5-2012

Fidaxomicin is a Superior Treatment to Vancomycin for Recurrent Clostridium Difficile Infection

Angela Mathison
St. Catherine University

Fidaxomicin is a Superior Treatment to Vancomycin for Recurrent *Clostridium Difficile* Infection

Angela Mathison

St. Catherine University

Abstract

Clostridium difficile has been historically viewed as a hospital acquired infection. However, the emergence of community acquired infection in low risk populations, the identification of new risk factors, detection of a hypervirulent strain of *C. difficile*, and increasing mortality have changed the epidemiology if this infection. Current standards of treatment have come into question due to increasing recurrence rates and treatment failures, possible resistance of Metronidazole, and concerns surrounding Vancomycin resistant *enterococci* (VRE). Fidaxomicin, a narrow-spectrum macrolide, is the first drug approved by the FDA in 20 years for the treatment of *C. difficile* infection. It has shown good in vitro and in vivo activity, has similar clinical cure rates, lower recurrence rates, and higher global cure rates compared to Vancomycin in non-hypervirulent strains and similar efficacy in all outcomes in the hypervirulent strain. Overall, Fidaxomicin appears to be a reasonable second line treatment option for recurrent *C. difficile* infection in patients who have failed to respond to treatment under the current guidelines.

Keywords: Clostridium difficile, Fidaxomicin, Vancomycin

Introduction

Clostridium difficile (C. difficile), an opportunistic gram positive, anaerobic, spore-forming bacillus, is the most widely recognized cause of infectious diarrhea with a high healthcare cost burden (McFarland, 2008). There are two primary virulence factors found in *C. difficile* infections, toxin A and toxin B (Warny, et al., 2005). These toxins bind to surface proteins in the intestinal epithelial cells and disrupt the cytoskeleton resulting in a rounding of the cell, opening of the tight junction between cells and a subsequent fluid release resulting in diarrhea (McFarland, 2008; Noren, 2010). Toxin A is unique in that it also induces apoptosis of the cells (McFarland, 2008). Depending on the virulence of the toxin and the host response, *C. difficile* can cause a wide array of symptoms ranging from mild, watery diarrhea to life threatening conditions including: fulminant pseudomembranous colitis, toxic mega colon, bowel perforation, septic shock and death (LoVecchio & Zacur, 2011; McFarland, 2008). Higher incidence rates, changing epidemiology, the emerging hypervirulent strain and apparent decreased efficacy of current treatment options have piqued much interest into the cause and transmission of *C. difficile* as well as renewed interest in the pursuit of new treatments for this disease.

Incidence of C. difficile

The rates of *C. difficile* have been climbing in the last 15 years with a dramatic rise in mortality. The CDC reports an eight-fold increase in the number of deaths due to *C. difficile* from 1999 to 2006 (Xu, Kochanek, Murphy & Tejada-Vera, 2010). In 2006, *C. difficile* was added to the rankable causes of death and is listed as one of the 20 leading causes of death for the

elderly accounting for nearly 92% of all deaths from *C. difficile* (Xu, Kochanek, Murphy & Tejada-Vera, 2010). This is in part due to the changing epidemiology of *C. difficile* infection.

Historically, the populations at greatest risk for contracting *C. difficile* have been those with traditional risk factors which include: previous antibiotic exposure, advanced age, co-morbid conditions, feeding tubes, immune suppression/compromise, previous episode of *C. difficile* infection, mucosal damage from chemotherapy or radiation, and hospitalizations (LoVecchio & Zacur, 2011; Freeman, et al., 2010; Noren, 2010). However, there have been increasing reports of *C. difficile* in atypical populations. Multiple reports have described a growing number of *C. difficile* infections emerging in the community in persons without the classic risk factors, including recent exposure to antibiotics, which have been implicated in the acquisition of this infection in children, peripartum women and young adults (Khanna, Pardi, Aronson, Kammer & Baddour, 2012; Kuntz, Chrischilles, Pendergast, Herwaldt & Polgreen, 2011; McFarland, 2008). It has been postulated that shorter inpatient lengths of stay have led to community identification of nosocomial infections (Prabaker & Weinstein, 2011).

Hypervirulent Strain

Complicating the epidemiology of this disease is the emergence of a hypervirulent strain of *C. difficile*, B1/NAP1/027 (McFarland, 2008). This hypervirulent strain has been implicated in multiple epidemic outbreaks in Canada and the United States since 1999. The B1/NAP1/027 strain can produce 16 times more toxin A and 23 time more toxin B than non-epidemic strains, is resistant to fluoroquinolones, and has higher morbidity and mortality rates than non-epidemic strains (LoVecchio & Zacur, 2012; McFarland, 2008; Warny, et al., 2005). To date, this

hypervirulent strain of *C. difficile* has been identified in 40 states in the U.S. as well as epidemic outbreaks in countries globally (Freeman, et al., 2010; Gerding, 2010).

Risk Factors

Exposure to high risk antibiotics remains the primary risk factor for *C. difficile* acquisition. Historically, the antibiotic most strongly implicated in the induction of *C. difficile* infection was clindamycin (Freeman, et al., 2010). However, more recently many other antibiotics have come into favor as the cause for *C. difficile* as the use or misuse of these medications continues to rise. All antibiotics have the potential to interrupt the normal flora of the bowel thereby altering the effectiveness of competitive exclusion and increasing the susceptibility of patients to *C. difficile* contraction (LoVecchio & Zacur, 2012; McFarland, 2008). Preservation of the normal flora, mainly comprised of the *Clostridium* and *Bacteroides* groups as well as *Lactobacillus,* and *Bifidobacterium* is important to maintain competitive exclusion (Noren, 2010). The fluoroquinolones specifically have been attributed to the increasing rates of *C. difficile* (Freeman, et al., 2010; McFarland, 2008; Noren, 2010).

In addition to antibiotic exposure, several other risk factors have been identified including age (>65), compromised immune system and comorbid conditions (Freeman, et al., 2010; LoVecchio & Zacur, 2012; McFarland, 2008). The number of hospitalizations and lengths of stay have also been identified as contributing risk factors (Freeman, et al, 2010; McFarland, 2008). More recently new sources of susceptibility for *C. difficile* have been described including animals and food, the use of feeding tubes, and the use of proton pump inhibitors, the latter of

which remains highly controversial (Freeman, et al, 2010; Gerding, 2010; LoVecchio & Zacur, 2012; McFarland, 2008; Noren, 2010).

Current Standards of Treatment

LoVecchio & Zacur (2011) describe the properties that pharmacologic therapy for *C. difficile* should possess including: oral administration ability, high activity levels in the colon, low systemic absorption and preservation of normal flora in the colon. Current guidelines call for discontinuing the offending agent and instituting antimicrobial therapy with oral Metronidazole or Vancomycin (Cohen, et al., 2010). These are the only two drugs recommended for therapy but Metronidazole has high systemic absorption with low fecal concentration whereas Vancomycin has poor systemic absorption and high levels of fecal concentration (Cohen, et al., 2010).

According to the Infectious Diseases Society of America (IDSA) guidelines, Metronidazole is the first line treatment for mild-moderate disease but is not approved by the Food and Drug Administration (FDA) for use in *C. difficile* and its efficacy appears to be declining (Cohen, et al., 2010; McFarland, 2008; Miller, 2010). Interestingly, Metronidazole has also been given a specific black box warning stating “Unnecessary use of the dug should be avoided. Its use should be reserved only for conditions for which it is approved” (FDA, 2010). For first recurrence of infection, repeating treatment with the initial choice of drug is recommended. However, if Metronidazole fails, is poorly tolerated, or contraindicated, second line treatment is Vancomycin (Cohen, et al., 2010). Repeated recurrences call for use of Vancomycin only in tapered or pulse dosing as Metronidazole has the “potential for cumulative neurotoxicity”

(Cohen, et al., 2010, p. 433). However, even with Vancomycin high rates of failure and recurrence have been described which may be, in part, due to colonization with VRE and the emergence of B1/NAP1/027 (Choi, et al., 2011; LoVecchio & Zacur, 2012; Prabaker & Weinstein, 2011; Tannock, et al., 2010).

Metronidazole is more cost-effective but has a higher systemic absorption than Vancomycin which may be the reason for treatment failures with this therapy. Others have suggested that *C. difficile* has become resistant to therapy with Metronidazole (Freeman, et al., 2010; McFarland, 2008; Miller, 2010). However, recurrence rates ranging from 5-47% have been described with current treatment options (Choi, et al., 2011; LoVecchio & Zacur, 2012; McFarland, 2008). Current standards of treatment have come into question due to the high rates of treatment failure and recurrence.

The rates of recurrence and treatment failures, increasing morbidity and mortality, systemic absorption, few treatment options and emergence of the hyper virulent strain have raised concern regarding the current treatment options. Optimer Pharmaceuticals has recently received FDA approval for Fidaxomicin, a narrow spectrum macrocyclic antibiotic, for the treatment of mild to moderate *C. difficile* infections and is the first drug to be approved for use in *C. difficile* in 25 years (Peterson, 2011). The aim of this study is to review the available evidence to determine whether fidaxomicin for the treatment of mild to moderate *clostridium difficile* infection improves cure rates and decreases the episodes of recurrence as compared to vancomycin.

Fidaxomicin Versus Current Standard of Treatment

Pharmacokinetics

Minimum inhibitory concentrations (MIC) are crucial in determining the efficacy of a medication. A low MIC indicates the lowest concentration of a drug that will inhibit the growth of the bacteria in question. In the case of *C. difficile* infection, the MIC against both *C. difficile* and the normal bacterial flora become important to understand as preservation of the normal flora is an important component of efficacious treatment.

In 2004, two quasi-experimental studies were published assessing the in vitro activity of Fidaxomicin (formerly known as OPT-80) against several hundred anaerobic intestinal bacteria. MICs were measured in both of these studies and compared to multiple other antibacterial agents including Vancomycin and Metronidazole. Table 1 summarizes the findings of Fidaxomicin, Vancomycin, and Metronidazole against *C. difficile*, all *clostridium* species, *bacteroides fragilis*, *lactobacillus* and *bifidobacteria*. Both studies showed good activity for Fidaxomicin, Vancomycin, and Metronidazole against *Clostridium* species but with varying MIC ranges between studies (Credito & Appelbaum, 2004; Finegold, et al., 2004). Superior activity of Fidaxomicin against *C. difficile* was shown in both studies. Credito & Appelbaum (2004) found that Fidaxomicin had superior activity against *C. difficile* and all *clostridium* species versus Vancomycin and Metronidazole, was equivalently active against *lactobacillus, bifidobacteria,* and had less activity against *bacteroides fragilis* than the two current recommended medications. This would presumably result in higher preservation of normal gut flora in vivo.

In contrast, Finegold, et al. (2004) found that Fidaxomicin was only superior to Vancomycin in certain *clostridium* species, specifically *clostridial* clusters I and XI (including *C.*

difficile), had more activity against *lactobacillus* and *bifidobacteria* than Metronidazole but not Vancomycin, and markedly less activity against the *bacteroides* group and *clostridial* clusters XIVa, XI, and XIII than either Vancomycin or Metronidazole. Of note is the variation in the MICs reported between studies. Finegold, et al. (2004) used a Wadsworth agar dilution technique whereas Credito & Appelbaum (2004) used a Brucella agar with sheep blood. This difference in technique may account for the variation in MIC results. However, the results of both studies support the narrow-spectrum activity of Fidaxomicin which is a desirable trait for antimicrobial therapy for *C. difficile*.

The in vivo efficacy of Fidaxomicin was evaluated in two small open-label Phase 2A randomized dose-finding trials in which authors tested fecal samples of patients for spared normal bacterial flora after treatment with Fidaxomicin versus Vancomycin. The return of normal flora, specifically *clostridial* clusters XIVa and IV, increased during and after treatment with Fidaxomicin but was not statistically significant ($p>0.05$), whereas Vancomycin reduced the population of these clusters as well as *bifidobacteria* with statistical significance ($p<0.05$) (Tannock et al., 2010). This study also reported a statistically significant increase in *lactobacilli* and *enterococci* in the Vancomycin treatment group ($p<0.05$) which was "coincident with the decrease in proportions of *clostridial* clusters and *bifidobacteria*" (Tannock, et al., 2010, p. 3357). In another study, Fidaxomicin was reported to suppress *C. difficile* (no p-value given) and lower recurrence ($p=0.03$) when compared to Vancomycin with no alteration in *bacteroides* ($p=0.11$-0.56) (Louie, et al., 2009). While the latter outcome was not statistically significant, in the Vancomycin treatment group alteration in *bacteroides* was significant ($p=0.03$) (Louie, et al., 2009).

In an additional Phase 2, dose-finding, randomized, open-label study by Louie, et al. (2009), plasma and fecal levels of Fidaxomicin were measured to assess systemic absorption and colonic retention of the drug. Plasma levels were found to be less than 20ng/ml in all subjects receiving the 200mg twice daily dosing and a high fecal concentration of 1433 ± 975 μg/ml (Louie, et al., 2009). These results were supported in their Phase 3 clinical trial which showed mean plasma concentrations of 22.8 ± 26.5 ng/ml and mean fecal concentrations of 1225 ± 759.0 μg/g (Louie, et al., 2011). These studies did not compare Fidaxomicin levels against Vancomycin levels. While no statistical significance was reported, this is clinically significant as effective treatment for *C. difficile* must have low systemic absorption and high fecal concentrations to be effective.

Clinical cure and recurrence

Clinical efficacy of Fidaxomicin versus Vancomycin was reported in three studies, two large randomized control trials and a systematic review. Initial clinical cure, recurrence and global cure were reported in both trials. Global cure was not reported in the systematic review. The studies are summarized in Table 2 with demographics and interventions outlined in Table 3.

Clinical cure.

Clinical cure was defined by the authors as resolution of diarrhea which is maintained until 2 days after treatment completion (Louie, et al., 2011; Mullane, et al., 2011). Fidaxomicin clinical cure rates were found to be non-inferior to Vancomycin in all three studies. Drekonja, et al. (2011) reported no significant difference between Fidaxomicin and Vancomycin, giving no p-value. When given with a concomitant antibiotic, Fidaxomicin was found to have higher clinical

cure than Vancomycin (p=0.04) but the clinical cure rate in the presence of high-risk concomitant antibiotics did not reveal a statistical significance (p=0.09) (Mullane, et al., 2011). One study reported clinical cure rates in Fidaxomicin for the modified intention to treat (mITT) and per protocol (PP) groups as non-inferior to Vancomycin "with a lower boundary of the 97.5% CI for the difference in cure rates of -3.1…[and] -2.6 percentage points" respectively (Louie et al., 2011).

Recurrence.

Recurrence rates were reported by all three studies. Clinical recurrence was defined in the randomized control trials as the reappearance of symptoms (more than three unformed stools per day) within 4 weeks after completion of therapy, *C. difficile* toxin A or B, or both in stool, and treatment requirement for infection (Louie, et al., 2011; Mullane, et al., 2011). Louie, et al. (2011) reports statistically significant lower recurrence rates with Fidaxomicin in both the mITT group (p=0.005) and the PP group (p=0.004). This study did show similar rates of recurrence between Fidaxomicin and Vancomycin on the B1/NAP1/027 hyper virulent strain which was not statistically significant (p=0.93) (Louie, et al., 2011). Administration of Fidaxomicin with concomitant antibiotics, was found to have increased recurrence rates but it did not reach statistical significance (p=0.48) and in conjunction with high risk antibiotics the difference in rate of recurrence between Fidaxomicin and Vancomycin was not statistically significant (p=0.54) (Mullane, et al., 2011). In a systematic review, Drekonja, et al. (2011) found that the overall recurrence rate for Fidaxomicin was lower than Vancomycin (p=0.005).

Global Cure.

Global cure is defined as "clinical cure with no recurrence" (Mullane, et al, 2011). Two studies reported results for global cure. Louie, et al. (2011) reports a statistically significant global cure rate for Fidaxomicin in both the mITT and PP groups with p=0.006 for both groups. In a study evaluating cure rates with concomitant antibiotic use, global cure rate was statistically significant (p=0.02) except when adjunctive high risk antibiotics were used (p=0.18) (Mullane, et al., 2011).

Strengths/Limitations

The studies conducted by Louie, et al. (2011) and Mullane, et al. (2011) were both double-blind randomized control trials. This approach has strong rigor, lends itself to generalizability and has strong external validity due to the "natural" setting. The remaining studies were quasi-experimental with quite small samples sizes which weakens the generalizability and external validity of these studies. Additionally, no study reported power analysis or effect size which further weakens their external validity. The results of these studies must be interpreted with caution. Bias is a major concern with each of the studies evaluated as it was either funded by Optimer pharmaceuticals, the manufacturer of Fidaxomicin, or written by an investigator employed by said manufacturer. The systematic review provides the strongest form of evidence and lessens the bias that may be present in the other studies.

Discussion

Fidaxomicin is the first antibiotic to be approved by the FDA for treatment of *C. difficile* in 20 years. It has good in vitro and in vivo efficacy, has been shown to be non-inferior to Vanco in clinical trials, in both epidemic and non-epidemic strains, and appears to significantly

decrease the rate of recurrent infection. Additionally, it meets the criteria for effective treatment of *C. difficile*: It is given orally, has low systemic absorption, high fecal concentrations and preserves the normal bacterial flora of the bowel, which the current treatments do not.

Fidaxomicin appears to be a reasonable alternative therapy for recurrent *C. difficile* but not for initial treatment. As the only randomized control studies that have been published were conducted by Optimer Pharmaceuticals, bias is a concern. Large, independent trials are warranted to provide a clearer picture of its overall efficacy against *C. difficile* and superiority in treatment versus Vancomycin.

Additionally, pharmacoeconomics cannot be disregarded when choosing therapy. In a review of this new drug, Grant (2011) reports wholesale pricing of Fidaxomicin much higher than Vancomycin for a 10-day course of treatment ($2,800 versus $1,061 respectively). Retail pricing shows Fidaxomicin is $3,260.19 for a 10-day course as opposed to Vanco which is $1,365 and Metronidazole is markedly less expensive than either of these drugs at $27 for a 10-day course (N. Bidinger, personal communication, April 2, 2011). It may be reasonable to offset the concern of cost with decreased recurrence rates in those patients who experience recurrent infection. However, this will prohibit many providers from prescribing and will not be covered under health insurance plans requiring, at minimum, a pre-authorization for coverage.

For health care providers, prudent prescription of antimicrobial agents is of utmost importance in preventing the contraction of *C. difficile*. If a high-risk antimicrobial must be used, such as Clindamycin or a flouroquinolone, signs and symptoms of *C. difficile* should be included in the counseling of patient, such as more than three watery stools a day, abdominal cramping,

fever, nausea, and dehydration so the offending agent can be discontinued and treatment for the infection can be instituted early (Mayo Clinic, 2010).

Polymerase chain reaction (PCR) testing is generally used to assess the presence of *C. difficile* in stool. This test is rapid, with high sensitivity and specificity (Cohen, et al., 2010). However, current guidelines report that more data is still needed on PCR testing before an official recommendation will be issued for use of PCR (Cohen, et al., 2010). Rather, guidelines state that identification of the infection should be obtained using an enzyme immunoassay test (EIA) to screen followed by a toxinogenic culture for confirmation (Cohen, et al., 2010). The IDSA guidelines support this method as an "interim recommendation" pending more data on sensitivity and support stool culture as the gold standard but acknowledge that "stool culture is not clinically practical because of its slow turnaround time" (Cohen, et al., 2010, p.9).

If recurrent *C. difficile* is diagnosed with failed response to current treatment guidelines, Fidaxomicin is a reasonable next line therapy. Patients should be counseled on duration of treatment (10 days of twice daily dosing), side effects of the medication including abdominal pain, nausea and vomiting, anemia, and neutropenia, as well as the more serious side effects of bowel obstruction and gastrointestinal hemorrhage (FDA, 2011). Follow-up should occur after therapy and with any progression of disease symptoms, non-resolution of symptoms, and recurrence of infection.

Table 1. In vitro activity of Fidaxomicin, Vancomycin and Metronidazole against select bacterial isolates

Study	Bacterial group	Antimicrobial agent	MIC_{50}	MIC_{90}
Finegold, et al (2004)	*C. difficile*	Fidaxomicin	0.12	0.25
		Vancomycin	1	2
		Metronidazole	0.25	0.5
	All *clostridium* species	Fidaxomicin	0.062	128
		Vancomycin	1	16
		Metronidazole	≤0.5	1.0
	Miscellaneous gram-positive non-spore-forming rods Includes *lactobacillus* and *bifidobacteria*	Fidaxomicin	1	32.0
		Vancomycin	1	2
		Metronidazole	4.0	>128
	Bacteroides fragilis	Fidaxomicin	256	1024
		Vancomycin	64	128
		Metronidazole	1	4
Credito, et al (2004)	*C. difficile*	Fidaxomicin	≤0.016	0.25
		Vancomycin	0.5	2.0
		Metronidazole	≤0.125	0.5
	All *clostridium* species	Fidaxomicin	≤0.016	0.25
		Vancomycin	0.25	2.0
		Metronidazole	≤0.125	2.0
	Miscellaneous gram-positive non-spore-forming rods Includes *lactobacillus* and *bifidobacteria*	Fidaxomicin	0.25	16.0
		Vancomycin	0.25	16.0
		Metronidazole	2.0	>16.0
	Bacteroides fragilis	Fidaxomicin	64.0	>128
		Vancomycin	>16.0	>16.0
		Metronidazole	0.25	1.0

MIC_{50} - MIC at which 50% of isolates tested were inhibited
MIC_{90} – MIC at which 90% of isolates tested were inhibited

Table 2. Efficacy of Fidaxomicin versus Vancomycin in clinical cure rates, recurrence, and global cure rates

Author	Clinical cure	Recurrence	Global cure
Drekonja, et al (2011)	no significant difference	p=0.005	not reported
Louie, et al (2009)			
mITT group	-3.1 percentage points	p=0.005	p=0.006
PP group	-2.6 percentage points	p=0.004	p=0.006
Mullane, et al (2011)			
With any CA antibiotic	P=0.04	p=0.048	p=0.02
With high-risk antibiotic	p=0.09	p=0.54	p=0.18

mITT: modified intention to treat group
PP: per protocol group

Table 3. Demographics and interventions of studies examining the efficacy of Fidaxomicin versus Vancomycin in clinical cure rates, recurrence, and global cure rates

Author	Purpose	Sample	Research Design	Measures	Intervention Outcomes
Drekojna, et al (2011)	To determine whether among adults with C. Diff, treatment with certain antibiotics compared with others results in differences in initial cure, recurrence, and harms	1324 subjects	Systematic Review	Fecal samples	IV: Fidaxomicin Vancomycin Flagyl Other Antibiotics DV: Initial Cure Recurrence
Louie, et al (2011)	Compare the efficacy and safety of fidaxomicin with those of vancomycin in treating C. Diff infection	629 patients 302 fidaxomicin 327 vancomycin **mITT: 596** 333 female 263 male 354 inpt 242 outpt **PP: 548** 329 female 219 male 308 inpt 240 outpt	Double Blind RCT	Fecal samples for toxin tests Blood samples for PD effects	IV: Fidaxomicin Vancomycin DV: Clinical Cure Recurrence Global Cure
Mullane, et al (2011)	To study the effects of concomitant antibiotics on response to fidaxomicin and vancomycin	999 subjects 584 female 415 male 393 outpatient 606 inpatient 481 fidaxomicin 518 vancomycin **Recurrence:** 794 subjects 391 fidaxomicin 403 vancomycin	Double Blind RCT	Fecal samples	IV: Fidaxomicin Vancomycin DV: Clinical cure Recurrence Global cure

mITT: modified intention to treat; PP: pre protocol; IV: independent variable; DV: dependent variable
RCT: Randomized control trial

References

Choi, H.K., Kim, H., Lee, S.H. & Lee, S.J. (2011). Risk factors for recurrence of *Clostridium difficile* infection: Effect of Vancomycin-resistant *Enterococci* colonization. *Journal of Korean Medical Science*, 26, 859-864. doi: 10.3346/jkms.2011.26.7.859

Cohen, S.H., Gerding, D.N., Johnston, S., Kelly, C.P., Loo, V.G., McDonald, L.C.,…Wilcox, M.H. (2010). *Clinical practice guidelines for* Clostridium difficile *infection* in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). *Infection Control and Hospital Epidemiology,* 31, 431-455.

Credito, K.L. & Appelbaum, P.C. (2004). Activity of OPT-80, a novel macrocycle, compared to those of eight other agents against selected anaerobic species. *Antimicrobial Agents and Chemotherapy,* 48, 4430-4434. Doi: 10.1128/AAC.48.11.4430-4434.2004

Drekonja, D.M., Butler, M., MacDonald, R., Bliss, D., Filice, G.A., Rector, T.S.,…Wilt, T.J. (2011). Comparative effectiveness of *Clostridium difficile* treatments, A systematic review. *Annals of Internal Medicine,* 155, 839-848.

Finegold, S.M., Molitoris, D., Vaisanen, M.L., Song, L., Liu, C. & Bolaños, M. (2004). In vitro activities of OPT-80 and comparator drugs against intestinal bacteria. *Antimicrobial Agents and Chemotherapy,* 48, 4898-4902. doi: 10.1128/AAC.48.12.4898-4902.2004

Freeman, J., Bauer, M.P., Baines, S.D., Corver, J., Fawley, W.N.,…Wilcox, M.H. (2010). The changing epidemiology of *Clostridium* difficile infections. *Clinical Microbiology Reviews,* 23, 529-549. doi: 10.1128/CMR.00082-09

Gerding, D.N. (2010). Global epidemiology of *Clostridium difficile* infection in 2010. *Infection Control and Hospital Epidemiology*, 31F(S1), S32-S34.

Khanna, S., Pardi, D.S., Aronson, S.L., Kammer, P.P., & Baddour, L.M. (2012). Outcomes in community-acquired *Clostridium difficile* infection. *Alimentary Pharmacology and Therapeutics,* 35, 613-618. doi: 10.1111/j.1365-2036.2011.04984.x

Kuntz, J.L., Chrischilles, E.A., Pendergast, J.F., Herwaldt, L.A., & Polgreen, P.M. (2011). Incidence of and risk factors for community-associated *Clostridium difficile* infection: A nested case-control study. *Biomed Central Infectious Diseases,* 11, 194-100.

Louie, T., Miller, M., Donskey, C., Mullane, K. & Goldstein E.J.C. (2009). Clinical outcomes, safety, and pharmacokinetics of OPT-80 in a phase 2 trial with patients with *Clostridium difficile* infection. *Antimicrobial Agents and Chemotherapy,* 53, 223-228. doi: 10.1128/AAC.01442-07

Louie, T.J., Miller, M.A., Mullane, K.M., Weiss, K., Lentnek, A.,…Shue, Y.K. (2011). Fidaxomicin versus Vancomycin for *Clostridium difficile* infection. *New England Journal of Medicine*, 364, 422-431.

LoVecchio, A. & Zacur, G.M. (2012). *Clostridium difficile* infection: an update on epidemiology, risk factors, and therapeutic options. *Current Opinion in Gastroenterology*, 28, 1-9. doi: 10.1097/MOG.0b013e32834bc9a9

Mayo Clinic. (2010). *C. difficile*: symptoms. Retrieved from http://www.mayoclinic.com/health/c-difficile/DS00736/DSECTION=symptoms

McFarland, L.V. (2008). Renewed interest in a difficult disease: *Clostridium difficile* infections – epidemiology and current treatment strategies. *Current Opinions in Gastroenterology,* 25, 24-35. doi: 10.1097/MOG.0b013e32831da7c4

Miller, M. (2010). Fidaxomicin (OPT-80) for the treatment of *Clostridium difficile* infection. *Expert Opinion in Pharmacotherapy,* 11, 1569-1578.

Mullane, K.M., Miller, M.A., Weiss, K., Lentnek, A., Golan, Y., Sears, P.S.,…Gorbach, S.L. (2011). Efficacy of Fidaxomicin versus Vancomycin as therapy for *Clostridium difficile* infection in individuals taking concomitant antibiotics for other concurrent infections. *Clinical Infectious Diseases,* 53, 440-447. doi: 10.1093/cid/cir404

Noren, T. (2010). *Clostridium difficile* and the disease it causes. In Mullany, P. & Roberts, A.P. (Eds.), *Methods in Molecular Biology* (pp. 9-35). Totawa, NJ: Humana Press.

Peterson, H. (2011). Optimer wins FDA panel's backing for antibiotic Fidaxomicin, *Bloomberg.* Retrieved from http://www.bloomberg.com/news/2011-04-05/optimer-wins-fda-advisory-panel-s-backing-for-fidaxomicin-1-.html

Prabaker, K. & Weinstein, R.A. (2011). Trends in antimicrobial resistance in intensive care units in the United States. *Current Opinion in Critical Care,* 17, 472-479. doi: 10.1097/MCC.0b013e32834a4b03

Sullivan, K.M. & Spooner, L.M. (2010). Fidaxomicin: A macrocyclic antibiotic for the management of *Clostridium difficile* infection. *The Annals of Pharmacotherapy,* 44, 352-359.

Tannock, G.W., Munro, K., Taylor, C., Lawley, B., Young, W., Byrne, B.,… & Louie, T. (2010). A new macrocyclic antibiotic, fidaxomicin (OPT-80), causes less alteration to the bowel microbiota of *Clostridium difficile*-infected patients than does Vancomycin. *Microbiology,* 156, 3354-3359. doi: 10.1099/mic0.042010-0

U.S. Food and Drug Administration. (2010). Fidaxomicin: Label and approval history. Retrieved from http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/201699s000lbl.pdf

U.S. Food and Drug Administration. (2010). Flagyl: Label approval and history. Retrieved from http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist

Warny, M., Pepin, J., Fang, A., Killgore, G., Thompson, A., Brazier, J.,…McDonald, L.C. (2005). Toxin production by an emerging strain of *Clostridium difficile* associated with outbreaks of severe disease in North America and Europe. *Lancet,* 366, 1079-1084.

Xu, J., Kochanek, K.D., Murphy, S.L. & Tejada-Vera, B. (2010). *Deaths: Final data for 2007* (National Vital Statistics Report v.58, No. 19). Hyattsville, MD: National Center for Health Statistics.