Can We Prevent All Healthcare-Associated *Clostridium difficile* infections in 10 Years?

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Advisory Board: 3M
Incidence of hospital-associated CDI in the US

2011 – 453,000 incident cases and 29,300 deaths

Pathogenesis

Exposure

Growth and toxin production

Antibiotics

Antibody response

Asymptomatic colonization

No antibody response

Disease

C. difficile prevention

Environmental disinfection, contact precautions

Exposure

Antibiotics

Growth and toxin production

Stewardship, Fecal transplant

Monoclonal antibody

Antibody response

Asymptomatic colonization

No antibody response

Disease

Poop? I need a poop transplant?
Know your enemy and yourself and you can win one hundred battles

Sun Tzu, The Art of War
Know your pathogens and your personnel if you want to prevent healthcare-associated infections.

The Art of Infection Control
What percentage of healthcare-associated CDI cases at the Cleveland VA Hospital are linked to other healthcare-associated cases?

- A. <5%
- B. 33%
- C. 66%
- D. >90%
Sources of healthcare-associated CDI cases based on whole genome sequencing

Top 10 questions we need to address to eliminate healthcare-associated CDI
10. Are many cases of healthcare-associated CDI acquired in non-healthcare settings?

- **Lessa NEJM 2015 (US)**
  - 66% of CDI cases healthcare-associated
  - 82% of community-associated CDI cases have recent outpatient healthcare exposures

- **Eyre NEJM 2013 (England)**
  - Diverse sources of acquisition
  - Only 35% of cases genetically linked to other cases

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Potential sources of *C. difficile* in the community

Downton Anatomy

https://youtu.be/-d4bhZRdD0
9. Are asymptomatic carriers a major source of transmission?

Asymptomatic carriers are a major source of transmission

**Yes**
- Pittsburgh - 29% of hospital-associated CDI cases linked to carriers (MLVA typing) \(^1\)
- Montreal - Screening for and isolating carriers reduced healthcare-associated CDI by 63% \(^2\)
- Denmark – exposure to carriers increased CDI risk \(^3\)

**No**
- Boston - Only 1% of cases linked to asymptomatic carriers (roommates and adjacent rooms) (PFGE/REA typing) \(^4\)
- UK – 18 carriers: no links to subsequent CDI cases (Whole genome sequencing) \(^5\)

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8. Can we develop horizontal approaches to prevent transmission?

- **Vertical approaches**
  - Directed at specific pathogens
  - Example: Screening patients and isolating carriers

- **Horizontal approaches**
  - Broad approaches that may impact multiple pathogens and that are applied to all patients
  - Example: Hand hygiene

Sources of pathogen transmission

- Infected patient
- Previously infected patient
- Newly infected patient not yet recognized
- Asymptomatic carrier
Horizontal infection control practices versus MRSA

Chlorhexidine bathing

Hand hygiene (alcohol)

Colonized or Infected Patient

Susceptible Patient

Decolonization

Environmental Cleaning

Environment

Deaths due to MRSA infection in the U.S.

Magill SS, et al. NEJM 2014;370:1198-208
Horizontal infection control practices versus *C. difficile*

- Chlorhexidine bathing
- Hand hygiene (alcohol)
- Decolonization
- Environmental Cleaning

Infected Patient → Environment → Susceptible Patient
Use more bleach

Mattress exposed to bleach versus quaternary ammonium disinfectant

Quat   Bleach wipe   Bleach 1:10

Cadnum JL, et al. SHEA 2017
Modify existing products:
Germinate to Exterminate

7. Are many patients with “healthcare-associated” CDI colonized on admission?

- Asymptomatic carriage of toxigenic *C. difficile* is common on hospital admission (4 to 15%) \(^1\)
- A significant proportion of patients diagnosed with CDI are colonized on admission:
  - 25% of ICU patients \(^2\)
  - 42% of stem cell transplant patients \(^3\)
  - 21% of hospitalized patients \(^4\)

False-positive diagnosis of CDI in an asymptomatic carrier

Hospital admission

↓

+ rectal culture = asymptomatic carrier

Laxative

2 unformed stools

C. diff PCR positive

CDI
6. What is the optimal strategy for diagnosis of CDI?

<table>
<thead>
<tr>
<th></th>
<th>UK - 2 or 3-stage algorithm</th>
<th>US - NAAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reject formed stool</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td># loose stools to trigger testing</td>
<td>≥1</td>
<td>≥3</td>
</tr>
<tr>
<td>Test unformed stools even if no CDI order</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Avoid diagnosis of carriers as CDI</td>
<td>Toxin negative = carrier</td>
<td>Avoid inappropriate testing</td>
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Over-diagnosis of CDI in the molecular test era

1416 patients tested

PCR -/Toxin –
1123 (79%)

PCR +
293 (21%)

Toxin EIA –
162 (55%)

Toxin EIA +
131 (45%)

5. Can we apply the revolution in omics to control of *C. difficile*?

- Genomics
- Proteomics
- Metabolomics

The problem

Urine or serum biomarkers derived from intestinal microbiota

Dietary Tryptophan

Indole

IPA

Gut bacteria

Blood

Liver

Indole

Indoxyl sulfate

Indoxyl sulfate (Indican)

Urine

Indole-3-propionic acid (IPA)

Targeted bacteriotherapy: oral non-toxigenic *Clostridium difficile* spores

4. Can we target stewardship interventions to control epidemic strains?

Fluoroquinolone restriction controlled fluoroquinolone-resistant *C. difficile*

3. Can we develop improved methods to decolonize carriers?

Treatment of carriers with metronidazole vs vancomycin

[Graph showing comparison of C. difficile positive rates between Vancomycin, Metronidazole, and Placebo treatments over 70 days.]

2. Can we continue to develop high-quality evidence to direct control efforts?

- **Quasi-experimental studies**
  - Multiple studies report reduced CDI with UV-C\(^1\)\(^-\)\(^7\)

- **Randomized trials**
  - Cluster randomized, multicenter, crossover study\(^8\)
    - No decrease in CDI with bleach + UV versus bleach alone
  - 16 hospital multicenter randomized trial\(^9\)
    - Improved room disinfection but no decrease in CDI

1. Can we find ways to involve patients in prevention efforts?
Patient hand washing to reduce spore contamination

Before hand wash

After hand wash

Fear of failure: Engaging patients in stewardship after fecal transplant for CDI

■ Of 73 patients receiving FMT, 25 (34%) consulted their FMT physicians regarding 43 antibiotic prescriptions
  ■ 26 (60%) deemed unnecessary
  ■ 7 (16%) necessary but alternative suggested
  ■ 10 (23%) necessary and appropriate
■ 95% of recommendations followed

Summary

- Current measures used to prevent healthcare-associated CDI are failing
- Eliminating healthcare-associated CDI will be difficult, but not impossible
- Beware of unintended consequences of trying to “get to zero”