"Clostridium difficile" infection: background, epidemiology and international perspectives

Thomas V Riley

Microbiology & Immunology, The University of Western Australia
&
Division of Microbiology & Infectious Diseases
PathWest Laboratory Medicine
Queen Elizabeth II Medical Centre
Nedlands 6009 Western Australia
**Background**

*Clostridium difficile* – an anaerobic Gram +ve bacillus

*C. difficile* disease gained prominence because of renewed interest in anaerobic bacteria in the 1960s and 70s

Specific anti-anaerobe drugs had been developed, e.g. clindamycin

Clindamycin-associated diarrhoea became a real problem in some hospitals in the USA

Outbreaks of pseudomembranous colitis

Cause elucidated in 1978
C. difficile-associated disease

- *C. difficile* the most common cause of diarrhoea in hospital patients
- Produces at least 2 major toxins:
  - toxin A (an enterotoxin)
  - toxin B (a cytotoxin)
- 3rd “binary” toxin

PaLoc
What are the major risk factors for *C. difficile*?

- Exposure to the organism
- Exposure to antibiotics - particularly clindamycin and extended spectrum cephalosporins (until now)
- Old age
Effect of Antibiotics on Normal Flora

Risk of developing CDI for various antimicrobials (Golledge *et al.* JAC 1989;23:929-31)

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Courses</th>
<th>Patients</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clindamycin</td>
<td>120</td>
<td>11</td>
<td>9.1%</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>1080</td>
<td>55</td>
<td>5.1%</td>
</tr>
<tr>
<td>Cephamandole</td>
<td>530</td>
<td>24</td>
<td>4.5%</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>160</td>
<td>7</td>
<td>4.4%</td>
</tr>
<tr>
<td>Amoxycillin</td>
<td>1570</td>
<td>19</td>
<td>1.2%</td>
</tr>
<tr>
<td>Cloxacilllin</td>
<td>1010</td>
<td>7</td>
<td>0.7%</td>
</tr>
</tbody>
</table>
CDI at SCGH 1983-92, rates, by age and gender, and cephalosporin use

(Riley et al. Epidemiol Infect 1994; 113: 13-20)
Cost of *Clostridium difficile*-associated diarrhoea at SCGH

- The median length of stay for cases was 24.5 days (range 1-166 days) and for controls 6.5 days (range 1-142 days) (Wilcoxon matched-pairs signed ranks-test, p<0.001)

- Approximately 100 cases of *Clostridium difficile*-associated diarrhoea per year

- Bed costs of approximately A$700 per day

- Total cost: **A$1,250,000** per year (Riley et al. 1995)
Canadian outbreak in Quebec (CHUS)
(Pepin et al. CMAJ 2004;171:466-72)

- In late 2002, increase in fulminant *C. difficile* colitis → emergency colectomy.
- Retrospective review of all cases 1991-2003
- Rates ↑ from 35.6/100,000 pop. in 1991 to 156.3 in 2003.
- In ≥65 years age group ↑ from 102 in 1991 to 866.5 in 2003.
- Complications ↑ from 7.1% in 1991 to 18.2% in 2003 (p<0.001)
- Death within 30 days of diagnosis ↑ from 4.7% (8/169) in 1991 to 13.8% (59/390) in 2003 (p<0.001)
Fig. 1: Annual incidence (per 100 000 population) of *Clostridium difficile*-associated diarrhea (CDAD) in Sherbrooke, Que., 1991–2003.
Resistance of current BI/NAP1 isolates to clindamycin and FQs compared with current non-BI/NAP1 isolates and historic BI/NAP1 isolates

<table>
<thead>
<tr>
<th>No. (%) Intermediate or Resistant to:</th>
<th>Current BI/NAP1 Isolates n=24 (%)</th>
<th>Current non-BI/NAP1 Isolates n=24 (%)</th>
<th>P-Value for BI/NAP1 vs. Non-BI/NAP1 Isolates</th>
<th>Historic BI/NAP1 Isolates n=14 (%)</th>
<th>P-Value for Current vs. Historic BI/NAP1 Isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clindamycin</td>
<td>19 (79)</td>
<td>19 (79)</td>
<td>1.0</td>
<td>10 (71)</td>
<td>0.7</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>24 (100)</td>
<td>23 (96)</td>
<td>1.0</td>
<td>14 (100)</td>
<td>1.0</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>24 (100)</td>
<td>10 (42)</td>
<td>&lt;0.001</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>24 (100)</td>
<td>10 (42)</td>
<td>&lt;0.001</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

National estimates of US short-stay hospital discharges with *C. difficile* as first-listed or any diagnosis

**Clostridium difficile** Surpasses MRSA

Infections with methicillin-resistant *Staphylococcus aureus* (MRSA) may have grabbed headlines the last few years, but a new study shows that *Clostridium difficile* infection rates have surpassed those of MRSA in at least 1 group of community hospitals.

Researchers at the Duke University Medical Center in Durham, NC, showed that during an 18-month period in 2008 and 2009, *C difficile* infections were 25% more common than MRSA infections in a network of 28 community hospitals in the southeastern United States. The report, presented in late March at the Fifth Decennial International Conference on Healthcare-Associated Infections 2010 in Atlanta, Ga, also showed that *C difficile* infections were just as common as hospital-wide bloodstream infections.

Lead author Becky Miller, MD, said her research team was surprised by the findings. “We knew *C difficile* was out there, but none of our hospitals [in the Duke Infection Control Outreach Network] had called us and said, ‘We think our *C difficile* rates are more than they used to be,’” said Miller.

Experts say the study is notable because it is the first to use patient surveillance data rather than hospital discharge diagnosis codes to compare *C difficile* and MRSA infection rates. Miller and her colleagues calculated infection rates based on the number of cases per 1000 patient-days. The results showed the *C difficile* infection rate was 0.28 cases per 1000 patient-days compared with MRSA’s 0.23 cases.
Figure 1: PFGE analysis of *C. difficile* study isolates from various geographical locations.
Outbreaks of PCR ribotype 027 in the UK – big problem at Stoke-Mandeville Hospital

- Between October 2003 and June 2004 there were 174 cases and 19 deaths that were definitely or probably due to *C. difficile*.
- Between October 2004 and June 2005 there were 160 new cases and 19 further deaths among patients that were definitely or probably due to *C. difficile*.
Investigation into outbreaks of *Clostridium difficile* at Stoke Mandeville Hospital, Buckinghamshire Hospitals NHS Trust

July 2006

Figure 5: PCR types of *C. difficile* in hospital patients in England and Wales: referrals to ARL 1995-2003
England distribution of PCR ribotypes 2005/6 to 2007/8 as percentages

2005-6 (n=881)


2007-8* (n=677)
Clostridium difficile rates from laboratory reports in people 45-64 years of age in England (excludes North West, South East and London regions) (Health Protection Agency, 2006).
Superbug kills war hero who survived three years as a PoW

By Luke Salteld

THE family of a distinguished war veteran have criticised the hospital where he was infected by a killer bug.

Major Sam Weller - who survived three years as a prisoner of war - died after catching Clostridium Difficile following an operation on his hip. Yesterday, his relatives said he had been let down by the country he fought for.

Major Weller, 88, had surgery at Gloucestershire Royal Hospital but he developed an infection and was given a course of antibiotics.

Weeks later he died and an inquest was told the medicine he received was found to be spreading the superbug.

Yesterday, his family criticised the hospital treatment he received and standards of care.

ALMOST 56,000 vulnerable and elderly patients have been infected with C. Diff in the past year.

Between January and March alone, 15,592 caught the bug - an astonishing 22 per cent rise on the previous three months.

C. Diff, which is spread by dirty hands and bedding, is a bigger killer than MRSA. It claimed 2,247 lives in 2005 - a 69 per cent rise on the previous year.

It exists naturally in the stomachs of many healthy adults, where it is kept under control by 'friendly' bacteria.

Problems start if the balance of bacteria is disturbed, perhaps as a result of taking antibiotics for another infection.

Once the 'friendly' bacteria are killed off, the C. Diff is able to multiply and produce the toxins which cause diarrhoea and, in the worst cases, a fatal infection of the abdomen.

Fearless officer: Major Sam Weller, left, who was decorated for his bravery, is pictured with his brother Tony in 1947

Major Weller: Hip operation as he neared the end of the life, was in great deal of pain.

2,247 died from Clostridium Difficile in 2005
Superbug kills one person an hour

Research suggests the supposed fall is due to a change in the way cases are counted, and that true figures show a substantial increase in infection of between 16 and 35 per cent during that period.

Professor Richard James, who is in charge of Nottingham University's centre for investigating hospital infections, said: "The figures for C. diff show more than 50 per cent of hospital trusts have a rate of infection that's more than 10 times that of any other country.

"If you look at the over-65s, which is the group where there are more deaths, then we have more cases there and therefore more deaths in that age group, than any country in the world by a factor of 10."

His remarks are based on a draft report on infection for the Department of Health, and while the figures are based on English acute NHS trusts, he says they are relevant to the whole of the UK. A Freedom of Information survey of every acute trust and health board in Britain carried out by TV's Panorama, got replies from 170 trusts - 83 per cent of the total.

In 95 of the trusts that replied, the bed occupancy rates were more than 85 per cent. Prof James said: "Experts would say if you go above 85 per cent bed occupancy that is not conducive to good control of infection measures."

The survey also reveals that 94 per cent of hospitals now put alcohol hand gels outside their infection wards, and while this destroys MRSA, it does not combat C. diff, though soap and water does offer protection.

Scientists are also worried that the superbug is becoming resistant to Metronidazole, one of the only two antibiotics that can destroy it. Although the Department of Health has put £270 million into a new initiative within hospitals and £57 million towards deep cleaning, experts say more money is needed for research.

One of the worst outbreaks was at the Maidstone and Tunbridge Wells Trust in Kent, where around 90 patients died in 2005-6.

Health minister Ann Keen said: "One case of avoidable infection is one too many and I challenge the NHS to make full use of their resources to eradicate avoidable infections."
Quarterly counts of *C. difficile*: comparison of mandatory and voluntary quarterly reporting

Please note that the voluntary *C. difficile* 2008 data at time of extraction may be under completed.
*C. difficile* voluntary data includes toxin negative reports.
Extraction date 26.01.2009

Courtesy Andrew Pearson
What about elsewhere?

Further outbreaks in the Netherlands, Belgium and France

Appears to be spreading across Europe

Generally not the same high mortality as reported in North America - but still significant

Asia/Pacific region?
Recent outbreaks in Spain, Austria and Denmark.


CDI in the community

- 1986 J Hyg (Camb), prevalence in diarrhoeal specimens 4.7%
- 1991 Pathology, prevalence 5.5%
- 1995 CID, prevalence 10.7%
**Figure 1:** Population rates of community-acquired *Clostridium difficile*-associated diarrhea among people 65 years and older who required hospital admission in Quebec. Error bars = 95% confidence intervals.
Contact with infants, <2 years old significantly associated with CDI

Figure 1. Comparative antibiotic usage in randomly selected community-associated CDI cases and controls. *P < 0.05; **P < 0.01; ***P < 0.001.

Emergence of *Clostridium difficile* Infection Due to a New Hypervirulent Strain, PCR Ribotype 078

- Compared 027 infections with 078
- 078 increased from 3% to 13% (2005-8)
- In parts of The Netherlands where 90% of pig farms 22.4% of human cases 078
- 078 patients were younger (67 vs 74 yrs)
- More community acquired 17.5% vs 6.7%
- Severity and attributable mortality similar
- Pig & human 078 strains genetically indistinguishable

Goorhuis *et al* Clinical Infectious Diseases 2008; 47:1162–70

Ribotype 078 now the 3rd most common isolate in Europe (Bauer *et al* ECCMID 2009)
What is driving this apparent epidemic?

- Aging population
- New fluoroquinolone use
- Gastric acid suppressant use
- ?Animal reservoir, pigs/cattle for example
Fig. 2: Proportions of patients with CDAD by class of antibiotic received in the 2 months preceding the diagnosis of CDAD, 1991–2003.
Antecedent fluoroquinolone use is associated with resistance in *C. difficile*

- Moxifloxacin has high activity against *C. difficile* (MICs ≤ 2 mg/L)
- 63 clinical isolates of *C. difficile* (45 toxigenic)
- 33 moxifloxacin resistant (MICs ≥ 16 mg/L) all in toxigenic group
- Resistance was associated with prior quinolone use (p = 0.009)
- Mutations in *gyrA* gene

Stomach acid-suppressing medications and community-acquired CDAD, England

CDI in Asia

Little is known about *C. difficile* in many areas of South-East Asia.

Recent work from China (Shanghai), Taiwan, Singapore, Hong Kong and earlier work from Thailand.

No useful data from Indonesia

Nothing from Vietnam, Philippines, Malaysia, Cambodia, etc.

Some data from India, none from Sri Lanka

Data from Japan/South Korea but not much
Singapore/Hong Kong

1985-89, 9.6% cases positive for *C. difficile* at NUS Hospital (Kumurasinghe *et al.* Trop Geogr Med 1992)

Koh *et al.* (Pathology 2007) SGH 2002-03, 54 cases/100,000 patient-days

HK ~5% samples positive, PCR ribotype 027 detected late 2008 (Cheng *et al.* IJAA 2009)

1990 - 26 month study, 269 diarrhoeal patients and 114 normal patients. *C. difficile* isolate from 13 (4.8%) of diarrhoeal patients & 3 (2.6%) normals. 52% diarrhoea & 22% normals had faecal cytotoxin! (Wongwanich et al. SEA J Trop Med Pub Health 1990)

**Table 1** Recovery of *C. difficile* from asymptomatic individuals and diarrheal patients  
(Wongwanich et al. Clin Microbiol Infect 2001)

<table>
<thead>
<tr>
<th>Patient group</th>
<th>No. of persons</th>
<th>No. (%) of <em>C. difficile</em> positive</th>
<th>No. (%) of toxin A gene positive by PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic infants &lt;12 months</td>
<td>235</td>
<td>28 (11.9)</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>Asymptomatic children 1–11 years</td>
<td>76</td>
<td>16 (21.1)</td>
<td>0</td>
</tr>
<tr>
<td>Adults</td>
<td>132</td>
<td>33 (25.0)</td>
<td>18 (13.6)</td>
</tr>
<tr>
<td>With diarrhea</td>
<td>84</td>
<td>13 (15.5)</td>
<td>8 (9.6)</td>
</tr>
<tr>
<td>With antibiotic-associated diarrhea</td>
<td>48</td>
<td>20 (41.7)</td>
<td>10 (20.8)</td>
</tr>
<tr>
<td>Total</td>
<td>443</td>
<td>77 (17.4)</td>
<td>20 (4.5)</td>
</tr>
</tbody>
</table>

2003 – Prevalence of *C. difficile* in AAD was 18.6%  
2007-08 – Clinical features of & risk factors for CDI in China similar to elsewhere in world (Huang et al. CID 2008)

2007-08 - Prevalence of *C. difficile* 12.6% in suspected CDI. High rates of resistance to fluoroquinolones. 25% due to A-B+ clone (Huang et al. IJAA 2009)

Subsequently shown that A-B+ strain was ribotype 017 (Huang et al. Clin Microbiol Infect 2009)
Ribotype 027 described in both countries


Testing not widespread in Japan

Fig. 2. The annual prevalence rate of $tcdA^+tcdB^+$, $tcdA^-tcdB^+$ and $tcdA^-tcdB^-$ C. difficile strains in each participating hospital.
We have CDT+ strains
We have hyper-toxin A & B producers
No evidence of widespread quinolone resistance (~1%)
Currently no evidence of all 3 features in one endemic strain – no PCR ribotype 027
First 027 case reported last year (Riley et al. Med J Aust 2009) – current outbreak in Melbourne
Continued surveillance required
Ten most common Australian ribotypes of *C. difficile* (Elliott *et al.* 2010 – submitted)

<table>
<thead>
<tr>
<th>PCR ribotype</th>
<th>No. isolates (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>014</td>
<td>82 (14.3)</td>
</tr>
<tr>
<td>002</td>
<td>41 (7.2)</td>
</tr>
<tr>
<td>020</td>
<td>38 (6.6)</td>
</tr>
<tr>
<td>010</td>
<td>27 (4.7)</td>
</tr>
<tr>
<td>019</td>
<td>18 (3.2)</td>
</tr>
<tr>
<td>054</td>
<td>16 (2.8)</td>
</tr>
<tr>
<td>070</td>
<td>14 (2.5)</td>
</tr>
<tr>
<td>005</td>
<td>13 (2.3)</td>
</tr>
<tr>
<td>001</td>
<td>12 (2.1)</td>
</tr>
<tr>
<td>103</td>
<td>12 (2.1)</td>
</tr>
</tbody>
</table>

The top 10 comprised 47.7% of 572 isolates while 82 ribotypes contained only one isolate.
Our next project!