COLUMBIA UNIVERSITY MEDICAL CENTER

DIVISION OF GENERAL MEDICINE

Senior Medicine Rotation: Evidence-Based Medicine Project

Student Name: Oye Imoisili Block: July 2013 Date: 7/31/13

Case SIGNOUT:

Mr. S is a 28 year old male with no past medical history who presents with bloody diarrhea. The patient was in his normal state of health until the early morning on the day prior to presentation, when he was woken from sleep by stomach pain and large volume loose stools. He was able to tolerate small amounts of PO intake during the rest of the day, but had episodes of watery diarrhea every 5 minutes. The next day he developed blood in his stool, prompting him to present to CUMC.

In the ED, he had vitals: T 37 C, HR 77 bpm, BP 122/78, RR 18, SpO2 99%. His CBC panel was WBC 8.6/ Hgb 16.5/Hct 48.3/Plt 251; BMP included Na^+ 140, K^+ 3.4, Cl^- 99, HCO_3^- 26, BUN 7, Cr 1.10, Glucose 85. Venous lactate was 4.3. Mr. S had at least 3-4 episodes of NBNB emesis in the ED, and could not tolerate anything PO. He vomited 750 mg of PO Levaquin, and was subsequently administered 500 mg of IV levofloxacin. In addition he received 4 L normal saline for rehydration, and 16 mg of morphine for pain control, before being endorsed to Senior Medicine A.

Clinical Question:

General: Should antibiotics be used empirically in the treatment of adult patients with severe acute infectious gastroenteritis?

Specific: What effect does a single dose of a quinolone drug have on the symptoms or prognosis of adults with severe acute gastroenteritis, compared to no antibiotic treatment or a full antibiotic regimen?

Background

Epidemiology: Annually there are 211 million – 375 million episodes of acute diarrhea in the United States. This results in 900,000 hospitalizations and 6000 deaths each year. In the US, most diarrheal illnesses occur during the winter, commonly caused by norovirus or rotavirus, and are self-limited.

Microbiology: Typically, microbiologic investigation is unnecessary if presenting within 24 hours of onset unless patients: a) are febrile, b) significantly dehydrated, or c) have blood or pus in stool. The most common non-viral organisms are: Salmonella (16.1/100,000); Campylobacter (13.4/100,000); Shigella (10.3/100,000); E. Coli O157:H7 (1.7/100,000); Cryptosporidium (1.4/100,000)

Mechanism: Specific mechanism of infection depends on the organism, but the patient may develop a secretory, exudative, or inflammatory diarrhea and/or dysentery. This frequently occurs when bacteria invades the bowel walls.

Clinical Presentation: Diarrhea ($\geq$3 loose stools per day) in addition to any of the following constellation of symptoms: abdominal pain, nausea and vomiting, bloody stools, fever.

Diagnosis: Severe acute diarrhea is a symptomatic diagnosis. It is not uncommon for an offending organism to never be determined.

Treatment: Regimens for treatment vary according to organism of infection; but part of the controversy is whether or not antibiotics are necessary or not for treatment. Antibiotics are useful in treatment of shigellosis, traveler's diarrhea, C. difficile diarrhea, or campylobacteriosis (if given early). However, antibiotics may prolong shedding duration for salmonella and C. difficile; induce resistance in patients with Campylobacter infection; or increase potential of life threatening risk of complications from Shiga toxin E. Coli infection. This specifically refers to Hemolytic Uremic Syndrome, which develops in 10% of cases and in turn has a 5-10% mortality.

Search Strategy

Database: PubMed

Search term: "acute gastroenteritis diarrhea adult antibiotic randomized controlled trial"

Group	Criteria or definition	n
Population screened	Adults who presented to Barzilai Medical Center Emergency Room (in Israel) with diarrhea between the months of June – October from 2002-2004.	1055
Inclusion criteria	Adults who fulfilled one or more of the DuPont criteria for severe acute diarrhea: 1. Profuse water diarrhea with dehydration 2. Passage of many stools containing mucus and blood. 3. Temperature $\geq$ 38.5 C. 4. Passage of more than 6 soft stools in 24 hours or duration of illness of more than 48 hours. 5. Severe abdominal pain in a patient over the age of 50. 6. Diarrhea in the elderly	139
Exclusion criteria	Children, or adult patients who presented with acute diarrhea but did not fulfill one of DuPont's criteria.	916
Treatment group	Patients who received general measures (defined below), in addition to one of six treatment groups: 1. Patients treated with ofloxacin 200 mg BID for 5 days 2. Patients treated with a single dose of ofloxacin 400 mg 3. Patients treated with ciprofloxacin 500 mg BID for 5 days 4. Patients treated with a single dose of ciprofloxacin 1000 mg 5. Patients treated with levofloxacin 500 mg once a day for 5 days 6. Patients treated with a single dose of lovefloxacin 1000 mg	 21 17 21 18 14 15
No treatment group	Patients treated with general measures such as hydration and alteration of diet (removal of dairy beverages, fruits, vegetables, and rice from the diet), and antiperistaltics.	33

Clinical Endpoints
No distinction was made between primary and secondary endpoints. The endpoints included: in hospital stay, fever, abdominal pain, diarrhea, and vomiting. All of these were endpoints were measured in days.

Are the Results of the Trial Valid?
Randomized? Patients were randomized, but the authors do not specify exactly how this was done.
All patients accounted for at end? Yes, all patients initially included were accounted for.
Intention to treat? There is no mention in this paper of patients switching treatment groups.
Blinding? A weakness of this study is that it was not blinded (at least, blinding was not explicitly stated).
Groups similar at start of trial? The only demographic details provided in comparison of treatment groups are the ages. Overall, the average age was 45.7 $\pm$ 18.7 years. However, the average age of different treatment groups range from 42.8 to 49.3 years.
Did randomization work? Also, the sex ratio within each treatment group was not reported (the overall study had 87 men and 52 women). Therefore, it cannot be ascertained whether randomization worked.
Equal treatment of groups? Except for difference in antibiotic regimen, it is presumed that the groups were treated equally. However, the control group did not receive a placebo, but only general standard of care to treat symptoms. There would likely be an inherent bias between people taking medications or not, and for what length they are taken.

Are the Results of the Trial important?
Overall: In all antibiotic treated groups, there was a significant reduction in duration of symptoms (except for fever in general, and for vomiting in levofloxacin). All 7 groups did not differ by severity of their disease or symptoms. However, length of hospitalization was significantly shorter in the supportive therapy group. Single dose therapy for antibiotics could be more cost effective than a 5 day regimen.
Size of treatment effect? Antibiotic treatment was associated with an average 1 day shorter duration of symptoms compared to the control group, whether administered as single dose therapy ($P<0.007$) or 5

days of therapy (P<0.001). Therefore the effect may be larger after 5 days of therapy, but the result is still that of statistical significance with single dose therapy, and there is very little clinical difference.
Precision of the estimate of the effect? Though there is a relatively small number in each treatment group in this study, the results are still significant. This implies enough power for this effect size, and a Type II statistical error seemed not to be an issue. However, greater numbers could have allowed the authors to stratify their resulting endpoints by illness symptoms, such as specifically bloody diarrhea.

Endpoint	Result	Significance	ARR	NNT
Please see table below for details. **Tarivid = ofloxacin** **Tavanic = Levofloxacin**	Significant reduction in symptoms except fever	P≤ 0.05 as marker of statistical significance. Please see table below.	N/A	N/A
Morbidity	**Result**	**Significance**	**ARI**	**NNH**
None	N/A	N/A	N/A	N/A

TABLE 2. Mean Differences Between Duration of Symptoms in Treated Groups (Compared With Supportive Therapy Group)

Manifestation of Disease	Single Dose of Ciprofloxacin	Single Dose of Tarivid	Single Dose of Tavanic	5 Days of Ciprofloxacin	5 Days of Tarivid	5 Days of Tavanic
In-hospital stay (d)	−1.2 $P < 0.05$	−0.6 $P < 0.05$	−1.1 $P < 0.05$	−1.5 $P < 0.05$	−0.8 $P < 0.05$	1.5 $P < 0.05$
Fever (d)	0 Nonsignificant	−0.1 Nonsignificant	0.2 Nonsignificant	−0.2 Nonsignificant	−0.2 Nonsignificant	−0.1 Nonsignificant
Abdominal pain (d)	1.4 $P < 0.05$	1.3 $P < 0.05$	1.1 $P < 0.05$	0.6 $P < 0.05$	1.4 $P < 0.05$	1.4 $P < 0.05$
Diarrhea (d)	0.8 $P < 0.05$	0.6 $P < 0.05$	0.7 $P < 0.05$	0.7 $P < 0.05$	0.9 $P < 0.05$	0.7 $P < 0.05$
Vomiting (d)	0.8 $P < 0.05$	0.8 $P < 0.05$	0.4 Nonsignificant	0.8 $P < 0.05$	1.1 $P < 0.05$	1.2 $P < 0.05$

Can I apply these results to my patient?
All clinically important outcomes considered? Endpoints that were clinically relevant to severe acute diarrheal illness were appropriate selected in this study. Perhaps while not as clinically relevant, a medically relevant endpoint may have been whether stools were culture positive or not. However, generally with a high percentage of acute diarrhea episodes, the offending agent organism is never detected. In this study, stool cultures were only obtained from 26.6% of patients.
Comparison of my patient to trial patients: In general, one cannot directly apply the results of a population based study to the individual treatment of one individual. Beyond this, there are several differences between Mr. S and the participants in this study that make generalizing difficult. In terms of demographics, at age 28 Mr. S is almost 18 years younger than the average age of participants of this study; although he still falls within the study age range. One large discrepancy is the clinical picture: only 8.7% (n=12) of the participants in this study presented with bloody diarrhea. Therefore, the etiology of Mr. S's diarrhea is likely different than the vast majority of those in this study. Another obvious difference is that this study is carried out at one rural community hospital in Israel. The geographic and demographic differences between there and a large, urban academic center in New York City may mean a lack of to external validity in terms of applying study results to the patient population at CUMC. .
Likely benefits outweigh potential harms and cost? Currently there is no rapid diagnostic method for identification of enteric pathogens. Therefore, treatment of severe acute diarrheal illnesses with antibiotics is empiric. Unknown etiology is a major issue because the differential includes E. Coli O157:H7, in which Hemolytic Uremic Syndrome is a possible adverse event following antibiotic treatment. The question is: what is the overall benefit of decreasing symptoms by 1 day in many people who present with severe acute gastroenteritis vs. the risk of developing HUS in those who present with the same symptoms, but have an underlying etiology of E Coli O157:H7? Although there was only one case (5.6%) of E. Coli positive stool in this study, it is possible that the prevalence was much higher, as only 26.6% of stool cultures were obtained.
Decision Making: Ultimately, the decision whether to treat severe acute infectious gastroenteritis with antibiotics or not depends on the clinical judgment of the healthcare provider. While treating with antibiotics may benefit a population overall, decision making is different at the level of one individual patient. Another possibility to consider is that HUS may not be seen as frequently if only a single dose of antibiotics – deemed by this paper to be as clinically effective as a five day regimen – is administered.

References

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