



Hamilton Health Sciences



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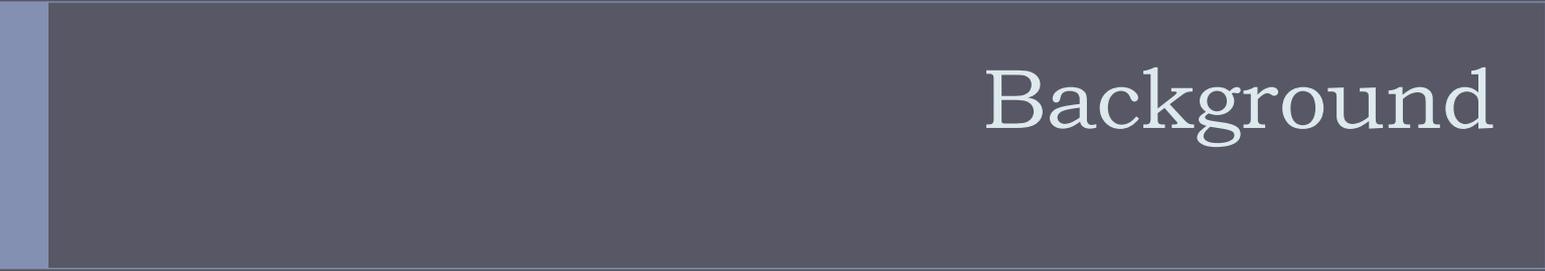
Inappropriate Use of Antibiotics and *Clostridium difficile* Infection

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November 1, 2012

Financial Disclosures

- ▶ No conflicts of interest
- ▶ The study was supported by a Hamilton Health Sciences Quality Assurance Project grant
- ▶ Jocelyn Srigley holds an AMMI Canada/Astellas Post-Residency Fellowship





Background

Clostridium difficile

- ▶ Significant cause of healthcare-associated infections and most common cause of hospital-associated diarrhea
- ▶ Clinical manifestations can range from asymptomatic colonization to toxic megacolon and death
- ▶ Incidence and severity has increased over the past 20 years largely due to emergence of the hypervirulent NAP1/027/BI (NAP1) strain
- ▶ Attributable mortality rate has risen to approximately 6%

C. difficile and Antibiotic Use

- ▶ Antibiotics are a well-established risk factor for *C. difficile* infection (CDI)
 - ▶ Almost every antimicrobial has been associated with CDI
 - ▶ Up to 99% of patients with CDI have been reported to have received antibiotics within 90 days prior to diagnosis
- ▶ Small studies have found that 40-83% of patients with CDI received inappropriate preceding antibiotics
 - ▶ Inappropriate antibiotic use may be a risk factor for CDI compared to appropriate use of antibiotics

Study Rationale

- ▶ We aimed to assess appropriateness of preceding antimicrobial therapy in a larger, more diverse CDI patient population
 - ▶ By identifying inappropriate antibiotic use in hospital, it may be possible to implement interventions to prevent CDI and/or improve outcomes
- ▶ We also implemented an intervention to modify inappropriate antibiotics at the time of CDI diagnosis
 - ▶ Receipt of concomitant antibiotics during treatment for CDI has been shown to reduce clinical cure rates and prolong time to resolution of diarrhea



Methods

Study Population

- ▶ 2 tertiary acute care teaching hospitals in Hamilton, with 412 and 370 beds
- ▶ Inclusion criteria
 - ▶ Adult patients (≥ 18 years old) with new onset of hospital-associated CDI between June 1, 2011 and May 31, 2012
- ▶ Exclusion criteria
 - ▶ Relapses (occurring within 2 months of a previous episode)
 - ▶ Cases attributable to prior admissions at other hospitals

CDI

Symptoms consistent with CDI and detection of *C. difficile* toxin genes by real-time PCR

Hospital-associated CDI

New onset of symptoms beginning 72 hours or more after hospital admission

Patient Review

- ▶ Identification of patients by IPAC through microbiology lab reports
- ▶ 2 study team members independently reviewed patients' charts
 - ▶ Paper charts, electronic medical records, pharmacy computer database
- ▶ All antibiotics prescribed at study hospitals to patients within 8 weeks of CDI diagnosis were independently reviewed for appropriateness, with discrepancies resolved by a third reviewer



Antibiotic Appropriateness

- ▶ **Inappropriate antibiotic use defined as any of:**
 - ▶ Incorrect diagnosis of infection, or continuation of therapy after bacterial infection ruled out
 - ▶ Spectrum of activity not consistent with guidelines for empiric therapy, or not de-escalated based on C&S
 - ▶ Excessive or insufficient duration of therapy
- ▶ **Diagnosis, spectrum, and duration based on:**
 - ▶ IDSA and other major practice guidelines
 - ▶ Sanford Guide to Antimicrobial Therapy 2011
 - ▶ Adapted internal guidelines
- ▶ **Appropriateness of CDI treatment based on internal guidelines (adapted from IDSA)**

CDI Treatment Guidelines

Category	Definition	Treatment
Uncomplicated	T \leq 38°C, and sBP \geq 120, and WBC count $< 18 \times 10^9$ / L, and No significant change in serum creatinine	Metronidazole 500 mg po 3 times daily TID x 14 days
Moderate	Not meeting criteria for uncomplicated or severe	Either as for uncomplicated or severe, depending on clinical judgment
Severe	T \geq 38°C, and sBP \leq 100, and WBC $> 18 \times 10^9$ /L, and Serum creatinine ≥ 200 μ mol/L	Metronidazole 500 mg IV Q6-8H plus vancomycin 500 mg po QID or vancomycin retention enema 0.5-1 g QID

Intervention Phase

- ▶ Patients were reviewed retrospectively for the first 4 months
- ▶ Starting October 1, 2011, review of antibiotic appropriateness was done on the day of CDI diagnosis or the next working day
- ▶ Reviewers provided direct feedback to the admitting team if there was ongoing use of a concurrent antibiotic deemed to be inappropriate, or inappropriate therapy for CDI



Outcomes

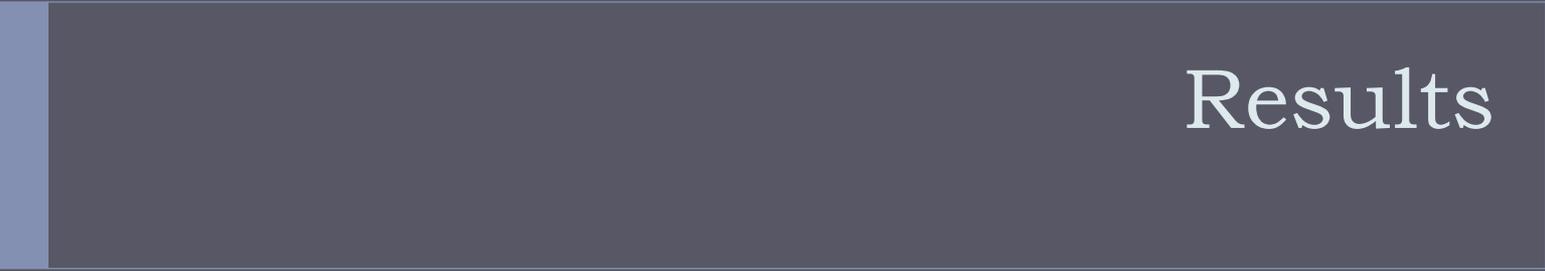
- ▶ **Primary outcome**

- ▶ Appropriateness of antibiotic treatment in the 8 weeks preceding CDI and on the day of CDI diagnosis

- ▶ **Secondary outcomes**

- ▶ Number of interventions and acceptance by admitting team
- ▶ Appropriateness of CDI treatment regimen
- ▶ In-hospital mortality
 - ▶ Minimum follow-up for in-hospital mortality outcomes was 3 months from CDI diagnosis





Results

Description of 126 CDI Episodes in 124 Patients

Characteristic		Number (%)
Age in years, mean [range]		69.8 [19-99]
Female sex		69 (54.8)
Length of stay in days, mean [range]		57.1 [3-360]
Antibiotics prior to CDI diagnosis		121 (96.0)
Proton pump inhibitors		86 (68.3)
Severity of CDI		
	Uncomplicated	53 (42.1)
	Moderate	58 (46.0)
	Severe	0 (0.0)
	Unknown	15 (11.9)



Description of 126 CDI Episodes in 124 Patients (2)

Characteristic	Number (%)
Presumptive NAP1 strain*	48 (38.1)**
Total deaths	30 (23.8)
Relationship between CDI and death	
CDI caused death	6 (4.8)
CDI strongly contributed	3 (2.4)
CDI somewhat contributed	8 (6.3)
No evidence of CDI at death	11 (8.7)
No evidence or information	2 (1.6)

*Detection of *CdtA*, the binary toxin gene

**Of 121 isolates in which PCR testing was performed at study sites

Antibiotic Appropriateness

- ▶ In 93 episodes (73.8%), patients received at least one inappropriate course of antibiotics
 - ▶ Including 12 (9.5%) in which there was no indication for any antibiotic courses during hospitalization
- ▶ 456 antibiotic courses were prescribed (median 3 per patient), of which 206 were inappropriate (45.2%)
- ▶ Reasons for inappropriateness
 - ▶ Incorrect diagnosis – 116 (56.3%)
 - ▶ Inadequate or excessively broad spectrum – 56 (27.2%)
 - ▶ Prolonged duration of therapy – 34 (16.5%)



Appropriateness of Antibiotics by Indication

Indication	Total Courses (%)	Inappropriate Courses (% within category)
Respiratory infections	128 (28.1)	52 (40.6)
Urinary tract infections	69 (15.1)	52 (75.4)
Intra-abdominal infections	55 (12.1)	23 (41.8)
Skin and soft tissue infections	50 (11.0)	22 (44.0)
Perioperative prophylaxis	33 (7.2)	7 (21.2)
Bacteremia	26 (5.7)	5 (19.2)
Sepsis	25 (5.5)	8 (32.0)
Febrile neutropenia	16 (3.5)	4 (25.0)
Bone and joint infections	13 (2.9)	4 (30.8)
Other	44 (9.6)	29 (65.9)

Appropriateness by Indication

- ▶ **Respiratory tract infections**
 - ▶ 116 of 128 courses (90.6%) were for pneumonia
 - ▶ 33 (28.4%) did not meet diagnostic criteria
 - ▶ 12 (10.3%) had inappropriate spectrum of activity.
- ▶ **Urinary tract infections**
 - ▶ 31 of 69 courses (44.9%) prescribed for asymptomatic bacteriuria
- ▶ **Patterns among patients in whom CDI caused or contributed to death were similar**



Inappropriateness by Specialty

- ▶ Internal medicine and subspecialties 105/234 (44.9%)
- ▶ Surgical specialties 70/142 (49.3%)
- ▶ Intensive care physicians 31/80 (38.8%)

- ▶ Infectious diseases specialists 11/38 (28.9%)



CDI Treatment

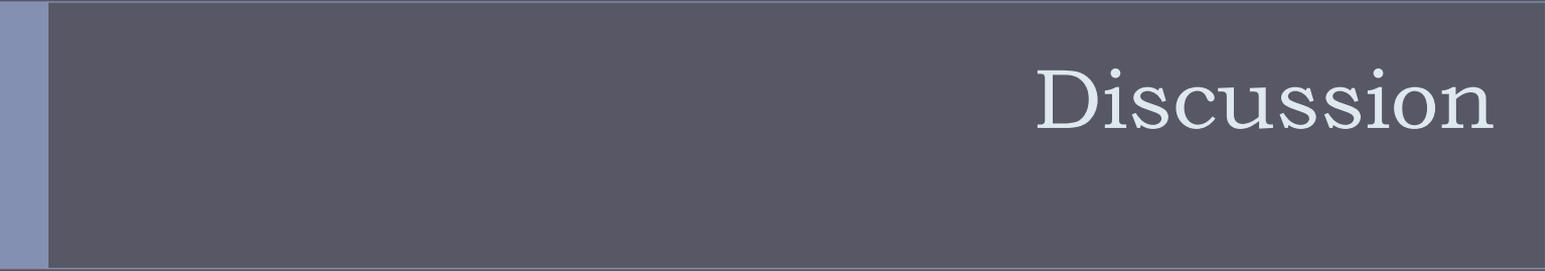
- ▶ 25 patients (19.8%) received inappropriate initial CDI therapy
- ▶ Reasons for inappropriateness
 - ▶ IV administration to patients who were able to tolerate po – 8
 - ▶ Duration too long – 7
 - ▶ Incorrect dose – 5
 - ▶ Vancomycin po in non-severe cases – 2
 - ▶ Combination therapy in patients without an indication – 2
 - ▶ Duration too short – 1



Interventions

- ▶ 74 (58.7%) CDI episodes in the intervention phase
- ▶ 18 interventions were conducted in 17 episodes (23.0%)
 - ▶ Including 13 of 38 (34.2%) who were on concurrent antibiotics
- ▶ Recommendations
 - ▶ Discontinue concurrent antibiotics – 6
 - ▶ Obtain consultation by Infectious Diseases team – 5
 - ▶ Change to appropriate CDI therapy – 5
 - ▶ Change to narrower spectrum of activity – 2
- ▶ All recommendations except one were accepted





Discussion

Summary of Results

- ▶ Inappropriate use of antibiotics prior to diagnosis of hospital-associated CDI was very common
- ▶ One-fifth of patients were on inappropriate antibiotics on the day of CDI diagnosis, potentially impacting outcomes
- ▶ Real-time feedback was appreciated and accepted by the admitting teams
- ▶ CDI caused or contributed to death in 17 patients (13.5%)



Literature on Inappropriate Antibiotics

- ▶ **Non-CDI patients**
 - ▶ Up to 50% of antimicrobial use in hospitals is inappropriate, based on studies over the past several decades
- ▶ **CDI patients**
 - ▶ 40% of preceding courses inappropriate during a CDI outbreak in a small rural hospital
 - ▶ 61% inappropriate in patients with chronic renal failure
 - ▶ 83% inappropriate perioperative antibiotic prophylaxis
 - ▶ Patients who received inappropriate prophylaxis were 5.1 times more likely to develop CDI as patients who received appropriate antibiotics

Specific Indications for Antibiotics

- ▶ **Respiratory tract infections**
 - ▶ Most common indication for antibiotics in hospitalized patients
 - ▶ Incorrect diagnosis of pneumonia in patients with normal CXR has been reported to occur in 29-50% of cases
- ▶ **Urinary tract infections**
 - ▶ Clear evidence and guideline recommendations that antibiotics are not indicated in the vast majority of asymptomatic cases
 - ▶ One study found that antibiotics were given to 41% of patients with positive urinalysis who did not meet criteria for UTI
- ▶ **Targeting treatment of respiratory and urinary tract infections would result in a substantial decrease in inappropriate antibiotic use**

CDI and Concurrent Antibiotics

- ▶ A recent study in community-acquired CDI found that 53% of concomitant antibiotics prescribed upon admission were inappropriate
 - ▶ Over half of our patients were on concomitant antibiotics on the day of CDI diagnosis, and 34.2% of those were on an inappropriate course
- ▶ Receipt of concomitant antibiotics has been shown to negatively affect outcomes in CDI
 - ▶ Prospective audit and feedback may have improved outcomes in these patients

CDI and Mortality

- ▶ Higher attributable mortality (13.5%) than previously reported (~6%)
- ▶ Possible explanations
 - ▶ Different definition in attributable mortality (7.1% using stricter definition)
 - ▶ More virulent strains (NAPI strain in 38.1%)
 - ▶ Differences in patient population

Limitations

- ▶ Assessment of antibiotic appropriateness was primarily determined through chart review, which can be limited by lack of appropriate documentation
 - ▶ Rate of inappropriate courses was very similar on day of diagnosis as in retrospective part of the study
 - ▶ Almost all recommendations were accepted
- ▶ Assessment of appropriateness involves some degree of subjectivity
 - ▶ Used published guidelines as a reference
 - ▶ Two independent reviewers



Limitations

- ▶ Quality of evidence underlying infectious diseases guidelines is subject to debate, and in some cases it may be appropriate to treat patients differently from guideline recommendations

Quality Improvement Initiatives

- ▶ Ongoing review of all CDI patients with audit and feedback if inappropriate treatment
- ▶ Case-based education at rounds
- ▶ Intervention to target asymptomatic bacteriuria
- ▶ Future suggestions
 - ▶ Increase awareness of CDI treatment guidelines
 - ▶ Target respiratory tract infections – guidelines, clinical pathways
 - ▶ Assess appropriateness of PPI use



Conclusions

- ▶ Our study adds to existing literature by including a large number of consecutive CDI patients from a broad hospital population
- ▶ Reviewing patients with hospital-acquired CDI was an effective approach to identify opportunities for improving antibiotic utilization throughout two hospitals
- ▶ Providing direct feedback made it possible to educate clinicians, modify antibiotic use, and potentially improve patient outcomes



Conclusion: Patient Safety

- ▶ Drugs are among the most common causes of adverse events in hospitalized patients
 - ▶ One study found that antibiotics were the class of drugs most frequently implicated in drug-related adverse events
- ▶ There is growing recognition that CDI is an adverse effect of antibiotics and is potentially preventable through antimicrobial stewardship
- ▶ Exposing patients to increased risk of CDI and other adverse events through administration of inappropriate antibiotics is unacceptable and should be an ongoing target for quality improvement efforts

Acknowledgements

- ▶ **Study coauthors**

- ▶ Annie Brooks, PharmD
 - ▶ Melani Sung, PharmD
 - ▶ Deborah Yamamura, MD
 - ▶ Shariq Haider, MD
 - ▶ Dominik Mertz, MD, MSc
- ▶ **Cindy O'Neill and the Infection Prevention and Control Department for notifying us of new CDI patients**
 - ▶ **Padman Jayaratne for providing the PCR data**

