Clostridium difficile infection: New Zealand perspective

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Clinical Lead for the IP&C Programme, HQ&SC
Introduction

• Historical
• Laboratory diagnosis
• Survey
  – 2009
  – 2011
• Other issues
  – RT 244
  – Paediatrics
• Infection prevention and control
History

LINCOMYCIN AS A CAUSE OF PSEUDOMEMBRANOUS COLITIS

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ALAN R. KERR

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Summary

Eight patients with pseudomembranous colitis are described. In seven of the eight the administration of lincomycin preceded the illness. Three of these patients died. An association between pseudomembranous colitis and lincomycin is supported by the frequency with which the disease has been diagnosed since the widespread introduction of the drug. This association also illustrates the role of a disturbance of gut flora in the pathogenesis of some forms of pseudomembranous colitis.

C. difficile was identified in 1977 as the major cause of antibiotic-associated colitis with fever, severe abdominal cramps, intestinal distention, leukocytosis and blood and mucus in the stool.” In 1970, four patients in whom pseudomembranous colitis developed as a sequel to lincomycin therapy were reported.

Pseudomembranous colitis has not, in our experience, proved to be a common condition. Yet in most cases there are distinctive rectal findings, radiological studies are often striking, and the gross pathological and the microscopic appearance of the lesions is always such as to make it difficult to suggest that the condition was occurring unrecognised. We have therefore been impressed by the occurrence of seven cases of the condition in as many months, six of the seven occurring as a sequel to lincomycin administration, while in the seventh patient the antibiotic history is unclear. Review of the post-mortem records of the two hospitals in which these patients were seen revealed only one other patient with pseudomembranous colitis over
Laboratory Diagnosis

• **Diagnosis**
  – Culture, cell cytoxicity assay and neutralisation
  – Immunologic methods
    • Enzyme immunoassays
    • Latex agglutination
    • Immunochromatogenic assay
      – Toxin A and B
      – Antigen – glutamate dehydrogenase (GDH)
  – DNA-based assays
    – PCR
    – Loop-mediated isothermal amplification (LAMP)
Testing in NZ

• Pathology 2011; 43(5); 482-487
  – Online survey of 48 Australian and New Zealand (10) Laboratories (2008-2010)
  – Most laboratories used EIA assays to detect toxin A and B
  – 5.3% of all tests were positive
  – Testing of isolates was rare
  – Conclusions
    • Low overall rates may reflect lack of sensitivity of diagnostic testing procedures
Testing in NZ

• 2011 Survey
  – All Diagnostic Laboratories in NZ asked to contribute
  – Assays in use
    • TechLab Quick Chek Complete® Assay
    • Meridian Premier™ C. difficile GDH, Premier™ Toxins A&B or ImmunoCard® Toxins A&B and illumigene® C. difficile test
Molecular Testing

• Shift to NAAT assays
  – ↑sensitivity
  – Test a variety of genes
• ADHB
  – Screen with GDH ICT
  – All positives tested by PCR
  – Cepheid Xpert™ *C. difficile* assay
    • *tcdB*, binary toxin, and *tcdC* deletion
Brief report

Improved detection of toxigenic Clostridium difficile using the Cepheid Xpert C difficile assay and impact on C difficile infection rates in a tertiary hospital: A double-edged sword

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*Department of Clinical Microbiology, Auckland District Health Board, Auckland, New Zealand

Table 1
Impact of the 2-step diagnostic algorithm on laboratory detection of toxigenic C difficile

<table>
<thead>
<tr>
<th></th>
<th>First testing period (July 2009 to June 2010)</th>
<th>Second testing period (July 2010 to December 2011)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of specimens tested</td>
<td>3,100</td>
<td>4,006</td>
</tr>
<tr>
<td>Number of GDH-positive specimens by EIA*</td>
<td>473</td>
<td>605</td>
</tr>
<tr>
<td>Number of GDH-positive/toxin-positive specimens by EIA</td>
<td>145</td>
<td>181</td>
</tr>
<tr>
<td>Number of GDH-positive/toxin-negative specimens by EIA</td>
<td>328</td>
<td>424</td>
</tr>
<tr>
<td>Number of GDH-positive/toxin-negative specimens positive for the presence of tcdB by PCR†</td>
<td>NA</td>
<td>218</td>
</tr>
<tr>
<td><strong>Overall laboratory rate of toxigenic C difficile detection, %</strong></td>
<td><strong>4.7</strong></td>
<td><strong>9.9</strong></td>
</tr>
</tbody>
</table>

NA, not applicable.

*EIA: C difficile Quik Chek complete test.

†PCR: Cepheid Xpert C difficile assay.
Testing Patterns

- July 2010-April 2012, specimen collected > 48 hours after admission

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Number of requests</th>
<th>Number (%) positive for toxigenic <em>C. difficile</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>General Medicine</td>
<td>533</td>
<td>35 (6.6)</td>
</tr>
<tr>
<td>Surgery/ICU</td>
<td>812</td>
<td>70 (8.6)</td>
</tr>
<tr>
<td>Haematology/Oncology</td>
<td>429</td>
<td>42 (9.8)</td>
</tr>
<tr>
<td>Liver/Renal</td>
<td>153</td>
<td>24 (15.7)</td>
</tr>
<tr>
<td>RehabPlus</td>
<td>113</td>
<td>37 (32.7)</td>
</tr>
<tr>
<td>Other</td>
<td>116</td>
<td>7 (6.0)</td>
</tr>
</tbody>
</table>
Epidemiology of *Clostridium difficile*

- Prior to 2009 little was known about the circulating strains of *C. difficile* in NZ
- Survey was a collaboration between ADHB and ESR
- A limited number of laboratories submitted all EIA positive stool specimens for culture at LabPlus.
- All isolates were sent to ESR for PCR-ribotyping
- Results
  - 108 isolates from 159 stool specimens or 101 isolates from 97 patients
PCR-ribotypes, n=108

Metropolitan Auckland
n=48
Survey 2011

- November 2011
- Funded by the Ministry of Health.
  Collaboration between ESR and LabPlus
- Same strategy as with 2009 survey
- Results
  - Non-duplicate isolates from 135 patients
  - Diverse range of PCR-ribotypes; 43 different RT including 32 Rt not seen in 2009
Patient Demographics

• Gender
  – Female 84
  – Male 48

• Age
  – Mean (±SD) 58 ±26 yrs
  – Median (range) 71 (2m – 100 years)

• Hospital-onset vs healthcare associated
  – 54 (42%) of patients had been in hospital > 48 hours when specimen collected
  – 55/73 (75%) hospitalised in last six months (via NMDS)
“Hypervirulent” strains?

• 2009 survey - one patient from South Island with RT 078
• 2011 Survey
  – Post Rugby World Cup
  – RT 027 in Australia

Severe infection with *Clostridium difficile* PCR ribotype 027 acquired in Melbourne, Australia

Michael Richards, James Knox, Briony Elliott, Kate Mackin, Dena Lyras, Lynette J Waring and Thomas V Riley

We report the first recognised case of infection with *Clostridium difficile* PCR ribotype 027 acquired in Australia. This pathogen has caused significant morbidity and mortality in widespread hospital-based outbreaks in the northern hemisphere. Clinicians need to be aware of the clinical picture, limitations of diagnostic tests, availability of further testing for epidemic strains, new therapeutic approaches, and in-hospital control strategies for this infection. (MJA 2011; 194: 369-371)
Epidemic strains of *Clostridium difficile* are present in Auckland, New Zealand

NZMJ 15 April 2011, Vol 124 No 1332; ISSN 1175 8716

<table>
<thead>
<tr>
<th>Age (years) and Gender</th>
<th>Comorbidities</th>
<th>Recent antibiotic use#</th>
<th>Diagnostic test$^4$</th>
<th>Minimum inhibitory concentration (mg/L)#</th>
<th>Strains§</th>
<th>Disease severity and outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>72 Female</td>
<td>Pancreatitis secondary to gallstones</td>
<td>Amoxicillin/ clavulanate</td>
<td>EIA and PCR</td>
<td>moxifloxacin &gt;32, clindamycin &gt;32</td>
<td>PCR-ribotype027</td>
<td>Diarrhoea resolved after treatment with metronidazole</td>
</tr>
<tr>
<td>24 Female</td>
<td>Chronic respiratory illness with bilateral lung transplant</td>
<td>Ciprofloxacin, co-trimoxazole and azithromycin</td>
<td>EIA</td>
<td>moxifloxacin 1.0, clindamycin 1.0</td>
<td>PCR-ribotype078</td>
<td>Recurrent diarrhoea, this episode resolved after treatment with metronidazole followed by vancomycin</td>
</tr>
</tbody>
</table>
Other current issues
RT 244

- ‘New strain’ in Australia, PCR-ribotype 244
- False-positive ‘presumptive O27’ with GeneXpert testing
- Associated with severe community-onset disease
- 2 deaths over short period of time
RT 244

• Case-control study
• Compare risk factors, disease severity and clinical outcome of CDI due to RT 244 with other strains
• To further characterise RT 244 isolates
  – Antibiotic susceptibility testing
  – Binary toxin gene PCR and tcdC gene sequencing

• Patients
  – Cases:
    • Patients from Auckland region with CDI due to RT 244
    • Oct 2011 – May 2012
  – Controls:
    • Patients from Auckland region with CDI due to other ribotypes.
    • Isolate included in Nov 2011 national C. difficile survey.
  – Matching
    • Controls matched 1:2 for age (± 10 yrs) and gender.
Results

- **Cases (10)**
  - Age, median (range)
    - 71 years (43-93)
  - 70% > 65 years
  - 50% male
- **Controls (20)**
  - Age, median (range)
    - 71 years (43-94)
  - 65% > 65 years
  - 50% male

- No difference in co-morbidity, antibiotic exposure, PPI use or chemotherapy
- RT 244 strains all had binary toxin and 1 bp deletion in \( tcdC \) gene at position 117 117
- RT 244 strains susceptible to moxifloxacin
<table>
<thead>
<tr>
<th></th>
<th>Cases (n=10)</th>
<th>Controls (n=20)</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community-associated CDI</td>
<td>5 (50%)</td>
<td>3 (15%)</td>
<td>5.67 (0.76-48.23)</td>
<td>0.078</td>
</tr>
<tr>
<td>Severe disease (ESCMID)</td>
<td>7 (70%)</td>
<td>4 (20%)</td>
<td>9.33 (1.27-82.59)</td>
<td>0.015</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>2 (20%)</td>
<td>0</td>
<td>-</td>
<td>0.103</td>
</tr>
<tr>
<td>Surgery</td>
<td>0</td>
<td>1 (5%)</td>
<td>-</td>
<td>1.000</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrence</td>
<td>4 (40%)</td>
<td>3 (15%)</td>
<td>3.78 (0.49-31.85)</td>
<td>0.181</td>
</tr>
<tr>
<td>30 day mortality</td>
<td>1 (10%)</td>
<td>3 (15%)</td>
<td>0.63 (0.02-8.9)</td>
<td>1.000</td>
</tr>
</tbody>
</table>
Key points

• Newly recognized strain causing severe community-onset CDI in Australia and New Zealand.

• Ongoing surveillance of RT 244 essential to allow early recognition and intervention if necessary.

• CDI should be considered in the differential in adult patients presenting with severe community-onset diarrhoea.
CDI and children

- Children are considered at low risk of *C. difficile* infection?
- Until recently testing is not recommended in those < 2 years of age.
- However, recent reports suggest that this is not the case
  - Diarrhea etiology in children presenting to ED. CID 2006;43:807-13
  - CDI amongst hospitalised children EID 2010;16:604-8
CDI in hospitalised children in Auckland

- Prospective cross sectional study of hospitalised children, Nov 2011- June 2012
- Starship Children’s Hospital and Kidz First Hospital
- *C. difficile* testing was carried out on all stool specimens sent for testing on hospitalised children
- SHEA/IDSA definitions were used
- Patient demographics, illness characteristics, co-morbidities, recent healthcare exposure and antibiotic use
- Testing = EIA for GDH and Toxin A and B and PCR
- All positive stools cultured for *C. difficile*
Results

• Non-duplicate specimens from 320 children
  – 299 from SSCH and 21 from Kidz First
  – 50 positive for *C. difficle*
    • 33 HA-CDI
    • 17 CO-CDI
<table>
<thead>
<tr>
<th></th>
<th>Cases N=50 (%)</th>
<th>Controls N=270 (%)</th>
<th>p</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>5 yrs (9 days to 15 yr)</td>
<td>3 yrs (3 days to 15 yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gender:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>31 (6)</td>
<td>160 (59)</td>
<td>0.76</td>
<td>1.12 (0.58-2.19)</td>
</tr>
<tr>
<td>Female</td>
<td>19 (38)</td>
<td>110 (41)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ethnicity:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NZ European</td>
<td>30 (60)</td>
<td>101 (37)</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>Māori</td>
<td>7 (14)</td>
<td>57 (21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pacific</td>
<td>4 (8)</td>
<td>67 (25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>9 (18)</td>
<td>45 (17)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Results

• No difference in symptoms, antibiotic usage
• Receipt of gastric acid suppressive Rx and chemotherapy significantly associated with CDI
• Microbiology
  – 87% tested for other pathogens; 4 cases (8%) and 28 controls (10%) had another pathogen identified
  – 37/50 patients had *C. difficile* isolated and 23 PCR-RT identified. RT 014 most common
Results

% of patients with a positive test stratified by age
Conclusions

• *C. difficile* is a common cause of healthcare-associated diarrhoea in children also
• Similar risk factors to adults
• Low rates in neonates
  – ? Due to improve IPC practices
Infection prevention and control
Issues

• Transmission-based precautions
• Hand hygiene
  – Soap and water vs alcohol-based hand rubs
• Surveillance
  – Notification to IPC Service
  – Hospital-wide surveillance
Hand Hygiene

• Soap and water more effective against the spores than ABHR
• Rates of CDI have not increased in centres that use ABHR
• Rates of VRE, MRSA and ESBL have been shown to decrease with increased use of ABHR but not with soap and water
• Outbreak vs non-outbreak approach
Surveillance for CDI
Surveillance

- Laboratory surveillance
  - Number of positive tests per month
- Clinical surveillance
  - Population-based
  - Hospital rates
    - Healthcare-associated
    - Community-onset healthcare-associated
Clinical Surveillance

• Definitions
  – SHEA/IDSA
  – England, Wales and Northern Ireland
    • Laboratory notification
    • Reported per 100,000 population
  – Scotland
    • Rate per NHS Board
  – Australia
    • VICNISS
    • Australian Commission on Safety & Quality in Healthcare
SHEA/IDSA

**Figure 1.** Time line for surveillance definitions of *Clostridium difficile*-associated infection (CDI) exposures. A case patient who had symptom onset during the window of hospitalization marked by an asterisk (*) would be classified as having community-onset, healthcare facility–associated disease (CO-HCFA), if the patient had been discharged from a healthcare facility within the previous 4 weeks; would be classified as having indeterminate disease, if the patient had been discharged from a healthcare facility within the previous 4–12 weeks; or would be classified as having community-associated CDI (CA-CDI), if the patient had not been discharged from a healthcare facility in the previous 12 weeks. HO-HCFA, healthcare facility–onset, healthcare facility–associated CDI.

- **Numerator =** case symptoms **and** positive laboratory diagnosis or PMC on endoscopy or histology
- **Denominator =** patient days
- **Rate =** cases per 10,000 patient days
England, Wales and Northern Ireland

- Mandatory reporting for patients >65 yrs from Jan 2004
- Expanded to include all >2 - 64 years in April 2007
- Numerator = lab reports
- Denominator = population
- Rate = lab reports per 100,000 population
Scotland NHS

- Numerator = number of CDI cases
- Denominator = population in Board area
- Rate = cases per 100,000 total occupied bed days
- Report for patients ≥ 65 years and for 15-64 years
Australia

• VICNISS
  – Numerator = patient episodes of healthcare associated CDI*
  – Denominator = occupied bed days
  – Rate = cases per 10,000 OBD

• Australian Commission
  – Numerator = patient episodes of hospital-identified CDI
  – Denominator = total patient days
  – Rate = cases per 10,000 patient days

* SHEA definition
# New Zealand

<table>
<thead>
<tr>
<th>DHB</th>
<th>Defn</th>
<th>Numerator</th>
<th>Denominator</th>
<th>Rate</th>
<th>Actual rates</th>
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</thead>
<tbody>
<tr>
<td>CMDHB</td>
<td>Australian</td>
<td>HA-CDI case</td>
<td>Patient days</td>
<td>HA-CDI cases /1000 patient days</td>
<td>0.22/1000</td>
</tr>
<tr>
<td>CDHB</td>
<td>IDSA/SHEA</td>
<td>Positive tests/cases</td>
<td>Patient days</td>
<td>Cases/1000 patient days</td>
<td>0.05-0.45/1000</td>
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<tr>
<td>WDHB</td>
<td>Australian</td>
<td>Positive tests/cases</td>
<td>Bed days</td>
<td>Cases/10,000 bed days</td>
<td>NSH-7.4-6.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Waitakere 8.6-7.9/10,000</td>
</tr>
<tr>
<td>CCDHB</td>
<td></td>
<td>Positive test/cases</td>
<td>OBD</td>
<td>Cases/100,000 occupied bed days</td>
<td>5.3/100,000</td>
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<tr>
<td>ADHB</td>
<td>IDSA/SHEA</td>
<td>Positive tests/cases</td>
<td>Patient days</td>
<td>Cases/10,000 patient days</td>
<td></td>
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## Laboratory-based

<table>
<thead>
<tr>
<th>DHB</th>
<th></th>
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<tbody>
<tr>
<td>Hawkes Bay DHB</td>
<td>Positive tests</td>
<td>Month</td>
<td>Postive test/month</td>
<td></td>
<td></td>
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<tr>
<td>Wairarapa DHB</td>
<td>Positive tests</td>
<td>Month</td>
<td>Positive test/month</td>
<td></td>
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<tr>
<td>SDHB</td>
<td>Positive tests</td>
<td>?</td>
<td>Positive test/month</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCDHB</td>
<td>Positive tests</td>
<td>Month</td>
<td>Positive test/month</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BOP and Lakes</td>
<td>Positive tests</td>
<td>Month</td>
<td>Positive test/month</td>
<td>Use Control Chart</td>
<td></td>
</tr>
</tbody>
</table>
Issues

• Which definition to use?
• Hospital onset vs healthcare-associated vs community onset
• Use of NMDS to assist with applying surveillance definition
• Need to standardise the laboratory testing strategy so rates are comparable.
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  – Helen Heffernan
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