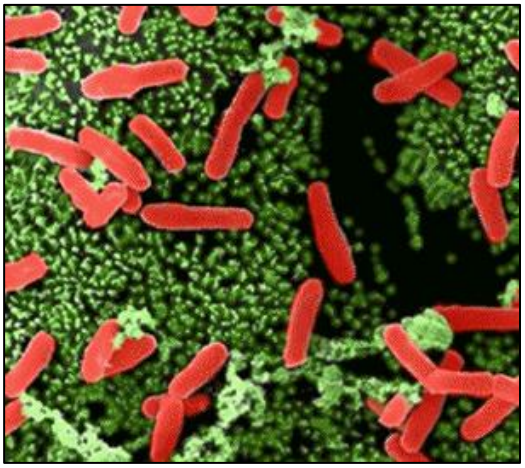
COLUMBIA UNIVERSITY MEDICAL CENTER

DIVISION OF GENERAL MEDICINE

Senior Medicine Rotation: Evidence-Based Medicine Project

Student Name: Chris Lawton **Block: August** **Date: 8/31/11**

CASE SIGNOUT: 41yo man with h/o epileptic seizures, PUD and EtOH dependence with many prior hospitalizations for withdrawal (most recently 7/30/11 at CUMC) who presented in mild EtOH withdrawal (CIWA 14) and 3 days of watery, non-bloody diarrhea. He reports one prior episode of *C. difficile* infection 2 months ago while hospitalized at Cedars Sinai for which he completed a 2-week course of metronidazole as an outpatient. On this admission he is reporting 10-12 loose BM daily, afebrile, abdomen non-tender, Cr 0.8, WBC 8.8, *C. difficile* toxin B gene positive by PCR. He is started on metronidazole 500mg TID. He tells primary team he wants to taper chlordiazepoxide as quickly as possible so he can be discharged promptly. Plan was to taper chlordiazepoxide for 5 days while monitoring for withdrawal sx, continue metronidazole while inpatient and discharge patient on vancomycin for completion of 10-day abx course.



Clinical Question: *Given concern for disulfiram-like reaction with metronidazole in setting of EtOH use, what options are available for outpatient treatment of non-severe C. difficile colitis in patients with EtOH dependence who are likely to resume EtOH use at the time of discharge?*

Search Strategy

Database: PubMed

- Limits: randomized controlled trial, humans, English, "clostridium difficile infection"
- Results: 19

1. Fidaxomicin versus vancomycin for **Clostridium difficile infection**.
Louie TJ, Miller MA, Mullane KM, Weiss K, Lentnek A, Golan Y, Gorbach S, Sears P, Shue YK; OPT-80-003 Clinical Study Group.
N Engl J Med. 2011 Feb 3;364(5):422-31.
PMID: 21288078 [PubMed - indexed for MEDLINE] **Free Article**
Related citations

2. Effect of probiotic Lactobacillus (Lacidofil® cap) for the prevention of antibiotic-associated diarrhea: a prospective, randomized, double-blind, multicenter study.
Song HJ, Kim JY, Jung SA, Kim SE, Park HS, Jeong Y, Hong SP, Cheon JH, Kim WH, Kim HJ, Ye BD, Yang SK, Kim SW, Shin SJ, Kim HS, Sung JK, Kim EY.
J Korean Med Sci. 2010 Dec;25(12):1784-91. Epub 2010 Nov 24.
PMID: 21165295 [PubMed - indexed for MEDLINE] **Free PMC Article**
Free full text Related citations

3. Treatment with monoclonal antibodies against **Clostridium difficile** toxins.
Lowy I, Molrine DC, Leav BA, Blair BM, Baxter R, Gerding DN, Nichol G, Thomas WD Jr, Leney M, Sloan S, Hay CA, Ambrosino DM.
N Engl J Med. 2010 Jan 21;362(3):197-205.
PMID: 20089970 [PubMed - indexed for MEDLINE] **Free Article**
Related citations

4. Nitazoxanide versus vancomycin in **Clostridium difficile infection**: a randomized, double-blind study.
Musher DM, Logan N, Bressler AM, Johnson DP, Rossignol JF.
Clin Infect Dis. 2009 Feb 15;48(4):e41-6.
PMID: 19133801 [PubMed - indexed for MEDLINE] **Free Article**
Related citations

5. Cranberry or trimethoprim for the prevention of recurrent urinary tract infections? A **randomized controlled trial** in older women.
McMurdo ME, Argo I, Phillips G, Daly F, Davey P.
J Antimicrob Chemother. 2009 Feb;63(2):389-95. Epub 2008 Nov 28.

Senior Medicine Rotation: Based Medicine Project (Cont)

Group	Criteria or definition	n
Population screened.	men and women in the United States and Canada	Not noted
Inclusion criteria	• ≥ 16yo • diagnosed with *C. difficile* infection, defined by: ➢ presence of diarrhea (change in bowel habits, >3 unformed BM during 24hrs prior to randomization) ➢ *C. difficile* toxin A, B or both in stool specimen collected within 48hrs prior to randomization	Not noted
Exclusion criteria	• Life-threatening or fulminant *C. difficile* infection (wbc > 30; T □40□C; evidence of hypotension, septic shock, peritoneal signs, significant dehydration) • Toxic megacolon • Previous exposure to fidaxomicin • History of ulcerative colitis of Crohn's disease • More than one episode of *C. difficile* infection within 3 months prior to start of study	Not noted
Treatment group	• Randomized to 10 day tx with either: ➢ 200mg fidaxomicin q12hrs with matching placebo ➢ 125mg vancomycin q6hrs • During 10 day course of tx, assessed daily for: ➢ clinical cure = resolution of diarrhea (≤3 unformed stools for 2 consecutive days) for duration of tx with no further req of tx as of 2nd day of end of tx course ➢ clinical failure = persistence of diarrhea, need for additional tx or both in opinion of investigator • If criteria for cure met, pt was followed for recurrence once weekly for 4 weeks after last dose of study med ➢ clinical recurrence = reappearance of >3 diarrheal BM within a 24 hr period during 4wks after tx end	596 vancomycin – 309 fidaxomicin – 287

Primary endpoint:

- Clinical cure at the end of therapy or at the time of early withdrawal from study

Secondary endpoints:

- Recurrence of *C. difficile* infection during the 4 week period after the end of tx course
- Global cure (resolution of diarrhea without recurrence)

- **Are the Results of the Trial Valid?**
  - **Randomized?** YES
  - **All patients accounted for at end?** YES
  - **Intention to treat?** YES
    - Modified intention to treat population = pts had documented *C. difficile* infection, underwent randomization and received at least 1 dose of study medication
    - Per protocol population = pts received at least 3 days of tx (in cases of clinical failure) and 8 days of tx (in cases of clinical cure), had documented adherence to protocol and underwent end-of-therapy evaluation
  - **Blinding?** YES, double
  - **Groups similar at start of trial?** YES, see below

- **Equal treatment of groups?** YES
  - Despite differences in dosing, placebos added so that both groups were given same number of antibiotic pills. Follow-up was the same in both groups with daily assessment for clinical cure or failure during the 10 days of abx therapy and weekly assessment for 4 weeks after the last abx dose.
- **Did randomization work?** YES
  - No significant differences in: age, sex, # unformed stools per day, inpatient vs. outpatient tx, h/o lack of response to metronidazole, previous *C. difficile* tx in last 24hrs, previous *C. difficile* infection, *C. difficile* strain isolated

Endpoint	**Result**	**Significance**
Clinical cure (1°)	mITT – fidaxomicin 88.2% mITT – vancomycin 85.8% PP – fidaxomicin 92.1% PP – vancomycin 89.8%	Lower boundary of confidence limit for mITT and PP were -3.1 and -2.6 respectively, both within the preset -10 % point non-inferiority margin
Global cure (2°)	mITT – fidaxomicin 74.6% mITT – vancomycin 64.1% PP – fidaxomicin 77.7% PP – vancomycin 67.1%	mITT, P=0.006 PP, P=0.006
Morbidity	**Result**	**Significance**
Recurrence (2°)	mITT – fidaxomicin 15.4% mITT – vancomycin 25.3% PP – fidaxomicin 13.3% PP – vancomycin 24.0%	mITT, P=0.005 PP, P=0.004
Adverse events (mild GI and nonspecific symptoms)	fidaxomicin 9.7% vancomycin 9.0%	not noted

- Results
  - Clinical cure
    - *Non-inferiority design*: Authors state that if lower boundary of the 97.5% CI for the difference in cure rates is within a -10 percentage non-inferiority margin, clinical non-inferiority was demonstrated (met in mITT and PP)
    - Rates of clinical cure were not statistically different between treatments in both mITT and PP populations across subgroup analysis
  - Recurrence
    - Fidaxomicin had significantly lower rate than vancomycin in mITT and PP
    - When broken down by subgroup, presence of significant difference between tx groups varied by subgroup, with significantly lower recurrence w/fidaxomicin in:
      - ≥65 (mITT), <65 (PP)
      - inpatient and outpatient (mITT), outpatient (PP)
      - no previous history of *C. difficile* (mITT and PP)
      - **no previous tx for *C. difficile* (mITT and PP)**
        - significant difference not found for pts with previous infection
      - mild or severe disease (mITT and PP)
      - Non-NAP1/BI/027 strains (mITT and PP)
      - Concomitant sys abx therapy (PP) or No concomitant tx (mITT and PP)
  - Global cure – fidaxomicin resulted in significantly higher rates of global cure

- **Are the Results of the Trial important?** **YES, size and precision of effect:**

Endpoint	**Modified ITT**	**Per protocol**
Clinical cure	2.5% ↑ w/ fidaxomicin *lower border 97.5% CI of -3.1*	2.3% ↑ w/ fidaxomicin *lower border of 97.5% CI of -2.6*
Recurrence	9.9% ↓ w/ fidaxomicin *95% CI [-16.6 to -2.9]*	10.7% ↓ w/ fidaxomicin *95% CI [-17.9 to -3.3]*
Global cure	10.5% ↑ w/ fidaxomicin *95% CI [3.1 to 17.7]*	10.6% ↑ w/ fidaxomicin *95% CI [3.1 to 17.9]*

- YES, these results are important
    - *C. difficile* infection is increasing in frequency and severity and this study offers another possible treatment with equivalent results with regards to clinical cure, decreased recurrence in certain subgroups and increased global cure rate which has the potential to reduce morbidity and mortality as well as healthcare expenditures on this common nosocomial infection

- **Can I apply these results to my patient?**
    - Comparison of my patient to trial patients
        - This patient fits the inclusion criteria as he is ≥16yo with significant diarrhea at the time of presentation and C. difficile toxin B positive by PCR.
        - He has no WBC elevation, fever, hypotension, peritoneal signs or evidence of dehydration to suggest fulminant *C. difficile* infection, an exclusion criterion. He has taken only metronidazole in the past for *C. difficile* infection and has no history of inflammatory bowel disease. He has had one episode of *C. difficile* infection in the past 3 months.
        - Additionally, his alcoholism limits his therapeutic options, making the results of this study particularly applicable
    - All clinically important outcomes considered
        - All clinically important outcomes do appear to be considered
            - Their primary outcome of cure is defined clinically in terms of symptom resolution which is helpful to clinicians using this data for practice.
            - They address the critical issue of recurrence which is currently seen in as many as 25% of cases of *C. difficile* infection. They achieve this by following patients for 4 weeks after the end of treatment which adequately covers the 1-3 week post-antibiotic window in which the majority of recurrences occur.
            - The secondary end point of global cure is defined after 4 weeks. Reports have shown recurrences as far out as 10 weeks after antibiotics end, so further investigation could examine the effectiveness of fidaxomicin in with regards to this secondary endpoint over a longer time interval.
            - Adverse events are considered adequately here with mild GI symptoms seen in approximately 10% of patients, consistent with the known side effect profile for fidaxomicin.
    - Likely benefits outweigh potential harms and cost?
        - Based on the evidence described here, I would not start fidaxomicin in this patient. While non-inferiority has been shown and decreased global cure rate is promising, decreased rate of recurrence over vancomycin has not been shown across certain subgroups that this patient fits into, including those having a previous episode of *C. difficile*. The significant reduction in recurrence rate in individuals <65 (per-protocol), on outpatient management and with mild disease is encouraging however. At present we do not know the strain of *C. difficile* carried by this patient so cannot assess any possible benefit of fidaxomicin from this regard. More study is needed here.
        - Additionally, despite the benefits discussed above, cost makes fidaxomicin presently less appealing as it is substantially more expensive than vancomycin.
            - vancomycin 10 day course – $1000-1500
            - fidaxomicin (Dificid™) 10 day course - $2800

- **Weaknesses/Limitations**
    - Authors do not include data on the screening population as well as the entire body of those screened that did not meet inclusion or met exclusion criteria
    - Lack of clear definition of mild, moderate and severe disease which makes application to patient in question more difficult

    - Non-inferiority design creates an inherent subjectivity because of need to choose the lower end of the confidence interval (here set at -10 percentage points)

- NOTE: Some of authors work for, own stock in and received funding to execute this study and present these results from Optimer Pharmaceuticals, the company that produces fidaxomicin. This is conflict of interest is fully acknowledged by authors.

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