is a barometer of *C. difficile* infection. It is one of the few infections where it works this way, but when the white count is more than 15,000 we say that we should be nervous. If it is more than 25,000, we should get real nervous. And the last patient I saw at Hopkins with severe *C. dif* had a white count of 48,000. The highest I've ever seen was 136,000, so the white count can go very high and, for some reason, it is a barometer of the severity of illness in this disease.

The other thing to think about is serum albumin. Serum albumin goes down fast in patients with *C. dif*. So if they've got an albumin of 3.5, then you are probably on the borderline. But if it's down to 2 or something like that, then you better be worried. That would make it in the category of severe infection. Severe infection would be treated with vancomycin preferentially. If it's very severe, let's say this man at 60 years old has got ceftriaxone, now has *C. dif* with 10 stools a day, watery stools a day, terrible cramps, another sign of colonic inflammation, has borderline renal function, has a white count of 40,000 and we're really worried about what's going to happen to him, this is the point at which we pull out all the stops. This is a patient who now gets vancomycin, but I don't use 125 milligrams 4 times a day, I go back to the originally FDA approved drug dose of vancomycin, 500 milligrams 4 times a day. The reason is because that man is likely to either have ileus or get ileus soon, and it is going to be tough to get it there.

The other option is to give it by a colonic enema, and that actually works quite well. So you can give a high dose from above, or you can give a colonic enema. I also give IV metronidazole, and the IV metronidazole is because of the backwash causing inflamed colon, so you get something in that way.

In addition, some people would use IV IG, because there is a checkered experience with that drug. It turns out that most people have immunoglobulin against toxin A and toxin B, and that if you give IV IG, then the patient will have immunoglobulin effect. Some of you may be aware of a recent paper in the New England Journal showing that monoclonal antibody to toxin A and toxin B was very beneficial in preventing relapse, and a lot of people think it may be beneficial in patients who are severely ill. That's a product not available yet. However, it does give testimony that serologic response is important and that the immunoglobulins are probably playing some role in the control of *Clostridium difficile*. And that is the justification for IV IG.

MR. BUSKER: And we'll return in a moment — with Dr. John Bartlett from Johns Hopkins.

DR. PAUL AUWAERTER: Hello. I'm Dr. Paul Auwaerter from the Division of Infectious Diseases at the Johns Hopkins University School of Medicine. I'm one of the Program Directors for eInfections Review. eInfections Review is a combination newsletter and

podcast program delivered via e-mail to subscribers. Newsletters are published every other month. Each issue reviews current literature in areas of importance to infectious disease specialists, primary care physicians and other clinicians caring for patients with infectious diseases. These podcasts, which are available as downloadable transcripts, provide case-based scenarios to help bring new information into practice in the exam room and at the bedside.

Subscription to *eInfections Review*[™] is provided without charge or prerequisite. Continuing medical education credit for each issue and each podcast is provided by The Johns Hopkins University School of Medicine. For more information on this educational activity or to subscribe and receive *eInfections Review* without charge and access to back issues, please go to our website, www.einfectionsreview.org.

MR. BUSKER: Welcome back to our February 2010 *eInfections Review* podcast. Our topic is *C. difficile* Infection. I'm Bob Busker, managing editor of *eInfections Review*. Our guest is Doctor John Bartlett, Professor of Medicine at The Johns Hopkins University School of Medicine.

We've been bringing the information presented in our January 2010 newsletter into clinical practice via case scenarios. So if you would, Dr. Bartlett, let's continue to our third objective, managing relapsing *C. dif* infection.

DR. BARTLETT: So let's start with the same patient, a 60-year old man who had ceftriaxone for community acquired pneumonia and has *Clostridium difficile* infection. We'll say it's proven. And now we'll say we treated him with oral vancomycin and he got all better, he got the 10-day course, he got 125 milligrams 4 times a day for 10 days. All of the diarrhea resolved, he got discharged from the hospital, he felt good. And now he is home, and he develops a recurrence of diarrhea.

MR. BUSKER: How often does that happen?

DR. BARTLETT: That probably happens about 20 percent of the time. It has been a problem right from the beginning. The penchant for relapses in *Clostridium difficile* infection occur with equal frequency with metronidazole or with vancomycin.

In the old days, when patients weren't very sick, we sometimes didn't treat them with an antibiotic, and if you don't treat them with an antibiotic they don't get a relapse. So the natural history of the infection is that if it goes away it doesn't come back, but if it goes away because of antibiotic treatment, then it has a 20 percent probability.

The frequency of relapse is probably higher in those that have advanced age. I said he was 60, and if you made him 75 it might be a higher risk of relapse. Other than age there is not an awful lot that would necessarily make him a good candidate, a better candidate for relapse.

You just have to be aware that relapses are common, and you also have to be aware that patients need to be warned about this as a potential complication and to notify you if it is.

Another caution is that a lot of these patients with *C. dif* infection will have what we call post *C. difficile* irritable bowel syndrome, or lactase deficiency. In other words, they have a recurrence of diarrhea, but it's not quite the same.

The key here is the patient tells you, Doctor, whatever I had before, I now have again, the cramps are the same, the stool looks the same, many of them can detect the unique odor of *Clostridium difficile*. That's not been well studied, but when you see a lot of cases you come to understand and appreciate it.

Clostridium difficile, you go in the lab and ask the microbiologist to grow up a culture of *Clostridium difficile* and take a whiff of it, you won't be able to describe it, you will just say it's awful. And patients learn that when they have *C. dif*, they have that smell, and when they get better it goes away, and when it comes back, the smell comes back. Now not everybody appreciates that smell, and it's never been studied, as I mentioned, but it could be a good diagnostic clue in the relapsing case.

At any rate, we'll say this man now has the first relapse. The first relapse is usually treated just as we did the first case, it might be treated with metronidazole, but you can't keep treating people with metronidazole. I mentioned its pharmacology deficit as a problem, but that is not the only problem with metronidazole. Long-term use of metronidazole leads to peripheral neuropathy and you don't want to go

down that path. So you get one or two cracks at metronidazole, and then the rest of it is oral vancomycin.

So we'll say this man was treated with oral vancomycin and then the second time was treated either with another course of oral vancomycin or metronidazole, and that he got better. Now in about 50 percent of cases that will be it, in other words, there is one relapse and that's it. However, there are a number of patients that go on to have relapse, after relapse, after relapse, and some of those patients can go on to have 20 or 30 relapses. Some of them will not be *C. difficile* free for years. It's a major, major problem in a subset of patients.

MR. BUSKER: What treatment can you recommend?

DR. BARTLETT: That is a different population, a different therapeutic challenge. I'm not sure exactly how to recommend therapy for this, but I can tell you what I do, and I can tell you what I think the guidelines will eventually recommend. When patients have multiple relapses, that is three or more, we usually give a standard dose of vancomycin orally, 125 milligrams 4 times a day for a total of 10, about 10 days, and that's to quiet it down, get them back to baseline. And then they'll be okay, but they are not *C. dif* free yet. Then you do a taper, and the taper means 125 milligrams twice a day for a week, then 125 milligrams once a day for a week, and then you go into what is called pulse therapy.

MR. BUSKER: Explain that for us, if you would.

DR. BARTLETT: Pulse therapy is a very low dose of oral vancomycin given for a prolonged period of time. I usually give 125 milligrams every other day for a total of 6 weeks. The theory is this: vancomycin, itself, has a profound effect on the fecal flora. That may surprise you because we view it as a narrow spectrum drug. But think of it this way— the colon is full of gram positive organisms, enormous number of clostridia, all kinds of clostridia, bifidobacteria, lactobacilli, enormous number of gram positive bacteria. So the pathophysiologic mechanism of *Clostridium difficile* infection is to have the pathogen, the organism, *Clostridium difficile* and a perturbed flora. Because don't forget, the only time we see *Clostridium difficile* infection, in general, is when we have given an antibiotic that perturbs the flora, and that gives *C. difficile* the opportunity to go from a

spore, to a vegetative form, then produce toxin, and it's a toxin induced disease.

So the theory is this, you give vancomycin, but you get down to a dose that is low enough that it does not perturb the flora, but is enough to inhibit *Clostridium difficile* and keep it as a spore. In a test tube it works beautifully, and in patients it works most of the time, but not all of the time. And then I think you are really going to have to refer a patient if they don't respond to that tapering and then pulse dose. Then I think they may have to see somebody who sees these kind of problems on a repeated basis.

MR. BUSKER: And your thoughts on the role — if any — of probiotics in the management of recurrent CDI?

DR. BARTLETT: Patients will ask you about it because they read about it on the web. The one that is probably used most commonly is Florastor, it's *Saccharomyces boulardi*, and it seems to work, it just doesn't work well enough to get FDA approval. But nevertheless, it's out there, and patients will ask about it.

There is also some interest in lactobacilli, as an attempt to replace the colonic flora. That does not have as much evidence to support it as Florastor or the *Saccharomyces boulardi*, and it does not make sense to give it with Vancomycin, because Vancomycin kills it, and is always very active against it, so I'm not very enthusiastic about it. Actually not very enthusiastic about either of them, but nevertheless, I have little objection to the patient using them because they're benign and they seem to want to do more than we can offer. And that may be a reason to allow it, but I would never give it in the context of saying, yes, you should do this. I would give it in the context of saying it may do something, we're not convinced at this point, but it does no harm.

When I say it does no harm, just be aware that there are a few cases of lactobacillus bacteremia and *Saccharomyces boulardi fungemia*, they are rare and they are usually in terribly compromised hosts, but it would probably be good to at least mention that as a potential adverse reaction to those drugs.

MR. BUSKER: Are there other alternative treatments worth considering?

DR. BARTLETT: One of the alternatives that the patient is going to ask you about because they see it on the web, and it's the topic of a lot of conversations, is fecal transplant. That is just what it says, taking stool from a healthy donor and transferring it into the colon of a patient that has recurrent *Clostridium difficile* infection. Of all the treatments we have for recurrent infection, that is by far the best. And, in fact, if you have ever done one, it can be amazing. The last one I had was a patient about 6 months ago who had 3 years of *Clostridium difficile* and 4 episodes of shock where they thought they might lose him, and finally we said the only thing we have left is a stool transplant, he has never had a relapse since. His next stool after the transplant, which he got from his son, was normal and it's been normal ever since.

So I think you have to pay respect to this as, first of all, having great pathophysiologic rationale. The second is that it really trumps all other methods of managing a relapse. But the third is that it is very hard to find a place to do it. Most people don't do it and the reason is they think that because there is no ICD-9 code for it they think it's experimental. Lawyers worry about putting stuff in and we don't know what's in there. We usually check it for all known viruses, HIV, HBV, HCV, all the viruses, we check all the viruses, we check for all enteric pathogens. To my knowledge, there has never been that kind of a complication, but, nevertheless, the number that do it is precious small.

The sum total of experience in the world, it was first done in actually 1974, first reported in 1974, actually before *Clostridium difficile* was discovered as a cause of this. And it worked then and it's worked in the places that have done it since then.

So if the patient inquires, I think what you could say is this. This is a last ditch effort, you have to try all the other methods first. If they really need it, there is probably the option of finding a place that can do it. It may involve an airplane ride because most cities don't have any place that will do it. But nevertheless, it is likely to come up in the conversation, it is awfully successful when it is done. Patients are very likely to be asking about it and colleagues are likely to talk about it.

I could give you the details, but I'm not sure it's really important because I don't think the people that are listening to this are probably likely to get involved in

it, and if they do get involved they are going to have to have much more information than what I can give you in the next few minutes.

I can tell you this, that the options are to give it from above with an NG tube, or from below with a colonic enema. My preference is to give it from below. And that you have to have a healthy donor who is screened, as I mentioned, and the patient has to be off of vancomycin for two to three days before this is done because, as mentioned, vancomycin will perturb the flora.

One additional point that I think is worth mentioning is that sometimes a patient will have the possibility of *Clostridium difficile* or the possibility of a recurrence, and you will be urged to try to do anything. And, of course, that would be oral vancomycin. Resist that urge, and the reason is because *Clostridium difficile* is caused and cured by Vancomycin. That is the ultimate paradox, but that, in fact, is true.

So we'll take that man I mentioned who has gone a long time after the fecal transplant, and there was one episode in the middle where he went into shock. The question is did he have *Clostridium difficile*? He didn't have diarrhea, but the angst was that he did and the doctor wanted to give him oral vancomycin. I said, please, please, don't give him vancomycin, you don't have enough evidence that this is *C. dif* and it will cause it again. And he resisted that urge and it turned out that it was an allergic reaction to almonds and we did not give him *C. difficile* again because of the use of vancomycin.

MR. BUSKER: Dr. Bartlett, your closing thoughts?

DR. BARTLETT: In general, the field of *Clostridium difficile* has mushroomed as a result of the remarkable increase in cases and the increase in the mortality rate. This occurred in the early 2000s, first noted in Canada, then in Europe and in the United States. A lot of this is now attributed to the appearance of the NAP-1 strain. The NAP-1 strain is the strain that is said to be "hypervirulent." It is a strain that is resistant to fluoroquinolones, and it produces a lot of toxin, and that is thought to be the explanation.

You, as a practicing physician, will not know if your patient has the NAP-1 strain or not. In fact, it really doesn't make any difference. It doesn't make any difference because if they are severely ill you will z

treat them the same, and if they get recurrences, you will treat them the same. There is no difference in management.

MR. BUSKER: Thank you, Dr. John Bartlett from the Johns Hopkins University School of Medicine, for participating in this eInfections Review Podcast

DR. BARTLETT: I am very glad to be able to talk about this topic because it's one that I have been interested in for 30 years.

MR. BUSKER: This podcast is presented in conjunction with the eInfections Review Newsletter, a peer-reviewed, CME-accredited literature review e-mailed monthly to clinicians treating patients with infectious diseases.

This activity has been planned and implemented in accordance with the essential areas and policies of the Accreditation Council for Continuing Medical Education through The Johns Hopkins University School of Medicine.

The Johns Hopkins University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education to physicians.

For physicians the Johns Hopkins University School of Medicine designates this activity for a maximum of 0.5 *AMA PRA Category 1*TM credits. Physicians should only claim credit commensurate with the extent of their participation in this activity.

This educational resource is provided without charge, but registration is required. To register to receive eInfections Review via e-mail, please go to our website, www.einfectionsreview.org.

The opinions and recommendations expressed by faculty and other experts whose input is included in this program are their own. This enduring material is produced for educational purposes only.

Use of the Johns Hopkins University School of Medicine name implies review of educational format, design and approach. Please review the complete prescribing information for specific drugs, combination of drugs or use of medical equipment, including indication, contraindications, warning and adverse effects before administering therapy to patients.

Thank you for listening. eInfections Review is supported by an educational grant from AstraZeneca, Cubist Pharmaceuticals and ViroPharma, Inc.

This program is copyrighted 2010, with all rights reserved by The Johns Hopkins University School of Medicine.