Prevention of Clostridium difficile Infection - What We Find in Guidelines

Dr. Walter Zingg, MD
Dr. Maria Martin, MD, MPH

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paul@webbertraining.com

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Outline

• PROHIBIT work package 2
• Guidelines in WP 2
• C. difficile
  – Studies and guidelines
  – Treatment
  – Summary
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PROHIBIT WP2

• Identification and analysis of current guidelines for prevention of HAI (CDI, VAP, CABS, SSI, UTI) in European countries

• Overview on current surveillance systems in European countries

• Overview of public reporting of HAI in European countries and consensus statement about benefits and challenges of public reporting

Deliverables WP2

• Systematic review of guidelines and recommendations in European countries

• Report on surveillance programmes in European countries

• Report on public reporting of HAI in European countries
Description WP2

- Countries enclosed: 27 EU member states plus Switzerland, Norway, Iceland and Croatia (total 34)

- Topics of interest:
  - CDI
  - SSI
  - VAP
  - CABSI
  - UTI

Questionnaires

- 1st Q: sent out End of August 2010
  - Elements: basic questions on available guidelines, surveillance systems and practices in (public) reporting of HAI rates
  - Return rate 100% (last in April 2011)

- 2nd Q (decided in Berlin Dec. 2010): sent out in March 2011
  - Elements: financing of health care services with focus on HAI ("pay for performance"); public interest in HAI prevention
  - Return rate 91%
Guidelines

- Extensive internet search according to specifications of NCPs or recontact

- Translation into English

- Development of matrices with QSR NVivo software (basis German and CDC guidelines)
Challenges: „Where are the guidelines...?“

Matrix for systematic review (NVivo software)

Example: Pneumonia
Matrix for systematic review (\textit{NVivo software})

Example: CABS

Guidelines in Europe

- No guidelines
- One guideline
- Two guidelines
- Three guidelines
- Four guidelines
- Five guidelines

In total: 101 national guidelines on the five topics of interest
Clostridium difficile

C. difficile in Europe

<table>
<thead>
<tr>
<th>Ribotype</th>
<th>n/n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>014/020*</td>
<td>61/389 (16%)</td>
</tr>
<tr>
<td>001</td>
<td>37/389 (10%)</td>
</tr>
<tr>
<td>078</td>
<td>31/389 (8%)</td>
</tr>
<tr>
<td>018</td>
<td>23/389 (6%)</td>
</tr>
<tr>
<td>106</td>
<td>20/389 (5%)</td>
</tr>
<tr>
<td>027</td>
<td>19/389 (5%)</td>
</tr>
<tr>
<td>002</td>
<td>18/389 (5%)</td>
</tr>
<tr>
<td>012</td>
<td>17/389 (4%)</td>
</tr>
<tr>
<td>017</td>
<td>14/389 (4%)</td>
</tr>
<tr>
<td>015</td>
<td>13/389 (3%)</td>
</tr>
<tr>
<td>126</td>
<td>12/389 (3%)</td>
</tr>
<tr>
<td>023</td>
<td>10/389 (3%)</td>
</tr>
<tr>
<td>046</td>
<td>8/389 (2%)</td>
</tr>
<tr>
<td>003</td>
<td>7/389 (2%)</td>
</tr>
<tr>
<td>011</td>
<td>6/389 (2%)</td>
</tr>
<tr>
<td>053</td>
<td>6/389 (2%)</td>
</tr>
<tr>
<td>056</td>
<td>6/389 (2%)</td>
</tr>
</tbody>
</table>

*reported together because of close relatedness

Bauer MP. Lancet 2011;377:63
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Mortality – England & Wales

Clostridium difficile infection by English NHS acute trusts

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**Costs**

![Costs Diagram]

- **CAbx***: $17,015 ($9,575, $24,456)
- **IBD**: -$1,395 (-$13,664, $10,864)
- **Cancer/BMT**: $636 (-$55,933, $7,198)
- **Age ≥ 65y***: $6,906 ($3,942, $9,871)
- **Renal Impairment**: $4,604 ($1,025, $8,182)

Total Costs

BMT: bone marrow transplant; CAbx, concomitant antibiotics; IBD, inflammatory bowel disease

*p-value for difference < 0.001; **p-value for difference = 0.012.

Campbell R.  *J Med Econ* 2013;16:440

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**C. difficile guidelines**

![Map of C. difficile guidelines]

- **UK**: England, Northern Ireland, Wales
- **Sc**: Scotland

Total: 16 guidelines

Presented on DGHM 2011

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Year of publication

CDI prevention guidelines

Level of evidence

Table III
Categories of strength of recommendation and underlying levels of evidence in national European Clostridium difficile infection prevention guidelines (PROHIBIT study group).

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>MALTA (SHEA/IDSA)</th>
<th>ECDC, Austria, Scotland, Italy</th>
<th>ENG</th>
<th>SWEDEN</th>
<th>Country and category of strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>B</td>
<td>C</td>
<td>IA</td>
<td>IB</td>
<td>IC</td>
</tr>
<tr>
<td>Meta-analysis or systematic reviews</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Randomized controlled trials</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Well-designed studies</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Suggestive studies</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Case-control and cohort studies</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Case reports, descriptive studies</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Theoretical rationale</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Expert consensus</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Legal regulations</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Unresolved question</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

PROHIBIT, Prevention of Hospital Infection by Intervention and Training; SHEA/IDSA, Society for Healthcare Epidemiology of America; Infectious Diseases Society of America; ECDC, European Centre for Disease Control and Prevention; LI, unresolved issue.

* Table adapted from Cookson et al. 25

Martin M et al., JHI 2014

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Transmission and *C. difficile*

Likelihood of *C. difficile* transmission from CDI patients to roommates, direct neighbors or patients hospitalized at the same bed position sequentially.

<table>
<thead>
<tr>
<th>Setting</th>
<th>Transmission, n/n (%)</th>
<th>Risk, RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequential patient</td>
<td>4/135 (3.0%)</td>
<td>1.21 (0.32-3.39)</td>
</tr>
<tr>
<td>Roommate</td>
<td>4/71 (5.6%)</td>
<td>2.37 (0.63-6.95)</td>
</tr>
<tr>
<td>Neighbor</td>
<td>16/249 (6.4%)</td>
<td><strong>3.40 (1.95-5.94)</strong></td>
</tr>
</tbody>
</table>

Chang VT. *Clin Infect Dis* 2000;31:717
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C. difficile in the environment

Department of Microbiology, Leeds Teaching Hospitals & University of Leeds

Fawley WN. J Clin Microbiol 2005;43:2685

C. difficile in the environment

Fawley WN. J Clin Microbiol 2005;43:2685

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Colonization pressure

Systematic review; three studies about CDI-transmission in the hospital setting:

Colonization pressure* was significantly associated (OR 2.9-4) with *C. difficile* transmission

*measured as the presence of CDI-cases as a risk factor for *C. difficile* transmission

Ajao AO. *Infect Control Hosp Epidemiol* 2011;32:481

Environment disinfection (CDI)

→ ECDC:
  - Regular disinfection, chlorine-based prefered -
    IB (Evidenz 2b (1), 2c (2), 4 (1))

  - Frequently touched surfaces, at least 1x /d - IB
    (Evidenz 1b (1), 2a (1), 4 (1))

  - Bathroom, toilets etc. clean scrupulously –
    IB (Evidenz 1b (1), 2a (1))

Martin M et al., *JHI* 2014
Environmental disinfection (CDI)

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Measure</th>
<th>Agent</th>
<th>Frequently touched surfaces</th>
<th>Bathroom, toilet etc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>2007</td>
<td>Sporicidal</td>
<td>1x d</td>
<td>2x d</td>
<td></td>
</tr>
<tr>
<td>Belgium</td>
<td>2008</td>
<td>Chlorine based</td>
<td>1x d</td>
<td>Min. 1x d</td>
<td></td>
</tr>
<tr>
<td>Denmark</td>
<td>2011</td>
<td>Chlorine based</td>
<td>1x d</td>
<td>1x d</td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td></td>
<td>Chlorine based</td>
<td>Min. 1x d</td>
<td>Min. 1x d</td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>2010</td>
<td>Chlorine based</td>
<td>Not specified</td>
<td>Not specified</td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>2009</td>
<td>H2O2 or chlorine</td>
<td>1x d</td>
<td>1x d</td>
<td></td>
</tr>
<tr>
<td>Ireland</td>
<td>2008</td>
<td>Chlorine based</td>
<td>1x d</td>
<td>After each use</td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>2009</td>
<td>Chlorine based</td>
<td>Min. 1x d</td>
<td>Not specified</td>
<td></td>
</tr>
<tr>
<td>Latvia</td>
<td>2007</td>
<td>Chlorine based</td>
<td>Not specified</td>
<td>Not specified</td>
<td></td>
</tr>
<tr>
<td>Luxembourg</td>
<td>2007</td>
<td>Chlorine based</td>
<td>Min. 1x d</td>
<td>Min. 1x d</td>
<td></td>
</tr>
<tr>
<td>Malta</td>
<td>SHEA 2008</td>
<td>Chlorine based</td>
<td>Not specified</td>
<td>Not specified</td>
<td></td>
</tr>
<tr>
<td>Netherlands</td>
<td>2006</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Not specified</td>
<td></td>
</tr>
<tr>
<td>Sweden</td>
<td>2006</td>
<td>Peracetic acid</td>
<td>Not specified</td>
<td>Not specified</td>
<td></td>
</tr>
<tr>
<td>Switzerland</td>
<td>1995</td>
<td>Mechanic effect of cleaning</td>
<td>„Die kontinuierliche Reinigung...“</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GB</td>
<td>2008</td>
<td>Chlorine based</td>
<td>Min. 1x d</td>
<td>After each use</td>
<td></td>
</tr>
<tr>
<td>Sc</td>
<td>2009</td>
<td>Chlorine based</td>
<td>Min. 1x d</td>
<td>Not specified</td>
<td></td>
</tr>
</tbody>
</table>

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Effectiveness of disinfectants

Spore germination after exposure to different disinfectants

Exposure time, minutes

- PCR ribotype 027 UK outbreak strain B
- Control
- Non-ionic surfactant and NaDCC (Chlor-clean®): 1,000 ppm Chlor
- Detergent and NaOCl (Dispatch®): 5,500 ppm NaOCl
- NaDCC (Sanichlor®): 1,000 ppm chloride

Fawley WN. Infect Control Hosp Epidemiol 2007;28:920

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Vaporized hydrogen-peroxide

Boyce JM. Infect Control Hosp Epidemiol 2008;29:723

Contamination of healthcare worker’s hands

Bobulsky GS. Clin Infect Dis 2008;46:447

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Hand hygiene (CDI)

→ ECDC: wearing of gloves for patient contact and immediate vicinity - IB  (Evidenz 1b (2), 2b (2))

• All guidelines recommend wearing of gloves

• Washing or disinfecting?
→ ECDC: Hand washing with soap, alcohol-based hand rub not sufficient – IB  (Evidenz 2a (2), 2b (3), 2c (1), 4 (1))

• Disinfecting, then washing (2): A, D
• Washing, then disinfecting (5): B, DK, F, GB, S
• Only washing (7): FIN, IRL, I, L, M, NL, Sc
• Latvia: washing or disinfecting with Chlorhexidine
• Switzerland: disinfecting or antiseptic soap

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Antibiotics and *C. difficile*

PROHIBIT

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**Antibiotics and CDI: a meta-analysis**

![Image of a meta-analysis graph showing the pooled OR (95% CI) for different antibiotics and their association with CDI.](image)

Owens RC. *Clin Infect Dis* 2008;46:S19

**Antibiotics and CDI**

<table>
<thead>
<tr>
<th>Low risk</th>
<th>Medium risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>Co-amoxiclav</td>
<td>Second/third generation cephalosporins</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Macrolides</td>
<td>Clindamycin</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>Amoxicillin/ampicillin</td>
<td>Fluoroquinolones</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piptazobactam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzylpenicillin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Monaghan T. *Postgrad Med J* 2009;85;152
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- Contact isolation precautions
- Bleach → 100 ppm first, then 1000 ppm
- Electronic flags and alerts
- Hand washing
- Prolongation of contact isolation (entire length of stay)
- Audits

Muto CA. Clin Infect Dis 2007;45:1266

Hosted by Paul Webber  paul@webbertraining.com
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Effects of a restrictive antibiotic policy on hospital-acquired *Clostridium difficile* – a district hospital

Dancer S. *Int J Antimicrob Agents* 2013;41:137

**Antibiotic Stewardship**

- ECDC: Stop antibiotic treatment - IA (Evidenz 1a (1))
  - A, B, CH, FIN, GB und Sc, I, IRL, L (9)

- ECDC: good antibiotic stewardship in outbreaks or in high endemic situations - IB (Evidenz 1a (1), 2b (5), 3b (9), 4 (4))
  - according ECDC (2): B, M
  - General recommendation for good antibiotic stewardship (8): A, B, D, GB und Sc, IRL, L, S

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Publications and Guidelines

Guidelines - Conclusions

• Most national CDI guidelines published or revised in last 10 years

• Only about half of guidelines state evidence and strength of recommendations

• Guidelines vary in scope and detailing

• Heterogeneity in terminology
### ESCMID treatment guidelines

**Teicoplanin/vancomycin > metronidazole**
- Efficacy of teicoplanin may be superior to vancomycin
- Vancomycin concentration in the colon is largely superior to metronidazole, which is readily absorbed in the small intestines and is found in feces only in (very) low concentrations
- High dose vancomycin is not superior to low dose vancomycin: most likely due to its non-absorption

**Treatment duration: 10 days**
There are studies of 7 days treatment duration; however, data to justify shorter treatment are not sufficient yet

Bauer MP. *Clin Microbiol Infect* 2009;15:1067

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### “Outside the box” CDI management

**Intraluminal toxin-binders or neutralizers**
Cholestyramine, cholestipol, tolevamer, whey protein in immunized cow’s milk

**Biotherapeutic agents to restore the protective microbiota**
*Probiotics, faecal transplants*, nontoxigenic *C. difficile* strains, synthetic mixture of bacteria

**Antibodies to improve CDI-immunity**
Monoclonal antibodies, active vaccination

**Anti-sporulation**
CamSA, a bile salt analog, inhibits *C. difficile* spore germination in vitro

Gerding DN. *Clin Infect Dis* 2010;51:1306
Howerton A. *J Infect Dis* 2013; epub, ahead of print

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Probiotics

<table>
<thead>
<tr>
<th>Study Year (Reference)</th>
<th>Experimental Group</th>
<th>Control Group</th>
<th>Weight</th>
<th>Relative Risk: 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arain et al. 2002 (26)</td>
<td>1</td>
<td>2</td>
<td>1.7</td>
<td>0.69 (0.46-1.08)</td>
</tr>
<tr>
<td>Rosell et al. 2003 (27)</td>
<td>1</td>
<td>2</td>
<td>3.9</td>
<td>0.68 (0.33-1.44)</td>
</tr>
<tr>
<td>Brennan et al. 2000 (28)</td>
<td>0</td>
<td>1</td>
<td>1.2</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Cugno et al. 2000 (29)</td>
<td>0</td>
<td>1</td>
<td>1.4</td>
<td>0.74 (0.43-1.28)</td>
</tr>
<tr>
<td>Dworkin et al. 2000 (30)</td>
<td>1</td>
<td>2</td>
<td>1.6</td>
<td>0.74 (0.39-1.40)</td>
</tr>
<tr>
<td>Greenfield et al. 2000 (28)</td>
<td>0</td>
<td>1</td>
<td>1.5</td>
<td>0.74 (0.30-1.81)</td>
</tr>
<tr>
<td>Lippi et al. 2009 (31)</td>
<td>1</td>
<td>2</td>
<td>1.3</td>
<td>0.74 (0.37-1.46)</td>
</tr>
<tr>
<td>McFerson et al. 2009 (32)</td>
<td>1</td>
<td>2</td>
<td>1.3</td>
<td>0.74 (0.37-1.46)</td>
</tr>
<tr>
<td>Wilber et al. 2009 (33)</td>
<td>1</td>
<td>2</td>
<td>1.3</td>
<td>0.74 (0.37-1.46)</td>
</tr>
<tr>
<td>Wilber et al. 2009 (33)</td>
<td>1</td>
<td>2</td>
<td>1.3</td>
<td>0.74 (0.37-1.46)</td>
</tr>
<tr>
<td>Ruffner et al. 2009 (34)</td>
<td>1</td>
<td>2</td>
<td>1.3</td>
<td>0.74 (0.37-1.46)</td>
</tr>
<tr>
<td>Parab et al. 2009 (35)</td>
<td>1</td>
<td>2</td>
<td>1.3</td>
<td>0.74 (0.37-1.46)</td>
</tr>
<tr>
<td>Kelly et al. 2009 (36)</td>
<td>1</td>
<td>2</td>
<td>1.3</td>
<td>0.74 (0.37-1.46)</td>
</tr>
<tr>
<td>Vermeulen et al. 2009 (37)</td>
<td>1</td>
<td>2</td>
<td>1.3</td>
<td>0.74 (0.37-1.46)</td>
</tr>
<tr>
<td>Tuffiau et al. 2009 (38)</td>
<td>1</td>
<td>2</td>
<td>1.3</td>
<td>0.74 (0.37-1.46)</td>
</tr>
<tr>
<td>Sall et al. 2009 (39)</td>
<td>1</td>
<td>2</td>
<td>1.3</td>
<td>0.74 (0.37-1.46)</td>
</tr>
<tr>
<td>Selig et al. 2010 (40)</td>
<td>1</td>
<td>2</td>
<td>1.3</td>
<td>0.74 (0.37-1.46)</td>
</tr>
<tr>
<td>Severino et al. 2010 (41)</td>
<td>1</td>
<td>2</td>
<td>1.3</td>
<td>0.74 (0.37-1.46)</td>
</tr>
<tr>
<td>Thomas et al. 2010 (42)</td>
<td>1</td>
<td>2</td>
<td>1.3</td>
<td>0.74 (0.37-1.46)</td>
</tr>
<tr>
<td>Total events, n</td>
<td>43</td>
<td>50</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Heterogeneity:** I² = 0.00; df (degrees of freedom) = 42; P = 0.78; F = 0.83%

**Test for overall effect:** Z = 4.24; P = 0.0001

S. boulardii
S. thermophilus
L. rhamnosus
L. casei
L. acidophilus

Fecal transplantation

RCT – 41 Adult patients with CDI relapse after at least one course of adequate antibiotic therapy (≥10 days of vancomycin or ≥10 days of metronidazole)

1. Vancomycin 4-5 days + bowel lavage (4 liters macrogol) + nasoduodenal infusion of donor feces
2. Standard vancomycin regimen for 14 days (500 mg orally four times per day)
3. Standard vancomycin regimen for 14 days + bowel lavage

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Cochrane: Antibiotic treatment for CDI

Uncertainty whether mild CDAD needs to be treated

Little evidence for antibiotic treatment of severe CDAD as many studies excluded these patients

Small numbers of patients were included in the studies and there was high risk of bias, especially related to dropouts

Most of the active comparator studies found no statistically significant difference in efficacy between vancomycin and other antibiotics including metronidazole, fusidic acid, nitazoxanide or rifaximin

Teicoplanin may be an attractive choice

Nelson RL. Cochrane Database Syst Rev 2011;9:CD004610

Summary

Infection control measures

Contact precautions (gloves, gowns)
→ Gloving is the most important measure of „hand hygiene”
→ Use disposable gowns

Hand washing during outbreaks or increased CDI-rates
→ Rinsing removes spores mechanically
→ No advantage by using medicated products

Isolation/cohorting
→ Given the high contamination of spores and patients moving in the room mixed accommodation of CDI and non-CDI-patients is a risk – isolate if possible!

Cleaning of the patient’s environment
→ Bleach (>1000 ppm)
→ Daily cleaning of the patient’s room
Prevention measures

**Antibiotic stewardship**
→ Treat as narrow as possible (improve diagnosis, local resistance data)
→ Almost all antibiotic groups have been shown to be associated with CDI!

**Surveillance**
→ Good surveillance detects problems in good time

**Audits**
→ Implementation of infection control measures is complex and sometimes difficult – Audits help assure compliance

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Prof. David Leaper, University of Huddersfield, UK

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Jessica Ng, Women’s College Hospital, Toronto

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