Managing CDI : what can we learn from the English experience?

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Disclosures

- Director, Healthcare Infection Prevention Ltd
- Speaker fees: Astellas, EUSA Pharma
- Advisory panel fees: Astellas, MSD, Novartis
Outline

- Features of Clostridium difficile infection (CDI)
- CDI in England
- CDI treatment options
- Real-world experience of fidaxomicin use:
  - Seven-centre study, UK
Features of Clostridium difficile infection (CDI)
The disease cycle of *C. difficile* infection (CDI)

1. Ingestion of spores transmitted from other patients, via hands of healthcare personnel and the environment.

2. Germination into growing (vegetative) cells.

3. Disruption of normal colonic microflora allows colonisation and overgrowth of *C. difficile* in the colon.

4. Toxin production leads to inflammation and damage to intestinal cells.

5. Transmission of spores via the faecal–oral route.

The effect of *C difficile* infection on the large bowel

Wolf PL & Kasyan A. NEJM 2005;353:23

Triadafilopoulos G. NEJM 2002;346:333
The lethal impact of *C. difficile* BI/NAP1/027 infection

Kaplan–Meier plot showing probability of death since diagnosis among inpatients in whom nosocomial *Clostridium difficile*-associated disease (CDAD) developed and among matched control subjects without CDAD. No. of days = time since diagnosis of CDAD (cases) or time since reaching the same interval after admission (controls).

The incidence of recurrent CDI

1st recurrence of CDI

Initial episode of CDI

Up to 25% of patients have recurrent CDI 1–3

Recurrence(s) of CDI

~45–65% of patients have further recurrences 4,5

Clostridium difficile infection in England
Clostridium difficile infections reported to voluntary surveillance scheme, England, 1990 to 2005

Health Protection Agency. *Clostridium difficile infection: How to deal with the problem* (2008)
Clostridium difficile public health policy initiatives, England – key milestone

2007 - Mandatory enhanced surveillance of C. difficile infection for NHS acute trusts

2007 - Saving Lives: Reducing infection, delivering clean and safe care. High Impact Intervention No. 7 – Care bundle to reduce the risk from Clostridium difficile (Department of Health)

2008 - Clostridium difficile infection: How to deal with the problem

2012 - Updated Guidance on the Diagnosis and Reporting of Clostridium Difficile

2013 – NHS England sets reduction targets with big fines for failure
Quarterly count of Clostridium difficile infections in England, 2007 to 2016

A comparison of CDI rates in the four UK administrations

Rates of CDI in the United Kingdom four nations

Number of cases per 100,000 population

Year

2010/11 2011/12 2012/13 2013/14 2014/15

Wales
England
Scotland
Northern Ireland
CDI treatment options
First lines treatment of CDI

- Metronidazole
- Vancomycin
- Fidaxomicin

(Faecal transplant – evidence base is for recurrent disease only)
Rates of clinical success for metronidazole and vancomycin

Rates of clinical success in two identical multicentre, randomised, double-blind, parallel-group trials

Clinical success was defined as diarrhoea resolution and absence of severe abdominal discomfort due to CDI on Day 10; NS, not significant.
# Fidaxomicin phase 3 trial results

### Subjects achieving endpoint (%)

<table>
<thead>
<tr>
<th>Category</th>
<th>Fidaxomicin</th>
<th>Vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical cure</td>
<td>88.2</td>
<td>85.8</td>
</tr>
<tr>
<td>Recurrence</td>
<td>15.4</td>
<td>25.3</td>
</tr>
<tr>
<td>Sustained clinical cure</td>
<td>74.6</td>
<td>64.1</td>
</tr>
<tr>
<td>Clinical cure</td>
<td>87.7</td>
<td>86.8</td>
</tr>
<tr>
<td>Recurrence</td>
<td>12.7</td>
<td>26.9</td>
</tr>
<tr>
<td>Sustained clinical cure</td>
<td>76.6</td>
<td>63.4</td>
</tr>
</tbody>
</table>

**Data from modified intent-to-treat population**

- NS, not significant;
- Study 003: USA, Canada;
- Study 004: Belgium, Canada, France, Germany, Italy, Spain, Sweden, UK, USA

### Difference (confidence interval) [p value]

<table>
<thead>
<tr>
<th>Study</th>
<th>Difference</th>
<th>Confidence Interval</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>003</td>
<td>2.4</td>
<td>(–3.1, 7.8)</td>
<td>p=NS</td>
</tr>
<tr>
<td>004</td>
<td>–9.9</td>
<td>(–16.6, –2.9)</td>
<td>p=0.005</td>
</tr>
<tr>
<td>005</td>
<td>10.5</td>
<td>(3.1, 17.7)</td>
<td>p=0.0006</td>
</tr>
<tr>
<td>006</td>
<td>0.9</td>
<td>(–4.9, 6.7)</td>
<td>p=NS</td>
</tr>
<tr>
<td>007</td>
<td>–14.2</td>
<td>(–21.4, –6.8)</td>
<td>p=0.0002</td>
</tr>
<tr>
<td>008</td>
<td>13.2</td>
<td>(5.2, 20.9)</td>
<td>p=0.001</td>
</tr>
</tbody>
</table>

1. European Public Assessment Report, 22 September 2011 (EMA/857570/2011);
Real-world experience of fidaxomicin use: Seven-centre study, UK
<table>
<thead>
<tr>
<th>Question</th>
<th>Methodology</th>
<th>Caveats</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>Can a treatment work (under ideal circumstances)?</td>
<td>Randomised clinical trials</td>
</tr>
<tr>
<td><strong>Effectiveness</strong></td>
<td>Does a treatment work in (non-ideal) real life?</td>
<td>Observational studies of routine clinical settings</td>
</tr>
<tr>
<td><strong>Efficiency</strong></td>
<td>Is a treatment worth its cost to individuals or society?</td>
<td>Health economic studies</td>
</tr>
</tbody>
</table>

Haynes B BMJ 319;1999:652-3
Efficacy versus effectiveness

“What works well at the Sloan Kettering (a high tech cancer centre) may not work very well in Kettering (a small UK community hospital).”

Brian Haynes professor of clinical epidemiology and medicine
McMaster University Health Sciences Center, Ontario, Canada

Haynes, B. BMJ 319;1999:652-3
Fidaxomicin local service evaluation
seven-centre study

Objective

- To collect robust real-world data to understand the cost-effectiveness of fidaxomicin when introduced in routine practice
  - Local treatment of CDI
  - Local rates of CDI recurrence
  - Local resource use associated with CDI management
  - Costs of managing CDI recurrence

Fidaxomicin local service evaluation
seven-centre study

- Seven centres introducing fidaxomicin between July 2012–July 2013
- Retrospective data collection on CDI episodes occurring 12 months before (pre-FDX) and after (post-FDX) the introduction of fidaxomicin
- Pre-fidaxomicin treatment: vancomycin or metronidazole
- Inclusion criteria
  - All hospitalised patients aged ≥18 years with primary CDI (and no CDI in previous 3 months)
- Recurrence
  - In-patient diarrhoea requiring treatment at any time within subsequent 3 months after initial episode
- Data collected
  - Patient characteristics, CDI severity, treatment, place of acquisition, date of onset/resolution, resource use and cost utilisation (length of stay, procedures, readmissions)

## Authors and affiliations

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Author</th>
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<tbody>
<tr>
<td>Leeds Teaching Hospitals NHS Trust</td>
<td>Philip Howard</td>
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<td>Guy's and St Thomas' NHS Foundation Trust</td>
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<td></td>
<td>Laura Whitney</td>
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<td>Derby Hospitals NHS Foundation Trust</td>
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<tr>
<td>University Hospitals of Leicester NHS Trust</td>
<td>David Jenkins, Leslene Edwards</td>
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Study design

- Trust introduction of FDX

12 month pre-FDX period

- Month -3
- All primary CDIs* & related recurrences

12 month post-FDX period

- Month 0
- Recurrences only
- Month 12
- All primary CDIs* & related recurrences
- Month 15
- Recurrences only

*primary CDI confirmed by checking for CDIs in previous 3 months

CDI diagnosis and fidaxomicin use policies

Diagnosis

- **Two-step**
  - GDH EIA -> C difficile toxin EIA
  - GDH EIA -> C difficile cytotoxin assay
  - And repeat >24h later if GDH+/Cdt-

- **Three-step**
  - GDH EIA -> C difficile toxin EIA , -toxin PCR if GDH+/Cdt-

Fidaxomicin treatment (Hospital)

- first line in all episodes (A,B)
- Recurrences and selected primary episodes (C)
- First line for recurrences only (D)
- All lab-confirmed CDI episodes unless patient already recovered, discharged or relative contraindications (E)
- All CDI cases >75 years old, <75 if relapse, co-morbidities, concurrent antibiotics (F)
- Recurrences and primary episodes if considered high risk for recurrence (G)

CDI recurrence rates in the pre- and post- fidaxomcin periods

Hospitals A and B

Fidaxomicin and 28-day mortality

- Centres A and B: fidaxomicin used for all primary episodes of CDI, D: first line for recurrences only

<table>
<thead>
<tr>
<th>Centre</th>
<th>Pre-FDX 28-day mortality (%)</th>
<th>Post-FDX 28-day mortality (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>18.2</td>
<td>3.1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>B</td>
<td>17.3</td>
<td>6.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>C</td>
<td>20.8</td>
<td>16.7</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>28.6</td>
<td>9.1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>E</td>
<td>22.9</td>
<td>20.0</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>14.6</td>
<td>22.5</td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>30.4</td>
<td>18.8</td>
<td></td>
</tr>
</tbody>
</table>

Summary of local service evaluation

- Variation between centres in diagnosis of CDI
- Wide variation in use of fidaxomicin
- Greatest relative reduction in two centres where fidaxomicin used first line in all CDI patients
- Significant reduction in 28-day all-cause mortality in both centres using fidaxomicin first line in all episodes (but also centre D)

Cost comparison: fidaxomicin vs vancomycin

14% recurrence rate with vancomycin

50 patients primary CDI

Primary episodes
vancomycin £61–84/episode
Total = £3,092

7 recurrences
secondary episodes
vancomycin £61–84/episode,
+ in-patient costs £20,249/episode
Total = £142,175.88

Total cost due to vancomycin treatment:
£145,267.88

4% recurrence rate with fidaxomicin

Primary episodes
fidaxomicin £1,640/episode
Total = £82,000

2 recurrences
secondary episodes
fidaxomicin £1,640/episode,
+ in-patient costs £20,249/episode
Total = £43,778

Total cost due to fidaxomicin treatment:
£125,778

Extra cost vancomycin treatment over fidaxomicin:
£19,489.88

Conclusions

• CDI numbers in England have fallen from a peak in 2007 but further reduction has stalled
• Good quality RCT evidence shows non-inferiority of fidaxomicin versus vancomycin for treatment of primary CDI episodes, and significant superiority for prevention of recurrence
• Local service evaluation results indicate the real-world potential for fidaxomicin to deliver better care by improving outcomes in this vulnerable group of patients
• Fidaxomicin can be a cost-effective treatment option when used first-line in a real-world setting