Community-Associated *C. difficile* Infection: Think Outside the Hospital

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Clostridium difficile
• *Clostridium difficile* (*C. diff*)
  - Anaerobic
  - Gram positive
  - Spore forming
  - Toxin-producing

• Ubiquitous in soil and the environment

• *C. diff* infection (CDI) is most common health care-associated infection (HAI) in US

• Transmitted through the fecal-oral route
CDI symptoms can range from asymptomatic colonization to life-threatening:

**Colonization**
- Asymptomatic
- 2-4% of general adult population is colonized

**Diarrheal Illness**
- Fever
- Cramping / abdominal pain
- Increased frequency of loose, watery, unformed bowel movements

**Severe Illness**
- Ileus
- Pseudomembranous colitis
- Toxic megacolon
<table>
<thead>
<tr>
<th>Risk Factors</th>
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<tbody>
<tr>
<td>Antimicrobial exposure</td>
<td>![Warning]</td>
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<tr>
<td>Acquisition of <em>C. difficile</em></td>
<td>![Warning]</td>
</tr>
<tr>
<td>Advanced age</td>
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<tr>
<td>Underlying illness</td>
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<tr>
<td>Immunosuppression</td>
<td></td>
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<tr>
<td>Gastric acid suppression</td>
<td></td>
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<tr>
<td>Use of nasogastric or gastrostomy feeding tubes</td>
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<tr>
<td>Use of proton-pump inhibitors (PPIs)</td>
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</table>
• An estimated 453,000 case occur in the US every year, resulting in 29,000 deaths

• Causes $1 billion in excess medical costs per year
• *C. difficile* is an extremely diverse bacteria, with hundreds of ribotypes currently identified

Percent of *C. difficile* Ribotypes Among All Submitted Isolates, Minnesota, 2012-2015
New IDSA guidelines were released in early 2018

Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)

L. Clifford McDonald,¹ Dale N. Gerding,² Stuart Johnson,³ Johan S. Bakken,⁴ Karen C. Carroll,⁵ Susan E. Coffin,⁶ Erik R. Dubberke,⁷ Kevin W. Garey,⁸ Carolyn V. Gould,⁹ Ciaran Kelly,⁹ Vivian Loo,¹⁰ Julia Shaklee Sammons,⁵ Thomas J. Sandora,¹¹ and Mark H. Wilcox¹²
• One of 10 sites participating in the CDC Emerging Infections Program (EIP)

• MDH has been conducting active, population-based surveillance in four counties since 2009, with a fifth added in 2012
  • Total population: ~400,000
CDI Surveillance Methods

- CDI surveillance team reviews outpatient and hospital medical records for the 12 weeks prior to the positive stool

- Cases with no overnight hospitalization or LTCF stay (community-associated or CA-CDI) are contacted for an interview
  - MDH is only state that interviews cases
Epidemiological Classifications

CDI cases are defined by onset and exposure:

**Healthcare associated (HA)**
- Overnight hospitalization or LTCF stay in previous 12 weeks

**Community associated (CA)**
- No overnight hospitalization or LTCF stay
Community-Associated CDI: A Growing Problem
National CDI Incidence Rates

The gap between healthcare-associated and community-associated CDI incidence has closed in recent years.
• In general, CA-CDI cases are younger, healthier, and female than HA-CDI cases.
Minnesota CDI Demographics

Gender:
- Female: 38%
- Male: 45%
- HA: 55%
- CA: 62%

Age Distribution:
- HA:
- CA:

Epidemiologic Class:
- HA
- CA

5/4/2018
CA-CDI cases are less likely to take antibiotics, proton pump inhibitors (PPIs), H2 blockers, and immunosuppressive therapy.
• From 2014-2015, MDH participated in a case-control study to identify risk factors for CA-CDI

• 62% of cases reported antibiotic use in the prior 12 weeks, compared to 10% of controls

• The most common antibiotics received were:
  • Beta-lactam or beta-lactamase inhibitor combinations (18%)
  • Clindamycin (12%)
  • Fluoroquinolone (11%)
  • Cephalosporin (8%)
• The most common indications for antimicrobial use included:
  • Ear, sinus, or upper respiratory tract infection (22%)
  • Skin infection (19%)
  • Dental surgery (16%)
  • Urinary tract infection treatment (12%)
  • Bronchitis or pneumonia (9%)
After running multi-variate analyses, multiple antibiotics were found to be independently significant.

**Antibiotic use**

- Cephalosporin
- Clindamycin
- Fluoroquinolone
- Beta-lactam / beta-lactamase inhibitor combination
Genetic diversity

Top 5 Ribotypes Among Community-Associated CDI

Top 5 Ribotypes Among Healthcare-Associated CDI
• Despite being generally less severe than HA-CDI, CA-CDI still can be severe
  • 26% hospitalized
  • 5% admitted to ICU
  • 3% toxic megacolon
  • 2% death
• 20% treatment failure
• 28% had recurrent CDI
Antibiotics Used for Dental Procedures in CA-CDI Cases
Indications for Antibiotic Prescriptions Reported by CA-CDI Cases During Interview, 2009-2015

% of Cases Who Took Antibiotics

- Upper respiratory infection

Surveillance Year:
- 2009
- 2010
- 2011
- 2012
- 2013
- 2014
- 2015
Antibiotic Prescriptions in Dentistry

• Dentists not considered a key stakeholder

• Dentists prescribe ~10% of antibiotics in outpatient settings
  - Over 24 million prescriptions in 2013
  - Treatment of oral infections
  - Prophylaxis during invasive procedures
Antibiotic Prescriptions in Dentistry

• Antibiotics are indicated to treat oral infections
  - Tooth abscesses

• Recommendations for prophylaxis exist for two groups of patients
  - Heart conditions that may predispose them to infective endocarditis
  - Prosthetic joints and may be at risk for developing infection at the site of prosthetic
• Dentists were asked for which scenarios they would prescribe antibiotics:
  - Prophylaxis for patients with high risk conditions (84%)
  - Localized swelling (70%)
  - Gum pain (38%)
  - Precautionary (38%)
  - Legal concerns (24%)

• Less than half reported a concern for adverse drug effects, antibiotic resistance, or *C. diff* as factors that influenced their prescribing decisions.
High Risk Conditions Reported as Warranting Antibiotic Prophylaxis Before Invasive Dental Procedures

% reporting indication

- Currently Recommended by ADA
- Not Currently Recommended by ADA

Conditions:
- Well-controlled type 2 DM
- Cardiac transplant with valvulopathy
- Mitral valve prolapse
- Chronic kidney disease
- Poorly-controlled type 2 DM
- Prosthetic joints
- Primary care physician recommends
- Selected congenital heart disease*
- Prosthetic cardiac valve
- Previous infective endocarditis
• Of CA-CDI cases who reported antibiotic use in the 12 weeks before diagnosis, 136 (15%) CA-CDI reported being prescribed antibiotics for a dental procedure
  • 116 (85%) were prescribed antibiotics only for dental reasons
  • 46 (34%) reported antibiotics in the interview that were not documented in the medical record
Antibiotics Taken by CA-CDI cases for a Dental Procedure in 12 Weeks Prior to Diagnosis

% of Cases

Antibiotic

- Clindamycin
- Penicillins
- Fluoroquinolones
- Sulfonamides
- Macrolides
- Glycopeptides
- Cephalosporins
- Nitrofurantoin
- Metronidazole

- Reported in interview
- Reported in medical record
<table>
<thead>
<tr>
<th>Dental Antibiotics n (%)</th>
<th>Non-Dental Antibiotics n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clindamycin n=136</td>
<td></td>
<td></td>
</tr>
<tr>
<td>68 (50)</td>
<td>78 (10)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cephalosporins n=136</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 (7)</td>
<td>237 (30)</td>
<td>0.001</td>
</tr>
<tr>
<td>Fluoroquinolones n=136</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 (6)</td>
<td>153 (19)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Antibiotic reported in interview or recorded in medical record*
In July 2015, MDH began collecting dental antibiotic indications and prescriber information in the interview.

76 CA-CDI cases with dental antibiotic use.

To date, the top indications are:
- Tooth infection/abscess (43%)
- Oral surgery prophylaxis (35%)
- Dental cleaning prophylaxis (13%)
51 (67%) of these cases were prescribed antibiotics by dentists.

4 (3%) cases reported heart conditions:
- 1 with valve replacement 15 years ago

4 (3%) cases reported having joint replacements.
• Antibiotics prescribed by dentists are contributing to CDI
  - Recent study showed dental prescribing increased by 62%
• Dentists most often prescribed antibiotics for tooth abscesses or prophylaxis before invasive procedures
• Generally not recommended for dental cleaning or oral surgery
Conclusions

• CA-CDI cases prescribed antibiotics for dental procedures were older and more likely to receive clindamycin
  - National data show dentists prescribe more penicillins than clindamycin
  - 7x more likely to develop CDI if taking any antibiotic
  - 20x more likely to develop CDI if taking clindamycin
• Dentists need to be included in antibiotic stewardship programs

• Dentists should consider the risk for CDI and other potential complications of antibiotic use

• Clarification and consistency between associations regarding dental prophylaxis for joint replacement recommendations

• More research needed to quantify risks of adverse events associated with invasive dental procedures with or without antibiotic prophylaxis
Antibiotic Prescribing in Pediatric *Clostridium difficile* Cases
• 60-70% of healthy newborns are colonized with *C. diff*
  • Rate decreases with age
  • Carriage rates being similar to adult population at one year
• As with adult CDI, pediatric CDI rates are increasing
• Pediatric CDI shares some risk factors with adult CDI, including healthcare exposure, PPI use, and antibiotic use
• 71% of pediatric cases are CA-CDI
• 8% of MN CDI cases were pediatric

• 367 had medical records available for antibiotic prescribing data abstraction

• 47% of pediatric cases were female

• 80% were CA

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
</tr>
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<tbody>
<tr>
<td>Female</td>
<td>175 (47)</td>
</tr>
<tr>
<td>White</td>
<td>271 (91)</td>
</tr>
<tr>
<td>Median Age (IQR)</td>
<td>5 (2-11)</td>
</tr>
<tr>
<td>Epidemiological Class</td>
<td></td>
</tr>
<tr>
<td>CA</td>
<td>295 (80)</td>
</tr>
<tr>
<td>CO-HCFA</td>
<td>57 (15)</td>
</tr>
<tr>
<td>HCFO</td>
<td>15 (4)</td>
</tr>
<tr>
<td>Underlying Conditions</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>272 (74)</td>
</tr>
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</table>
Among these, 209 (57%) pediatric cases received 393 prescriptions in the 12 weeks prior to developing CDI.

- 50 (14%) cases were prescribed ≥3 antibiotics.

- The median time between prescription end date and CDI diagnosis was 13 days.

- Most (73%) of antibiotics were prescribed in an outpatient setting.

<table>
<thead>
<tr>
<th>Variable</th>
<th>n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Antibiotic Prescriptions</td>
<td>393</td>
</tr>
<tr>
<td>No. Cases Prescribed Antibiotics</td>
<td>209 (57)</td>
</tr>
<tr>
<td>1</td>
<td>103 (28)</td>
</tr>
<tr>
<td>2</td>
<td>56 (15)</td>
</tr>
<tr>
<td>3+</td>
<td>50 (14)</td>
</tr>
<tr>
<td>Median days between last antibiotic dose and CDI diagnosis* (IQR)</td>
<td>13 (3-40)</td>
</tr>
<tr>
<td>Prescriber Location</td>
<td></td>
</tr>
<tr>
<td>Outpatient</td>
<td>282 (73)</td>
</tr>
<tr>
<td>Hospital</td>
<td>74 (19)</td>
</tr>
<tr>
<td>ED</td>
<td>31 (8)</td>
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</tbody>
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Antibiotic Indications

Antibiotics were prescribed most frequently for:

- Otitis media (22%)
- URIs (21%)
- Gastrointestinal infection (12%)

Other indications include:

- Pneumonia 6%
- Urinary tract infection 6%
- Acne or skin infection 7%
- Surgery or chemotherapy prophylaxis 8%
- Unknown 2%
- Dental 1%
- Other* 15%

Legend:
- Otitis media 22%
- Upper respiratory infection 21%
- Gastrointestinal infection 12%
Diagnostic Tests Conducted at Time of Antibiotic Prescription

- **Otitis Media**:
  - No diagnostic test conducted
  - Diagnostic test conducted, no pathogen detected
  - Diagnostic test conducted, pathogen detected

- **Gastrointestinal illness**:
  - No diagnostic test conducted
  - Diagnostic test conducted, no pathogen detected
  - Diagnostic test conducted, pathogen detected

- **Acute Sinusitis**:
  - No diagnostic test conducted
  - Diagnostic test conducted, no pathogen detected
  - Diagnostic test conducted, pathogen detected

- **Pharyngitis**:
  - No diagnostic test conducted
  - Diagnostic test conducted, no pathogen detected
  - Diagnostic test conducted, pathogen detected

- **UTI**:
  - No diagnostic test conducted
  - Diagnostic test conducted, no pathogen detected
  - Diagnostic test conducted, pathogen detected

- **Bronchitis**:
  - No diagnostic test conducted
  - Diagnostic test conducted, no pathogen detected
  - Diagnostic test conducted, pathogen detected
Impact of Diagnostics

• For antibiotics that were prescribed prior to testing results being available, once test results were received:
  • 11% were changed
  • 27% were discontinued
  • 59% were continued
Appropriateness of Antibiotics Prescribed to Pediatric CDI Cases

*American Academy of Pediatrics (AAP) guidelines used
*^Infectious Disease Society of America (IDSA) guidelines used

Antibiotic Indication

<table>
<thead>
<tr>
<th>Condition</th>
<th>Met criteria for appropriate prescribing</th>
<th>Did not meet criteria for appropriate prescribing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Otitis media*</td>
<td>50</td>
<td>30</td>
</tr>
<tr>
<td>Acute sinusitis*^</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Pharyngitis*</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Bronchitis*</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>UTIs*</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Gastrointestinal illness*^</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>
Conclusions

- Outpatient clinics and EDs remain a major source of antibiotic prescriptions among pediatric CDI cases

- Diagnostic stewardship is important
  - Potentially narrow the antibiotic spectrum
  - Discontinue unnecessary antibiotics

- Enhanced prevention efforts focusing on URI antimicrobial stewardship in pediatric outpatient settings are needed to reduce pediatric CDI
Tying it All Together

• Antimicrobial stewardship is important in all healthcare settings and for all prescribers

• Even young, otherwise healthy patients can contract CDI
Practical Steps

• Follow national guidelines for prescribing antibiotics

• When appropriate, conduct diagnostic tests to identify a pathogen
  • Let the results of diagnostic tests impact antibiotic prescribing

• Ask patients about antibiotics or conditions possibly not listed in their medical record
  • Dental visits and medications taken for dental reasons
Practical Steps

• When prescribing antibiotics, warn patients about adverse effects, like CDI
  -Encourage them to reach out to you if symptoms develop

• Consider using CDI rates as a measure of antimicrobial stewardship in your facility

• Benchmark antimicrobial use at your facility to identify areas for improvement
## Acknowledgements

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<thead>
<tr>
<th>MDH</th>
<th>CDC</th>
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<tr>
<td>Dr. Stacy Holzbauer</td>
<td>Lauren Korhonen</td>
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<td>Dr. Amanda Beaudoin</td>
<td>Dr. Alice Guh</td>
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<tr>
<td>Dr. Ruth Lynfield</td>
<td>Dr. Shelley Magill</td>
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<tr>
<td>MDH HAI Unit</td>
<td>Dr. Lauri Hicks</td>
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<tr>
<td>MDH Public Health Laboratory</td>
<td>EIP CDI Surveillance Teams</td>
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<tr>
<td>MDH Zoonotic Disease Unit</td>
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<tr>
<td>Team <em>C. diff</em></td>
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Thank you!