Emerging Therapies in the Treatment of *Clostridium difficile*–Associated Disease

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OBJECTIVE: To describe emergent therapies, such as rifaximin, nitazoxanide, intravenous immunoglobulin (IVIG), tinidazole, tolevamer, and the possible use of a vaccine, in *Clostridium difficile*–associated disease (CDAD), one of the most common causes of diarrhea in hospitalized adults in North America.

DATA SOURCES: A literature search was performed using MEDLINE (1996–October 2006), PubMed (1996–October 2006), abstracts from Infectious Diseases Society of America (September 2006) and International Conference on Antimicrobial Agents and Chemotherapy (September 2006), Internet (October 2006), Genzyme product Web site (October 2006), and Romark Laboratories Web site (October 2006) using the terms *Clostridium difficile*, rifaximin, nitazoxanide, intravenous immunoglobulin, tolevamer, vaccine, and tinidazole.

STUDY SELECTION AND DATA EXTRACTION: Data presented in this article were selected based on clinical relevance and power of the studies. In vivo and in vitro studies supporting the use of drugs available for treatment of refractory CDAD were reviewed. Some of the information on new and emerging modalities was also included, although there were limited published data available.

DATA SYNTHESIS: Clinical trials evaluating the use of nitazoxanide and tolevamer for the treatment of CDAD have been published. Tinidazole use is based on structural similarities to metronidazole; however, clinical trials have not been conducted and the cost of this agent may be a limiting factor. The use of rifaximin and IVIG will require randomized clinical trials to establish their place in therapy. Limited information in the literature suggests that a vaccine may be effective for CDAD prevention.

CONCLUSIONS: CDAD is a debilitating disease with increasing treatment failure rates and recurrences using standard therapies. Clinicians need to look at other options to expand the available treatment arsenal in addition to placing a greater emphasis on prevention.

KEY WORDS: *Clostridium difficile*, intravenous immunoglobulin, nitazoxanide, rifaximin, tinidazole, tolevamer, vaccine.

Ann Pharmacother 2006;40:2164-9.

Published Online, 21 Nov 2006, *www.theannals.com*, DOI 10.1345/aph.1H340

Clostridium difficile is a gram-positive, spore-forming, anaerobic bacillus that was first described in 1935 but has become one of the most important causes of diarrhea in hospitalized adults. Illness may range from mild watery stool to life-threatening colitis and toxic megacolon.[1] The basis for the variable expression of the disease may be related to the host immunofactors and virulence of the organism. The identified risk factors for *C. difficile*–associated disease (CDAD) include previous exposure to an antimicrobial, chemotherapeutic, or immunosuppressive agent; surgery; host immunity; exposure to gastric acid suppressants; advanced age; and low serum antitoxin A immunoglobulin levels.[1-7]

Currently CDAD is seen primarily as a nosocomial and long-term care facility concern, with an incidence of more than 300 000 cases per year in the US.[8] Although the incidence of CDAD in the ambulatory setting is much lower, the cost of treatment and hospital admissions is substantial. It is estimated that a case of CDAD can have a mean cost of approximately $4000 per case and can prolong hospital stay by 3.6 days.[2,3,9]

In addition to *C. difficile* being a financial burden, the emergence of a more virulent strain of *C. difficile* (BI/NAP1) is alarming. BI/NAP1 is capable of producing 16–23

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times the amount of toxins (TcdA and TcdB) as well as a binary toxin (CDT), which has altered fluoroquinolone resistance patterns and increased sporulation capacity.[2,6,10,11] Historically, the response to therapy with metronidazole or oral vancomycin has been around 90%[3]; however, recent reports suggest increasing treatment failure rates with the first-line agent metronidazole (as high as 22%, with 28% of the patients having a recurrence within 90 days).[12] Although the rate of treatment failures with oral vancomycin has not been consistently high,[3] failures do occur. In a cohort study in 1985, Young et al.[13] found that treatment failure with oral vancomycin was 19%; however, others have documented failure rates of less than 8% with vancomycin.[3] In addition, the potential selection of vancomycin-resistant bacteria and the high cost of the formulation are important factors that may limit its use as a first-line agent.

Current problems with management of CDAD clearly illustrate the need for new treatments and an expanded focus on prevention. In this article, we focus on agents such as rifaximin, nitazoxanide, intravenous immunoglobulin (IVIG), tolevamer, and tinidazole, which can be used when conventional therapies fail. Other nonstandard strategies (eg, rifampin, probiotics, cholestyramine, colestipol, fecal transplant, intracolonic vancomycin or vancomycin taper) are beyond the scope of this discussion.

Data Sources

Relevant information was identified through a search of MEDLINE (1996–October 2006), PubMed (1996–October 2006), abstracts from Infectious Diseases Society of America (September 2006) and International Conference on Antimicrobial Agents and Chemotherapy (September 2006), Internet (October 2006), Genzyme product Web site (October 2006), and Romark Laboratories Web site (October 2006) using the terms *Clostridium difficile*, rifaximin, nitazoxanide, intravenous immunoglobulin, tolevamer, vaccine, and tinidazole.

Rifaximin

Rifaximin is a semisynthetic analog of the rifamycin antimicrobial rifampin. The addition of a benzimidazole ring makes rifaximin essentially nonabsorbed (bioavailability <0.4%); hence, its usefulness for treatment of intraabdominal infections. The Food and Drug Administration (FDA) approved this agent for the treatment of travelers' diarrhea caused by noninvasive strains of *Escherichia coli* in patients who are 12 years of age or older. Rifaximin has been used in Italy since 1987 for the treatment of various infections. It has also been useful in hepatic encephalopathy, as well as in pre- and postsurgical prophylaxis.[14,15] This drug exerts its activity by inhibiting the initiation of RNA synthesis by binding to the β subunit of the RNA polymerase.[14]

In vitro, the minimum inhibitory concentration (MIC) values of *C. difficile* are among the lowest of any enteric pathogen for rifaximin. Gerard et al.[14] identified one study in which 34 of 56 clinical isolates of *C. difficile* were inhibited by rifaximin at a concentration of 0.78 µg/mL, with the remainder inhibited at concentrations greater than 25 µg/mL. Although the interpretation of these MIC results is difficult in the absence of known gastrointestinal concentrations, it is likely that the drug concentration achieved at the site of action would largely exceed the reported MIC values. Fecal levels after oral administration of the agent have been shown to range from 4000 to 8000 µg/g of stool.[15] In addition, the microorganism shows a particularly low incidence of spontaneously resistant mutants ($<1 \times 10^{-9}$), which could prove useful in treating the emergent strain.

In an open-label study, Boero et al.[16] compared rifaximin 200 mg 3 times daily for 10 days with oral vancomycin 500 mg twice daily for 10 days (N = 20). Time to toxin disappearance ± SD was significantly shorter with vancomycin, at 4.8 ± 1.48 days, versus rifaximin, at 8.1 ± 1.79 days ($p < 0.005$). Time to stool normalization was similar with vancomycin, at 3.8 ± 1.48 days, versus rifaximin, at 4.9 ± 2.38 days (p = NS). Overall, rifaximin was found to be effective in 9 of 10 patients, while vancomycin was successful in all 10 patients who received it.

We have identified several cases in our practice in which rifaximin was successfully used for CDAD when other agents failed or were contraindicated, but more supportive evidence is needed. Overall, rifaximin appears to be a valid alternative for the treatment and management of CDAD, although further, larger studies are needed to clearly define its role.

Nitazoxanide

Nitazoxanide is a new thiazolide antiparasitic agent that has excellent activity in treating both interstitial protozoal and helminthic infections.[3,17] Pharmacokinetic studies in humans have shown that nitazoxanide is absorbed from the gastrointestinal tract, with approximately one-third of the oral drug excreted in the urine and two-thirds in the feces. The FDA-approved indications for this agent include treatment of diarrhea caused by *Cryptosporidium* spp. and *Giardia* infections.[17] The presumed mechanism of action of nitazoxanide is inhibition of pyruvate–ferredoxin oxidoreductase, an enzyme essential to anaerobic energy metabolism.

In vitro, nitazoxanide has shown excellent activity against *C. difficile*. In one study, the 90% MIC (MIC_{90}) of the toxigenic strains of *C. difficile* was 0.5 µg/mL for nitazoxanide, which was identical to the MIC_{90} of metronidazole and vancomycin.[18] Other investigators have reported lower MICs, ranging from 0.06 to 0.125 µg/mL.[19] McVay and Rolfe[18] examined the in vitro activity of nitazoxanide against some toxigenic strains of *C. difficile*. Hamsters

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were inoculated with toxigenic strains of *C. difficile* and later treated with different concentrations of nitazoxanide as well as vancomycin, metronidazole, or NaCl 0.9% (saline). The hamsters who received saline died within 3 days. The nitazoxanide-treated hamsters, like those treated with metronidazole and vancomycin, were free from CDAD. In fact, all of the nitazoxanide-treated animals survived the 15 day postinfection period.

Nitazoxanide was studied as part of a small (N = 19), open-label, compassionate use trial for patients who failed to respond to metronidazole.[20] These patients established an initial response rate of 74% (n = 14). Unfortunately, one-third of the patients later relapsed, demonstrating an overall success rate of 42% (n = 8).

In a larger, prospective, randomized, double-blind study, nitazoxanide was compared with metronidazole in treatment of hospitalized patients with *C. difficile* colitis.[21] The study initially enrolled 174 patients and 142 were included in final analysis: 44 received metronidazole 250 mg 4 times daily for 10 days, 49 received nitazoxanide 500 mg twice daily for 7 days, and 49 received nitazoxanide 500 mg twice daily for 10 days. Of the enrolled patients, 32 were excluded from analysis due to discontinuation of therapy, dropout from the study, and nonadherence. The per-protocol results showed an 82.4% response rate (28 of 34 pts.) in the metronidazole arm compared with 89.5% (68 of 76) in the nitazoxanide 7- and 10-day arms combined (p = 0.20).

This study also evaluated for recurrence rate for 31 days after the start of treatment. A sustained response rate was demonstrated in 19 of 33 (57.6%) patients who received metronidazole for 10 days compared with 25 of 38 (65.8%) patients who received 7 days of nitazoxanide and 26 of 35 (74.3%) patients who received 10 days of nitazoxanide. No statistically significant differences were observed among the groups; however, this study involved a limited number of patients. The authors concluded that nitazoxanide should be considered safe and effective for initial treatment for *C. difficile* colitis or for treating recurrent disease. Other studies are comparing vancomycin and nitazoxanide for the treatment of this disease.[21]

Nitazoxanide is available as an oral suspension at a dose of 100 mg per 5 mL or in tablets of 500 mg. It is generally well tolerated, with the most common adverse events being headache, nausea, abdominal pain, and diarrhea. Allergic reactions are rare with this agent.[17]

Intravenous Immunoglobulin

IVIG contains a heterogeneous group of humoral antibodies derived from the plasma of healthy donors. These antibodies can effectively supplement or replace deficient components in the immune system lacking primary humoral immunity. The FDA has approved IVIG for several indications including primary immunodeficiency and idiopathic thrombocytopenic purpura. The off-label uses are far more numerous. In *C. difficile* infections, research found that patients who develop serum antitoxin A immunoglobulin G (IgG) titers in response to exposure tend to be 48 times less likely to develop diarrhea than are those who do not mount a response.[2] In immunodeficient patients, IVIG would introduce a level of passive immunity.

In a study of 5 children with relapsing *C. difficile* colitis and low baseline serum levels of antitoxin A IgG, Leung et al.[22] found that administration of IVIG 400 mg/kg every 3 weeks for 4–6 months was associated with a marked increase in serum antitoxin antibody and resolution of recurrent diarrhea. Another study involved 5 patients with protracted and/or recurrent diarrhea (median duration 50 days, range 45–64); 2 of the patients had biopsy-proven pseudomembranous colitis treated with IVIG.[23] Three of the patients had good therapeutic response, 1 patient had a partial response, and 1 patient had therapeutic failure resulting in death. The doses used in the study varied between 300 and 500 mg/kg (average 400) daily or every other day for 1, 2, or up to 6 doses (6 doses administered to the patient who eventually died). A recently published retrospective review of 14 patients given adjunctive IVIG (150–400 mg/kg once or twice, with the second dose given 3 weeks later) in addition to conventional treatment found a response to treatment by stool normalization in 64% (n = 9) of patients with severe, refractory, or recurrent disease.[24]

In addition to these studies, case reports describing the use of IVIG are available. Murphy et al.[25] reported on a 57-year-old woman who failed to respond over a 6 month period to multiple treatments used singly or in combination. Eventually, she was given IVIG 400 mg/kg daily for 3 consecutive days. Even though her stools remained positive for *C. difficile* toxin 4 months later, the woman experienced no recurrence of diarrhea.

Although some published information suggests a benefit of IVIG therapy in refractory cases or in severe cases in patients who are unable to develop an immune response alone or as adjunct to traditional therapy, randomized clinical studies are lacking. In addition, the cost associated with the use of IVIG may limit its use (Table 1).[26] Additional drawbacks of using IVIG include its intraclass variability, the intermittent supply of the compounds due to shortages, and adverse effects, which include acute renal failure, vascular thrombosis, and anaphylaxis, as well as infusion-associated reactions.

Tinidazole

Tinidazole is a structural analog of metronidazole and has been available in Europe for more than 2 decades. After activation, its toxic intermediates covalently bind to DNA, resulting in DNA damage in the form of loss of helical structure, impaired template function, and strand breakage,

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which eventually leads to cell death. Tinidazole was approved by the FDA in May 2004 for the treatment of trichomoniasis, giardiasis, amebiasis, and amebic liver abscess.

Although tinidazole was not approved for treatment of *C. difficile* infections, it does have excellent in vitro activity against the bacteria, especially against the more resistant strains.[25,27] Jokipii et al.[28] studied the activity of metronidazole and tinidazole against 38 strains of *C. difficile*. The results showed that tinidazole was more active than metronidazole against the less-susceptible strains, while metronidazole was relatively more active against the more susceptible strains.

Tinidazole is generally well tolerated, with bitter taste, nausea, abdominal discomfort, anorexia, and vomiting being the most commonly reported adverse effects. The optimal dose of tinidazole has not yet been established for the treatment of *C. difficile* infections, although the literature suggests doses between 500 mg orally twice daily to a maximum daily dose total of 2 g for various indications.[25]

Tolevamer

Tolevamer is a nonantibiotic, high molecular weight (>400 kDa)[29] anionic polymer introduced by Genzyme Corporation. It is given orally for the treatment of CDAD.[30,31] Tolevamer binds and neutralizes toxins A and B. By this mechanism, it may prevent CDAD -associated injury to the gastrointestinal tract without disrupting the reestablishment of normal bacterial growth.[31-33] An additional benefit of tolevamer is the reduction of selective pressure for bacterial resistance, especially the emergence of vancomycin-resistant *Enterococcus*.

In a multicenter, multinational, double-blind study, Louie et al.[29] evaluated the use of tolevamer in patients with mild to moderately severe CDAD. Patients were randomized to 1 of 3 arms: tolevamer 3 g/day (n = 97), tolevamer 6 g/day (n = 95), or oral vancomycin 500 mg/day (n = 97) for 14 days. In the per-protocol analysis, with the primary endpoint being resolution of diarrhea, tolevamer 6 g/day was not inferior to vancomycin, with 58 of 70 (83%) patients achieving the primary endpoint versus 73 of 80 (91%) patients in the vancomycin-treated group. However, the 3 g/day dose of tolevamer was found to be inferior to vancomycin treatment.

The median time to resolution of diarrhea was 2.5 days with tolevamer 6 g/day (95% CI 2.0 to 3.0 days) and 2.0 days with vancomycin (95% CI 1.0 to 3.0 days). There was also a trend toward lower recurrence rate in patients treated with tolevamer 6 g/day versus those who received vancomycin (per-protocol results, 10% vs 19%, respectively; p = 0.19).[29]

Dosage optimization studies suggest that tolevamer is tolerated at doses up to 15 g/day in healthy volunteers, with flatulence being the major adverse event at this dose. The most common adverse events, regardless of causality, were similar among the treatment groups in the Louie et al.[29] study. The most frequent adverse effect in the 3 treatment groups was minor gastrointestinal complaint. A unique effect was hypokalemia, which occurred significantly more often with tolevamer 6 g/day (23%) compared with 17% with tolevamer 3 g/day and 7% with vancomycin. It is unclear what the exact mechanism of action is for the hypokalemia. An ongoing Phase III study worldwide involving more than 1000 patients is excluding patients with low baseline serum potassium levels (≤3 mEq/L).[29] The study (GD3-170-302) is comparing tolevamer with vancomycin and metronidazole for the treatment of CDAD. The daily dose of tolevamer used in the study will be 9 g/day to potentially maximize efficacy.[29-33]

Tolevamer is a much needed alternative to antibiotics in the treatment of this debilitating disease. Clinicians hope that this study will provide evidence for an addition to our arsenal of agents.

Table 1. Summary of Recommended Therapies

Treatment Regimen	Cost ($)[a]	Reference
Rifaximin 200 mg tid 10 days	124	16
Nitazoxanide 500 mg bid 10 days	312	19, 21
IVIG[b] 400 mg/kg 1–6 doses	2835–17 010	22–25
Tinidazole 500 mg bid 10 days	95	27
Tolevamer, Phase III study in progress		
Standard treatment		
vancomycin 125 mg qid[c] 7–14 days	452–905	
metronidazole 500 mg tid 7–14 days	14–29	

IVIG = intravenous immunoglobulin.
[a]Based on average wholesale price accessed September 1, 2006, rounded to the nearest US dollar for course of treatment.[26]
[b]Dose based on 70 kg patient.
[c]Dose may range from 125 to 500 mg qid.

Other Agents

Tiacumicin B and the use of a *C. difficile* vaccine are other potential future options for the treatment or prevention of CDAD. Tiacumicin B is an 18-membered macrolide antibiotic originally isolated from the fermentation broth of *Dactylsporangium aurantiacum* subsp. *hamdenensis*. This antibiotic has demonstrated in vitro and in vivo activity against *C. difficile* and has a favorable pharmacokinetic profile for its potential use in CDAD as demonstrated in a hamster model.[34,35] Further studies are needed to prove efficacy in treating human disease.

The need for effective prevention approaches becomes clear when you consider the reported increasing incidence of CDAD, its recurrence rates, and its impact on morbidity and mortality, as well as the costs associated with treatment and appropriate isolation procedures to limit its spread. There is a growing need to develop a vaccine that would either prevent CDAD from occurring in high-risk

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individuals or prevent recurrence. There is strong evidence that host immune response to *C. difficile* toxin A has a substantial role in determining clinical outcome of infection and some cases of CDAD that are related to toxin B; however, it is unknown whether serum antitoxin B IgG is associated with disease protection. Currently, trials using a toxoid vaccine (Acambis; Phase I) and monoclonal antibodies to toxin A and toxin B (Medarex; Phase II) are ongoing.

The vaccine is given in 3 doses (days 1, 8, and 30) and has a favorable side effect profile, with the most common adverse effects being mild abdominal pain, arthralgias, and diarrhea.[36] It has proven to be highly immunogenic. Median concentration of serum antitoxin A IgG in the test group was 50-fold higher than the level associated with protection in the previous studies.[35,36]

Previous studies were done among healthy volunteers,[35] and it is not clear at this time whether the vaccine will be effective in elderly, debilitated patients. There is one small study in which 3 patients with recurrent CDAD were able to discontinue treatment with oral vancomycin without any recurrence after they were vaccinated.[37-39]

Ramoplanin (Oscient Pharmaceuticals; Phase III), OPT-80 (Optimer Pharmaceuticals; Phase III), and rafalazil (ActivBiotics; Phase II) are other agents in the therapeutic pipeline.[40]

Summary

CDAD is debilitating, occurring with an increasing incidence, and a major cause of morbidity and mortality in North America. With the changing face of the disease and emergence of more resistant strains, clinicians need to look at other treatment options and expand our arsenal to meet the growing threat.

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EXTRACTO

OBJETIVO: La enfermedad causada por *Clostridium difficile* (CDAD, *Clostridium difficile* associated disease) constituye una de las causas más comunes de diarrea en los adultos hospitalizados en Norteamérica. Las opciones terapéuticas disponibles son variadas, no obstante, debido a la aparición de resistencias, y a la creciente incidencia de fracasos de tratamientos, ha aumentado el interés por nuevos tratamientos y medidas de prevención. Este artículo se centra en los tratamientos emergentes como rifaximina, nitazoxanida, inmunoglobulina intravenosa, tinidazol, tolevamer, y el posible uso de una vacuna.

FUENTES DE DATOS: Se llevó a cabo una búsqueda en la literatura usando MEDLINE (1996 – octubre 2006), PubMed (1996 – octubre 2006), extractos de la Sociedad estadounidense de Enfermedades Infecciosas (Infectious Disease Society of America, IDSA) (septiembre 2006) y de la Conferencia Internacional Sobre Antibióticos y Quimioterapia (septiembre 2006), Internet (octubre 2006), la página Web de los productos de Genzyme (octubre 2006), y la página Web de los Laboratorios Romark (octubre 2006) introduciendo los términos *clostridium difficile*, rifaximina, nitazoxanida, inmunoglobulina intravenosa, tolevamer, vacuna, y tinidazol.

SELECCIÓN DE DATOS Y MÉTODO DE EXTRACCIÓN DE LA INFORMACIÓN: Los datos presentados en este artículo se seleccionaron según su relevancia clínica y la potencia de los estudios. Se incluyó algo de información sobre las nuevas modalidades y los tratamientos emergentes pero los datos publicados disponibles eran escasos.

SÍNTESIS DE LOS DATOS: Se analizaron los estudios in vivo e in vitro que respaldan el uso de estos fármacos para la CDAD resistente. Hay ensayos clínicos publicados sobre el uso de nitazoxanida y tolevamer para el tratamiento de CDAD. El uso del tinidazol se basa su similitud estructural con metronidazol, pero los ensayos clínicos con este fármaco son escasos y el su coste puede ser un factor limitante. El uso de rifaximina y de inmunoglobulina intravenosa requiere la realización de ensayos clínicos aleatorizados que indiquen la utilidad de estos fármacos en el tratamiento. Escasa literatura sugiere el uso de una vacuna para la prevención de CDAD.

CONCLUSIONES: La CDAD es una enfermedad debilitante, cuyos tratamientos habituales presentan crecientes tasas de recurrencia y de ineficacia. Los médicos deben a buscar otras opciones terapéuticas para ampliar sus horizontes y prestar mayor atención a la prevención.

Violeta Lopez Sanchez

RÉSUMÉ

OBJECTIF: La maladie associée à *Clostridium difficile* (MACD) est une des plus fréquentes causes de diarrhée chez les adultes hospitalisés en Amérique du Nord. Plusieurs options thérapeutiques sont disponibles, cependant l'émergence de résistance et l'incidence augmentée d'échec thérapeutique nécessitent le développement de nouvelles thérapies et de mesures préventives. Cet article vise les nouvelles thérapies émergentes telles le rifaximin, la nitazoxanide, les immunoglobulines intraveineuses, le tinidazole le tolevamer ainsi que l'utilisation potentielle d'un vaccin.

REVUE DE LITTÉRATURE: Une recherche informatique sur MEDLINE (1996 à octobre 2006), PubMed (1996 à octobre 2006), ainsi qu'une recherche des abrégés de la Infectious Disease Society of America (septembre 2006) et la International Conference on Antimicrobial Agents and Chemotherapy (septembre 2006), l'Internet (octobre 2006), le site internet des produits Genzyme (octobre 2006), et celui des laboratoires Romark (octobre 2006) utilisant les mots clés suivants: *clostridium difficile*, rifaximin, nitazoxanide, les immunoglobulines intraveineuses, le tolevamer, le tinidazole, et le vaccin.

SÉLECTION DES ÉTUDES ET DE L'INFORMATION: Les études sélectionnées furent choisies selon leur pertinence et leur puissance statistique. Des informations sur les thérapies nouvelles et émergentes furent inclues bien que les données publiées soient limitées.

RÉSUMÉ: Les études in vitro et in vivo supportent l'utilisation de ces nouveaux agents dans les cas de MACD réfractaire. Des études cliniques existent concernant l'utilisation du nitazoxanide et du tolevamer dans le traitement du MACD. L'utilisation du tinidazole est basée sur sa similarité structurelle à celle du métronidazole; cependant il existe peu d'études cliniques et le coût de cet agent semble être limitatif. L'utilisation de la rifaximin et des immunoglobulines nécessitera des études cliniques en vue d'établir leur place dans l'arsenal thérapeutique. Il existe peu de littérature sur l'utilisation d'un vaccin en prévention.

CONCLUSIONS: La MACD est une maladie débilitante associée à des taux d'échecs importants et à des récurrences possibles. Les cliniciens doivent se tenir au courant des nouvelles options disponibles en plus d'attacher une importance particulière à sa prévention.

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