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HEALIX

Clostridium difficile Associated Diarrhea Incidence and Outcomes for Patients Treated with Intravenous Antibiotics in Infectious Disease Physician Office Infusion Centers

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Abstract (revised)

Background: Patients (pts) receiving intravenous antibiotic (IVAB) therapy are considered at risk for acquiring *C. difficile* infection (CDI). Pts receiving IVAB at an infectious disease (ID) physician office infusion center (PCIC) may spend less time in a health care facility, thus potentially reducing the risk of serious health care facility-associated (HCFA) CDI. The study purpose was to evaluate the incidence of CDI for pts receiving IVAB at ID POICs.

Methods: A retrospective database review was conducted of pts in 7 ID POICs nationally treated with selected IVAB from Jan 1st, 2010 through June 30th, 2010. Selected IVAB included all carbapenems, cephalosporins, fluoroquinolones, monobactams, and penicillins. Pts were identified with confirmed or suspected CDI. Data collection included demographics, comorbidities, oral antibiotic (AB) use, and treatment (tx) of CDI. Clinical outcomes were measured in cases of confirmed CDI.

Results: We reviewed 934 patients who received IVAB from the aforementioned list. Twenty nine (3.1%) pts were identified as either confirmed (8, <1%) or suspected (21, 2%). Three confirmed cases met criteria for community-associated CDI and 3 confirmed cases met criteria for community-onset, HCFA CDI. Incidence of CDI was estimated at 2.5 per 10,000 days. Mean age was 70. Pts received an average of 2 AB over a mean duration of 30 (16-56) days. This included tx with both IVAB and oral AB. The most causative IVAB was ceftriaxone (3) and the most causative oral AB agent was ciprofloxacin (3). Risk factors included diabetes (5) and immunodeficiency (3). Three pts were taking concomitant acid-suppressive medications. Six confirmed pts were treated for CDI with single agent metronidazole (MTZ) and 1 with dual agents, including MTZ and vancomycin. Additionally, 8 suspected CDI pts were treated with MTZ. Confirmed CDI was cured in 5/8 pts and improving in 2/8 at discharge. One tx failure occurred in the pt with HCFA CDI.

Conclusion: Pts receiving broad-spectrum IVAB at ID POICs had a very low rate of CDI. This study further validates the safety in treating patients, when clinically appropriate, through an ID POIC. Additional studies are warranted to demonstrate differences in outcomes between pts treated in ID POICs versus other healthcare settings.

Background

Clostridium difficile infection is the leading cause of infectious diarrhea in hospitalized patients and incidence has increased to greater than 250,000 cases annually.[1,2] The mortality rate is 1 – 2.5% and the attributable healthcare cost has been estimated to range from $433 to $797 million per year.[3] Risk factors for CDI include advanced age (>65), antacid use, duration of hospitalization and exposure to antimicrobial agents.[4,5] Historically, antibiotic (AB) use has been observed as the most important modifiable risk factor. As outpatient parenteral antimicrobial therapy (OPAT) becomes a standard modality for stable patients requiring long-term antibiotics, this can also be implemented as a mechanism to decrease hospitalization duration and possibly reduce CDI incidence. The purpose of this study was to determine the incidence and outcomes of CDI in patients receiving OPAT at 7 POICs.

Methods

We retrospectively reviewed charts and electronic databases to identify all patients who received therapy with one or more intravenous antibiotics in 7 POICs nationally.

Inclusion Criteria:
Treatment at a participating POIC with at least one of the following intravenous antibiotic classes during the 2010 calendar year: carbapenems, cephalosporins, fluoroquinolones, monobactams, penicillins

Exclusion Criteria:
- Prior gastrointestinal surgery or any manipulation of the gastrointestinal tract
- Confirmed HIV diagnosis
- Concomitant cancer chemotherapy
- Co-morbidity with diarrhea symptoms, e.g. diverticulitis, Crohn's disease
- Diarrhea upon admission to POIC or history of chronic diarrhea prior to POIC admission
- Prior antimicrobial therapy (IV/PO) use within 2 months preceeding diagnosis of *C. difficile* infection

Outcomes definitions:
- Cured: clinical signs and symptoms are resolved, and/or no additional CDI tx is needed
- Improved: partial resolution of clinical signs and symptoms and/or additional CDI tx is necessary
- Failed: inadequate response to CDI treatment, worsening or new/recurrent signs and symptoms, or need for admission to the hospital due to worsening signs and symptoms from CDI
- Nonevaluable: unable to determine response at the end of CDI tx

Definitions of CDI:
- Confirmed primary or secondary diagnosis of CDI as defined by:
  - Presence of diarrhea defined as passage of 3 or more unformed stools in 24 or fewer consecutive hours, and
  - Stool test result positive for the presence of toxigenic *C. difficile* or its toxins, or
  - Colonoscopic or histopathologic findings demonstrating pseudomembranous colitis[4]
- Suspected CDI as defined by: Two or more episodes of diarrhea in 24 hrs that did not spontaneously resolve or with AB discontinuation OR treatment with PO vancomycin, metronidazole or cholestyramine
- CDI case definitions were made based upon SHEA and IDSA Clinical Practice Guidelines.[4]

Data Analysis:
- Descriptive statistics (mean, standard deviation) were used for demographic and culture data.
- Percentages were used for culture, safety and efficacy data.

Results

Demographics:

- 934 patients met inclusion criteria
- 29 patients met the definition of confirmed or suspected CDI
- 8 patients were confirmed with CDI and treated

Table 1: Demographics

Characteristics	No. (%)
Gender	
Female	4 (50%)
Male	4 (50%)
Age in yrs	
Mean (range)	70 (58-88)
> 64	4 (50%)
≤ 64	4 (50%)
Comorbidities	
Diabetes	5
Chronic Lung Disease	4
Hyperlipidemia	3
Hypertension	3
Immunocompromise, Cancer History	3
Genitourinary Disease	3
Peripheral Vascular Disease	2
Other*	3
Comorbidities per Patient	
≥ Three	8 (100%)
Location Prior to Antibiotic Therapy	
Community	6 (75%)
Hospital	2 (25%)
Antacid Use (PPI or H2RA)	3 (38%)

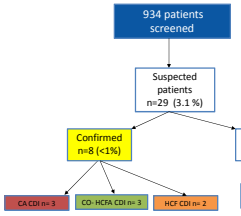
*Other category included cardiac disease, dermatomyositis, myasthenia gravis

Table 2. Diagnoses

Diagnosis	No. (%)
Osteomyelitis	3 (38%)
Genitourinary Infection	2 (25%)
Cellulitis	1 (12%)
Sinopulmonary Disease	1 (12%)
Bacteremia	1 (12%)

CDI Characterization:

Figure 1. Characterization and Case Definitions



CA CDI=community acquired CDI; CO-HCFA=community onset, health care facility associated; HCF=Health care facility onset

Antibiotic Utilization:

Table 3: Antibiotic Therapy Characteristics by Patient

Patient Number	Drug Therapy	Treatment Days by Drug	Total AB Therapy Duration (days)	Time to CDI Occurrence (days)
1	Oral Ciprofloxacin§	4	56	53
	Piperacillin/Tazobactam*	52		
2	Ceftriaxone*	18	18	15
	Vancomycin*	16		
	Oral Fluconazole*	18		
3	Imipenem-Cilastatin*	31	31	9
4	Ceftriaxone‡	3	16	10
	Vancomycin‡	3		
	Oral Azithromycin‡	5		
	Cefazolin**	11		
	Oral Ciprofloxacin**	10		
5	Ertapenem**	2	26	8
	Daptomycin**	1		
	Vancomycin†	10		
	Vancomycin*	14		
6	Cefepime*	19	24	24
	Oral Ciprofloxacin§	5		
7	Ceftriaxone†	6	23	37
	Ceftriaxone*	9		
	Oral Amoxicillin/Clavulanate§	8		
8	Oral Cephalexin§	10	47	70
	Ceftazidime†	5		
	Ceftazidime ‡‡§	9		
	Ceftazidime**	7		
	Piperacillin/Tazobactam**	23		

*HDIC Medications †Hospital Medications §Community Medications
**HDIC Concurrent Medications Hospital Concurrent Medications

- 7/8 patients with confirmed *C. difficile* were treated ≥ 2 or more antibiotics
- Intravenous agent associated with most cases was ceftriaxone (3)
- Overall intravenous use accounted for 65% of use
- Oral agent associated with most cases of CDI was ciprofloxacin (3)
- Mean time to occurrence of CDI was 28 days following AB initiation

Figure 2. Antibiotic Use Per Patient

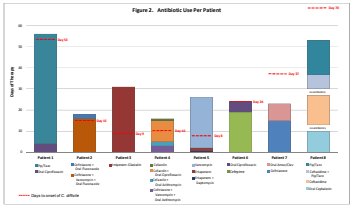


Figure 3. Total IV Antibiotic Use

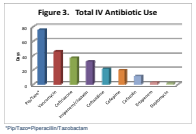
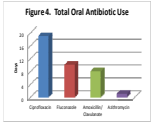


Figure 4. Total Oral Antibiotic Use



*Pip/Tazo=Piperacillin/Tazobactam

Drug Therapy for *Clostridium difficile:*

Table 4: *C. Difficile* Drug Therapy and Outcomes

Patient No.	Type of CDI[a]	Initial CDI Treatment	CDI Duration (Days)	Subsequent CDI Treatment	Subsequent Duration (days)	Final Outcome
1	CA	MTZ 500mg TID	10			Cured
2	HCF	MTZ 500mg TID	23			Cured
3	CA	MTZ 500mg TID	17	Vancomycin 500mg TID, Vancomycin 125mg BID	36	Cured
4	CO-HCFA	Immodium A+D 2mg Q 6 Hrs prn	5	MTZ 250mg TID X 1 day, Vancomycin 250mg QID	10	Failed
5	HCF	MTZ 500mg BID	21			Cured
6	CA	MTZ 500mg TID	19			Cured
7	CO-HCFA	MTZ 500mg TID	11			Cured
8	CO-HCFA	MTZ 250mg TID	11			Cured

CA: community associated; CO-HCFA: community onset, healthcare facility acquired; HCF: healthcare facility acquired

- Patients received CDI treatment within 2.7 days average following the onset of symptoms (range 1-6)
- 2 patients experienced AEs during their treatment period
  - Pt 3 was admitted to the hospital with fever and a possible PICC line infection
  - Pt 4 had nausea and cramping which resolved upon discontinuation of MTZ

Outcomes:

- At completion of therapy, 63% were evaluated as cured, with two patients noted as improving
- Upon return visits and follow-up, 88% (7/8) were cured
  - Pt 2 was noted to be cured upon later follow-up visit
  - Pt 3 remained cured for 1 year without relapse even with multiple AB therapy for severe bronchial infections
  - Pt 4 failed therapy and ultimately expired with complications from bacteremia

Fig 5. Outcomes

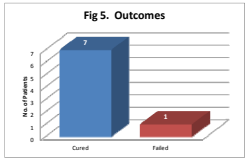


Table 5: Identified Risk Factors for Outpatient CDI

Potential Risk Factor	Patients No. (%)
1. Age > 55 years	8 (100%)
2. ≥ 3 Cormorbidities	8 (100%)
3. ≥ 2 Antibiotics	8 (100%)
4. Antibiotic Duration ≥ 18 days	8 (100%)
5. Previous Hospitalization	5 (63%)

Discussion

- The rate of CDI in patients with confirmed (n=8) *C. difficile* infection was 2.5 per 10,000 patient days, lower than reported in the literature (up to 9 per 10,000 patient days).[4]
- The IVAB most associated with CDI was ceftriaxone, while the oral AB most associated was ciprofloxacin.
- Patients received an average of 2 drugs per patient. Mean length of time to onset of CDI was 28 days following initiation of antibiotics. Treatment time for CDI following symptom onset was 2.7 days.
- The most commonly prescribed first line treatment for *C. difficile* in our patient population was metronidazole.
- Adverse event rate was low in our patient population.
- Overall treatment success in our patient population was 88% (7 of 8).

Conclusions

- Patients receiving broad-spectrum IVAB at ID POICs had a low CDI rate, compared to published data.
- Thus, OPAT is a safe method of treating appropriate patients while minimizing the risk of CDI.
- Rapid initiation of treatment may have contributed to overall success.
- Patients who contracted CDI had multiple risk factors, possibly predictive of outpatient CDI. Additional studies with larger patient sample are warranted to further study this important issue.

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