Inappropriate Use of Antibiotics and *Clostridium difficile* Infection

Jocelyn Srigley, MD, FRCPC
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 (NAPI) 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

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)

Infect Control Hosp Epidemiol 2010;31:431-455.
## CDI Treatment Guidelines

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncomplicated</td>
<td>T ≤ 38°C, and sBP ≥ 120, and WBC count &lt;18 x 10⁹/L, and No significant change in serum creatinine</td>
<td>Metronidazole 500 mg po 3 times daily TID x 14 days</td>
</tr>
<tr>
<td>Moderate</td>
<td>Not meeting criteria for uncomplicated or severe</td>
<td>Either as for uncomplicated or severe, depending on clinical judgment</td>
</tr>
<tr>
<td>Severe</td>
<td>T ≥ 38°C, and sBP ≤ 100, and WBC &gt;18 x 10⁹/L, and Serum creatinine ≥ 200 μ mol/L</td>
<td>Metronidazole 500 mg IV Q6-8H plus vancomycin 500 mg po QID or vancomycin retention enema 0.5-1 g QID</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean [range]</td>
<td>69.8 [19-99]</td>
</tr>
<tr>
<td>Female sex</td>
<td>69 (54.8)</td>
</tr>
<tr>
<td>Length of stay in days, mean [range]</td>
<td>57.1 [3-360]</td>
</tr>
<tr>
<td>Antibiotics prior to CDI diagnosis</td>
<td>121 (96.0)</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>86 (68.3)</td>
</tr>
<tr>
<td>Severity of CDI</td>
<td></td>
</tr>
<tr>
<td>Uncomplicated</td>
<td>53 (42.1)</td>
</tr>
<tr>
<td>Moderate</td>
<td>58 (46.0)</td>
</tr>
<tr>
<td>Severe</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>15 (11.9)</td>
</tr>
</tbody>
</table>
Description of 126 CDI Episodes in 124 Patients (2)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presumptive NAPI strain*</td>
<td>48 (38.1%)**</td>
</tr>
<tr>
<td>Total deaths</td>
<td>30 (23.8)</td>
</tr>
<tr>
<td>Relationship between CDI and death</td>
<td></td>
</tr>
<tr>
<td>CDI caused death</td>
<td>6 (4.8)</td>
</tr>
<tr>
<td>CDI strongly contributed</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>CDI somewhat contributed</td>
<td>8 (6.3)</td>
</tr>
<tr>
<td>No evidence of CDI at death</td>
<td>11 (8.7)</td>
</tr>
<tr>
<td>No evidence or information</td>
<td>2 (1.6)</td>
</tr>
</tbody>
</table>

*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

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