Antibiotics - Use and Misuse

Karen MacSween
Risk factors for *C. difficile*

- Antibiotics
- ↑ age
- Prolonged hospital stay
- GI surgery
- ITU
- Enteral feeding
- Immunosuppressant drugs
- Organ transplantation
- Diabetes mellitus
- PPI & H2 blockers
- ? Contact with infants
### Prevalence

<table>
<thead>
<tr>
<th>Number of Antimicrobials</th>
<th>Inpatients Surveyed</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>0</td>
<td>7887</td>
<td>67.9</td>
</tr>
<tr>
<td>1</td>
<td>2224</td>
<td>19.2</td>
</tr>
<tr>
<td>2</td>
<td>1140</td>
<td>9.8</td>
</tr>
<tr>
<td>3</td>
<td>270</td>
<td>2.3</td>
</tr>
<tr>
<td>4</td>
<td>87</td>
<td>0.8</td>
</tr>
<tr>
<td>Total</td>
<td>11608</td>
<td>100.0</td>
</tr>
</tbody>
</table>

NHS Scotland National HAI Prevalence Survey 2007
<table>
<thead>
<tr>
<th>Antimicrobial Group</th>
<th>Frequency of all Antimicrobial Prescription</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>112</td>
</tr>
<tr>
<td>Antifungal</td>
<td>518</td>
</tr>
<tr>
<td>Antiviral</td>
<td>122</td>
</tr>
<tr>
<td>Carbapenems and Monobactams</td>
<td>76</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>591</td>
</tr>
<tr>
<td>Glycopeptide</td>
<td>241</td>
</tr>
<tr>
<td>Macrolides, Lincosamides, Streptogramin</td>
<td>489</td>
</tr>
<tr>
<td>Penicillins</td>
<td>1745</td>
</tr>
<tr>
<td>Quinolones</td>
<td>558</td>
</tr>
<tr>
<td>Sulphonamides and Trimethoprim</td>
<td>250</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>52</td>
</tr>
<tr>
<td>Other</td>
<td>908</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>5662</td>
</tr>
</tbody>
</table>

NHS Scotland National HAI Prevalence Survey 2007
Variation in Hospital Prescribing

Vander Stichele et al 2006 JAC 58:159
Variation in primary care

Davey et al 2008 JAC in press
Hospital use penicillins Europe 2002

Vander Stichele et al 2006 JAC 58:159
Penicillin type in primary care

Goosens et al 2005 Lancet 365: 579
Sub-optimal hospital prescribing

• Huge variation
• Documentation in notes
• Excess duration
• Rx non-infectious / non-bacterial syndromes
• Rx colonisation / contamination
• Excess or overlapping spectrum
• Not susceptible to antimicrobial
• Inappropriate route, dose or timing

Cosgrove et al 2007 Infect Control Epidemiol 28: 641
Hecker et al 2003 Arch Int Med 163: 972
Kissule et al 2008 J Hosp Med 3: 64
Sub-optimal prescribing

- 58% of patients received at least one day of unnecessary antimicrobial therapy
- 30% of the total antimicrobial days unnecessary
- 26% of patients no antimicrobial indicated
  
  Hecker et al 2003 Arch Int Med 163: 972

- 70% of vancomycin inappropriate
  
  Lipsky et al 1999 Am J Infect Control 27: 84

- 57% prescriptions inappropriate
- Excess spectrum (30%), not indicated (27%)
  
  Kissule et al 2008 J Hosp Med 3: 64
In-patient antibiotic misuse

- Nature of patients
  - acutely ill, complicated
- Diagnostic uncertainty
- Clinical inexperience
- Busy staff
- Pressure to release beds
- Lack of awareness re adverse effects
  - individual
  - wider community
- Continuation of drug initiated in eg A+E

Hecker et al 2003 Arch Int Med 163: 972
Kissule et al 2008 J Hosp Med 3: 64
Investigation into outbreaks of *Clostridium difficile* at Stoke Mandeville Hospital, Buckinghamshire Hospitals NHS Trust

July 2006

Investigation into outbreaks of *Clostridium difficile* at Maidstone and Tunbridge Wells NHS Trust

October 2007
HCC - criticisms of antibiotic prescribing

• Cause for concern in 42%
• Unnecessary use of a broad spectrum agent
• Excessive numbers of antibiotics, additive rather than substitutive
• Use of broad spectrum agent where little/no evidence of infection
• Excess duration
• Failure to stop antibiotics despite *C. difficile*
• Antibiotic therapy of *C. difficile* itself

Investigation into Outbreaks of *Clostridium difficile* at Maidstone and Tunbridge Wells NHS Trust, Healthcare Commission, October 2007
Frequent problems with CDI case management

- Patient not examined
- Severity assessment not performed
- Vancomycin not given
- Precipitating antibiotic continued
- Stool chart not completed
- Cholestyramine co-prescription
- Loperamide, opiates
Treatment not given

<table>
<thead>
<tr>
<th>Drug (Approved Name)</th>
<th>Route</th>
<th>Start Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VANCOMYCIN</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>105</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Signature</td>
<td>Start Date</td>
<td>Pharmacy</td>
</tr>
<tr>
<td></td>
<td>02/01/87</td>
<td></td>
</tr>
<tr>
<td>Notes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CODES FOR NON-ADMINISTRATION OF PRESCRIBED MEDICINE**

If a dose is not administered as prescribed, initial and enter a code in the column with a circle drawn round the code according to the reason as follows:

- Patient Refuses......................................................1
- Patient not present on ward.........................................2
- Medicines not available .............................................3
- Instructions not clear or legal ....................................4
- Nil by mouth ..................................................................5
- Asleep/drowsy ..................................................................6
- Unable to swallow/Route not available..............................7
- Vomiting/nausea ................................................................8
- Time varied on Dr's instructions ....................................9
- Once only/prn medication given ......................................10
- Dose withheld on Dr's instructions .................................11
- Possible drug reaction/side effect .................................12
- Self administered by patient ..........................................13
- Other reasons ..................................................................14
Studies of antibiotics and *C. difficile*

- Observational
- Single dose
- In vitro
- Intervention
Methodological weaknesses

- Retrospective
- Inadequate controls for confounders
  - (LOS before infection, age, multiple antibiotics, patient location, strain)
- Regression to mean effect
- Variation in denominators
- Mortality and LOS data
Duration of Antibiotic Therapy

• Prospective multicentre n=2799 age >12 years
  Significantly less diarrhoea in those treated ≤3 d
  Wiström et al 2001 JAC 47: 43

• Retrospective cohort n=36,086
  ↑ OR for >7 d all cephalosporins, quinolones
  Dubberke et al 2007 CID 45: 1543
Relation between use of cefotaxime (as measured by expenditure) and new cases of *C. difficile* diarrhoea, April 1993 to November 1994
<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Doses administered</th>
<th>No of patients with CDAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ticarcillin/clavulanate</td>
<td>61,925</td>
<td>0</td>
</tr>
<tr>
<td>third generation cephalosporins</td>
<td>39,916</td>
<td>51</td>
</tr>
<tr>
<td>ceftriaxone</td>
<td>23,707</td>
<td>29</td>
</tr>
<tr>
<td>ceftazidime</td>
<td>16,209</td>
<td>22</td>
</tr>
<tr>
<td>second generation cephalosporins</td>
<td>20,636</td>
<td>10</td>
</tr>
<tr>
<td>first generation cephalosporins</td>
<td>17,837</td>
<td>5</td>
</tr>
<tr>
<td>ampicillin</td>
<td>38,429</td>
<td>5</td>
</tr>
</tbody>
</table>
## Effect of single dose of cephalosporin

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Privitera et al</td>
<td>119 VV or hernia surgery patients prior colonisation excluded cephalosporin or mezlocillin prophylaxis 5 cephalosporins</td>
<td>17/74 (23%) colonised, 14/74 (19%) toxin pos after single dose cephalosporin 1/30 (3%) mezlocillin 0/15 controls</td>
</tr>
<tr>
<td>Ambrose et al</td>
<td>78 volunteers none with prior colonisation 8 cephalosporins 5 penicillins (ben pen, amp, mezlo, pip, ticarcillin)</td>
<td>15/48 (31%) colonised, 5/48 (10%) toxin pos, 10/48 (21%) diarrhoea in cephalosporin group, 0/30 penicillin group 0/6 controls</td>
</tr>
</tbody>
</table>

Privitera et al 1991 AAC 35: 1217
Ambrose et al 1985 JAC 15: 319
Surgical prophylaxis

• Risk of CDI after surgical prophylaxis may be increasing – after 027
  – 0.7 per 1000 surgical procedures ’99-’02
  – 14.9 per 1000 surgical procedure ’02-’05

• prophylaxis and therapeutic antibiotics OR 3.3 (95% CI 2.2-4.9)

Carignan et al 2008 CID 46: 1838
Surgical Prophylaxis

• Often of excess duration

• Orthopaedics Hip HTA – no convincing evidence to support use of new-generation cephalosporins in preference to 1st generation

Glenny and Song 1998 HTA 2 (7)
Glenny and Song 1999 HTA 3 (21)
Quinolones

• Temporal association ↑ quinolones and CDI epidemic

• 1/3 of cases attributed to quinolones

Muto et al 2005 Infect Control Hosp Epidemiol 26: 273
Pepin et al 2005 CID 41: 1254
C. difficile and antibiotic susceptibility

Clindamycin, Cephalosporins, Fluoroquinolones, and Clostridium difficile–Associated Diarrhea: This Is an Antimicrobial Resistance Problem

Dale N. Gerding
Hines Veterans Affairs Hospital and Loyola University Stritch School of Medicine, Hines, Illinois

Clinical Infectious Diseases 2004;38:646–8
 Quarterly report on the surveillance of CDAD in Scotland, Oct-Dec 2007
The HPS C. difficile Working Group, March 2008
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Antibiotic policy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomas et al 2002</td>
<td>Retrospective analysis of admission data, microbiology and pharmacy data</td>
<td>3rd generation cephalosporins withdrawn from wards, microbiology approval required for use</td>
<td>&gt; 50% reduction. Rate decreased from 2.09 per 1000 discharges to 0.87 per 1000 discharges p&lt;0.0001</td>
</tr>
<tr>
<td>Carling et al 2003</td>
<td>Prospective study with comparison with pre-intervention trends</td>
<td>Review of all iv prescriptions for 3&lt;sup&gt;rd&lt;/sup&gt; generation cephalosporins, aztreonam, fluoroquinolones, imipenem by pharmacist and ID physician, automatic stop at 7 days</td>
<td>Reduction from 2.2/1000 1000 bed days to 1.4/1000 bed days p=0.002</td>
</tr>
<tr>
<td>Valiquette et al 2007</td>
<td>Retrospective interrupted time series analysis of microbiology, antibiotic usage and computerised hospital records</td>
<td>Restriction of 2&lt;sup&gt;nd&lt;/sup&gt; and 3&lt;sup&gt;rd&lt;/sup&gt; generation cephalosporins, ciprofloxacin, clindamycin and macrolides, education, telephone feedback by pharmacists</td>
<td>60% reduction in CDI, after no change with infection control measures</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Antibiotic Policy</td>
<td>Outcome</td>
</tr>
<tr>
<td>------------------------------</td>
<td>------------------------------------------------</td>
<td>--------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Ludlam et al 1999 Addenbrooke’s Hospital, Cambridge</td>
<td>Prospective analysis 2 consecutive years in MOE, comparison with rest of 900 bed hospital</td>
<td>Cephalosporin restriction in 4 MOE wards to meningitis only pen and cipro for severe CAP</td>
<td>54% reduction in CDAD p&lt;0.001 (98 cases to 45) in MOE, rest of hospital 19% increase (213 to 253)</td>
</tr>
<tr>
<td>O’Connor et al 2004 Unselected admissions to acute geriatric unit, Cork</td>
<td>Retrospective analysis, comparison with historical data and controls</td>
<td>Restriction of cephalosporins, co-amox or cip+pen for CAP, moxifloxacin or tazocin HAP, tazocin for asp pneumonia, trim, nit or co-amox for UTI</td>
<td>In same 4 month period 2 different years 13 CDAD with old policy 4 with new policy (of whom 3 had received cephalosporins) p=0.03 RR old policy vs new policy 3.24</td>
</tr>
<tr>
<td>McNulty et al 1997 MOE Gloucester Royal Hospital</td>
<td>Outbreak intervention</td>
<td>Antibiotic restriction to penicillin, trimethoprim and gentamicin</td>
<td>37 cases in 7 mo before intervention 16 cases in 7 mo after intervention</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Antibiotic Policy</td>
<td>Outcome</td>
</tr>
<tr>
<td>-------</td>
<td>--------</td>
<td>-------------------</td>
<td>---------</td>
</tr>
</tbody>
</table>
| Stone et al 1998  
Acute MOE admissions, Royal Free Hospital, London | Prospective analysis of prescribing, microbiology and admission data with monthly feed back to medical and nursing staff | Cephalosporins withdrawn, antibiotic courses -7 days, amoxicillin -chest infection, trimethoprim - UTI gentamicin for gram neg sepsis | 3.35 CDAD per 100 admissions reduced to 1.94/100 admissions post policy |
| Fowler et al 2007  
3 acute MOE wards Royal Free Hospital, London | Prospective interrupted time series, defined pre and post intervention periods | Co-amoxiclav, cephalosporins and ciprofloxacin restricted | 56% decrease in CDAD cases (59 in 22 months before, 25 in 21 months after) |
| Settle et al 1998  
MOE Leeds | Prospective cross-over design 2 MOE wards | Cefotaxime replaced by piptazobactam | 1/14 (7%) CDAD with PT 18/54 (53%) CTX p=0.006 Increased contamination of environment with cefotaxime use |
| Wilcox et al 2004  
5 MOE wards Leeds General Infirmary | Retrospective analysis of antibiotic use DDD and CDAD | Cefotaxime restricted to meningitis only, replaced by piptazobactam for severe CAP or HAP or severe sepsis of unknown origin | 52% reduction in CDAD cases, supply problems with PT 370% rise in CTX prescribing, CDAD increased by 232% |
| Gourlay et al  
Acute medical unit | Prospective | Cephalosporins, quinolones & co-amoxiclav restricted | Reduction from 1.8/1000 bed days to 0.4/1000 bed days |
CDC Campaign to Prevent Antimicrobial Resistance in Healthcare Settings

12 Steps to Prevent Antimicrobial Resistance Among Hospitalized Adults

12 Steps to Prevent Antimicrobial Resistance Among Surgical Patients

12 Steps to Prevent Antimicrobial Resistance Among Long-term Care Residents
The missing care bundle

Documentation at Initiation
1) Rationale for starting
2) Specimens sent to microbiology
3) Agent selected considering local policy, patient risk group & accounting for allergy
4) Removal of foreign body / drainage of pus / surgical intervention considered

Documentation for Continuation
1) Daily consider de-escalation / oral switch / stopping
2) Antibiotic levels as indicated

Cooke & Holmes 2007
Call to stewardship

• Optimising clinical outcome
• Necessary and appropriate?
  – selection
  – duration
• And documented
Research and Audit

• Most effective strategies to ↓ *C. difficile*
• Most cost effective strategies
• New agents for treatment
• Outcomes with surgical prophylaxis
• Pharmaco-epidemiology
<table>
<thead>
<tr>
<th>Antimicrobial Group</th>
<th>Inpatients Surveyed</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Antimicrobials</td>
<td>7 887</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>17</td>
</tr>
<tr>
<td>Antifungal</td>
<td>197</td>
</tr>
<tr>
<td>Antiviral</td>
<td>28</td>
</tr>
<tr>
<td>Carbapenams and Monobactams</td>
<td>14</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>221</td>
</tr>
<tr>
<td>Glycopeptide</td>
<td>84</td>
</tr>
<tr>
<td>Macrolides, Lincosamides, Streptogramin</td>
<td>138</td>
</tr>
<tr>
<td>Penicillins</td>
<td>807</td>
</tr>
<tr>
<td>Quinolones</td>
<td>301</td>
</tr>
<tr>
<td>Sulphonamides and Trimethoprim</td>
<td>159</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>16</td>
</tr>
<tr>
<td>Multiple1</td>
<td>1 497</td>
</tr>
<tr>
<td>Other</td>
<td>242</td>
</tr>
</tbody>
</table>
| Total                                      | 11 608              | 100.0