Antibiotic stewardship

David M Livermore

Norwich Medical School
University of East Anglia
## What antibiotics have achieved Major reductions in mortality

<table>
<thead>
<tr>
<th>Condition</th>
<th>Mortality, Pre-Antibiotic</th>
<th>Mortality Post-antibiotic</th>
<th>Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community pneumonia$^1$</td>
<td>~35</td>
<td>~10</td>
<td>71</td>
</tr>
<tr>
<td>Hospital pneumonia$^2$</td>
<td>~60</td>
<td>~30</td>
<td>50</td>
</tr>
<tr>
<td>Endocarditis$^3$</td>
<td>100</td>
<td>~25</td>
<td>75</td>
</tr>
<tr>
<td>Meningitis / brain infection$^4$</td>
<td>~80</td>
<td>~23</td>
<td>71</td>
</tr>
<tr>
<td>Skin / soft tissue infection$^5$</td>
<td>~11</td>
<td>~0.5</td>
<td>95</td>
</tr>
</tbody>
</table>

How resistance accrues
Evolution, genes & mechanisms

• Resistant bacteria survive, susceptible ones perish
  - Mechanisms include drug inactivation, efflux, impermeability and various types of target change

• Mutations change chromosomal genes
  - Alter products or their expression

• Plasmids and transposons move genes among bacteria
  - Spread resistance to previously susceptible genera

• Treatments lost include penicillin vs. staphylococci, ampicillin vs. E. coli and ciprofloxacin vs. gonococci
Dwindling supply of new antibiotics
FDA approvals by 5-year period

Updated from Spellberg et al., Clin Infect Dis 2008 46 :155-164
Aims of Antibiotic Stewardship

... conserve antibiotics whilst ensuring optimum $R_x$

Optimize clinical outcomes while minimizing harmful consequences of antibiotic use

- Toxicity
- Superinfection e.g. by *C. difficile*
- Emergence of resistance

Infection control to limit transmission of resistant strains

$Reduced$ need to use antibiotics

$Reduced$ costs without degrading quality of care

David Livermore August 2012
“Start Smart” with empirical antibiotics
...and within 1h in life-threatening infections

Don’t start without **clinical** evidence of infection

Use **local** guidelines to choose appropriate antibiotic

- Reflect likely pathogens & patient risk factors for a resistant strain
- Consider relevant allergies and interactions

Obtain specimens for culture **before** dosing

**Right drug, dose, duration**......

- Record on drug chart and in medical notes

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UK Dept Health: ‘Start Smart, then Focus
“Right drug” - In sepsis, early antibiotics are vital
Mortality increases with each hour’s delay

Adequate antimicrobial therapy should start within 1 hour

Kumar et al. Crit Care Med 2006;34:1589
“Right drug” - Inadequate Empiric Therapy
..Single biggest contributor to mortality

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Adjusted odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate antibiotics</td>
<td>4.26</td>
<td>3.35-5.44</td>
</tr>
<tr>
<td>Organ system failure (1-organ increments)</td>
<td>3.25</td>
<td>2.98-3.54</td>
</tr>
<tr>
<td>Vasopressors</td>
<td>2.20</td>
<td>1.81-2.66</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1.81</td>
<td>1.44-2.27</td>
</tr>
<tr>
<td>APACHE II (1-point increments)</td>
<td>1.05</td>
<td>1.04-1.07</td>
</tr>
<tr>
<td>Increasing age (1-yr increments)</td>
<td>1.02</td>
<td>1.01-1.03</td>
</tr>
<tr>
<td>Surgical inpatient</td>
<td>0.40</td>
<td>0.33-0.49</td>
</tr>
</tbody>
</table>

“Right drug” - Changes with time and place
Resistance makes empirical therapy harder

Inappropriate

<table>
<thead>
<tr>
<th>No. resistances</th>
<th>Frequency (% patients)</th>
<th>Mortality (% patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>1</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>≥3</td>
<td>40</td>
<td>20</td>
</tr>
</tbody>
</table>

“Right drug” - Risk of collateral damage

C. difficile risk varies with therapy

![Graph showing the risk of C. difficile with different therapies](image-url)
“Right drug” - Once microbiology results available ... typically 48h after specimen / Rx initiation

### Clinical & microbiology review

<table>
<thead>
<tr>
<th>STOP</th>
<th>Switch to oral</th>
<th>Move to narrow spectrum agent</th>
<th>Continue &amp; re-review after 24h</th>
<th>OPAT</th>
</tr>
</thead>
</table>

[UK Dept Health: ‘Start Smart, then Focus](http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_131181.pdf)
“Right dose”
Pharmacodynamics vary with drug class

\[ C_{\text{max}} = \text{Peak} \]

\[ C_{\text{max}} / \text{MIC} \]

Aminoglycosides

\[ \text{AUC} / \text{MIC} \]

Fluoroquinolones
Macrolides
Glycopeptides
Tetracyclines
Oxazolidinones

\[ T > \text{MIC} \]

\[ \beta\text{-lactams} \]
“Right dose” - May vary with the patient
Co-morbidities change pK/pD

Sepsis

Increased cardiac output
Increased CL
Low plasma concentrations

Leaky capillaries &/or altered protein binding
Increased Vd

Normal organ function
Unchanged Vd
Normal plasma concentration

End organ dysfunction (e.g. renal or hepatic)
Decreased CL
High plasma concentrations

“Right duration”- Easier to demand than define
Lack of good studies, BUT

- Excessively durations associated with
  - More collateral damage to normal flora
  - No improvement in outcomes

- Excessively short durations associated with
  - Failures
  - Selection of resistance e.g. in tuberculosis

Esposito et al., J Antimicrob Chemother 2012 Jul 24. [Epub ahead of print]
“Right duration”- 8 or 15 days in ventilator pneumonia

Kaplan-Meier estimates of patient survival

No increase of mortality or recurrence with 8-day $R_x$
Longer $R_x$ advised with $P. aeruginosa$

CAVEAT

Trial comparing 7 days doripenem (1g tds) vs 10 days imipenem (1g tds) in VAP
stopped owing to worse outcomes in doripenem arm

Chastre et al. *JAMA* 2003; **290**:2588
Pugh et al. *Cochrane Database Syst Rev* 2011 10:CD007577
Challenges and uncertainties
It is easier to regulate than to be right...

- How restrictive should guidelines be?
  - Class restriction
  - Cycling,
  - Diversity among appropriate agents
Three models of empirical prescribing control
Restrictive policy, cycling & diversity

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>A</th>
<th>A</th>
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<th>A</th>
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<th>A</th>
<th>A</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Restrictive</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usual $R_x$ is A; B &amp; C reserved</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>A</th>
<th>A</th>
<th>B</th>
<th>B</th>
<th>B</th>
<th>C</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cycling</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diverse (Mixed)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

3 month periods
Restrictive policy or guideline
One favoured empirical therapy per setting

- Easy to audit / easiest to enforce
- Applies *de facto* in the UK for severe infection
  - Piperacillin-tazobactam hugely used; carbapenems reserved; cephalosporins & quinolones avoided for fear of *C. difficile*
- Concentrates all selection pressure on a few agents
- Led to sequential loss of therapies in gonorrhoea

David Livermore August 2012
Chisholm *et al.* *J Antimicrob Chemother* 2010; 65: 2141
Sequential destruction of antibiotics vs *N. gonorrhoeae*

<table>
<thead>
<tr>
<th>Year</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre 1937</td>
<td>No good treatments</td>
</tr>
<tr>
<td>1937</td>
<td>Sulphonamides active in 75-80% of cases; some persistence</td>
</tr>
<tr>
<td>WW2</td>
<td>Sulphonamide resistance well recognised</td>
</tr>
<tr>
<td>1943</td>
<td>Penicillin 100% effective at 72 mg, as 6 x 12 mg doses q3h</td>
</tr>
<tr>
<td>1969</td>
<td>Penicillin MICs 10-50 x higher than in 1940s; dose up to 3g + probenicid</td>
</tr>
<tr>
<td>1974</td>
<td>Penicillinase producing <em>N. gonorrhoeae</em> high level resistance</td>
</tr>
<tr>
<td>1984</td>
<td>Ciprofloxacin, 250 mg single dose- standard Rx</td>
</tr>
<tr>
<td>1994</td>
<td>9% cipro resistance in GC from Philippine sex workers</td>
</tr>
<tr>
<td>2000-5</td>
<td>Cipro R &gt;10% in UK, Europe, USA; &gt;50% China</td>
</tr>
<tr>
<td>2000-on</td>
<td>Massive switch to cephalosporins, esp cefixime 400 mg p.o</td>
</tr>
<tr>
<td>2005-on</td>
<td>Low level cefixime resistance– Japan, later UK &amp; Europe, switch to higher dose ceftriaxone (in UK from 2010 combined with azithromycin)</td>
</tr>
<tr>
<td>2010-on</td>
<td>Reports of ceftriaxone resistance – Japan, then France &amp; Spain</td>
</tr>
</tbody>
</table>
Has avoiding cephalosporins (& quinolones) been taken to extremes?

• **C. difficile** rates have been reduced greatly
  - England: 55000 cases in 2007/8, vs 18000 in 2011/12

• But, we have concentrated selection on other agents

• No evidence that targeted cephalosporin use, within overall diversity, will re-ignite **C. difficile** epidemic
  - Should remain cautious for high-risk elderly patients

http://www.hpa.org.uk/web/HPAweb&Page&HPAwebAutoListName/Page/1179745282408
Carbapenemase Enterobacteria referred to HPA, 2003-Nov 2011
Pip-tazobactam for carbapenemase producers
Is there a risk in our heavy use?

David Livermore
Antibiotic cycling
Many studies, including major CDC trial

- Kollef reviewed….mixed results:
  - No worsening of coverage of empirical $R_x$
  - No worsening of patient outcomes
  - Little impact on resistance rates or rates of acquisition of resistant bacteria
  - Many studies confounded by changes in disease incidence or infection control practice
Antibiotic diversity vs. cycling & restriction
Prospective cohort study 44 months, one ICU

<table>
<thead>
<tr>
<th>Months 1-10</th>
<th>Months 11-22</th>
<th>Months 23-34</th>
<th>Months 35-44</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Specific</td>
<td>Priority / Cycling</td>
<td>Single agents restricted</td>
<td>Mixing</td>
</tr>
</tbody>
</table>

- **Physician choice, based on risk factors**
  - Months 1-10: Patient Specific
  - Months 11-22: Priority / Cycling
  - Months 23-34: Single agents restricted
  - Months 35-44: Mixing

  - **Carbapenem**
  - **Cephalosporin**
  - **Pip/tazo**
  - **No Cephalosporin**
  - **No Pip/tazo**
  - **No Carbapenem**

  - **Sequential patients allocated to different Rx**
Different strategies to control resistance
One unit, lot of caveats, but mixing & choice seem best

1 Acinetobacter – solid, carbapenem R
2 Enterobacteria – ESBL
3 P. aeruginosa – any R
4 S. aureus – methicillin R
5 E. faecalis

Adapted from Sandiumenge et al. J Antimicrob Chemother. 2006;57:1197
# Options vs. MRSA

<table>
<thead>
<tr>
<th>Old</th>
<th>Newer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>Quinupristin-dalfopristin</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>Linezolid</td>
</tr>
<tr>
<td>In combination</td>
<td>Daptomycin</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Tigecycline</td>
</tr>
<tr>
<td>Fusidic acid</td>
<td>Ceftaroline</td>
</tr>
<tr>
<td>Variable susceptibility</td>
<td>Telavancin</td>
</tr>
<tr>
<td>Minocycline / doxycycline</td>
<td>In phase III</td>
</tr>
<tr>
<td>Co-trimoxazole</td>
<td>Dalbavancin</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Oritavancin</td>
</tr>
<tr>
<td></td>
<td>Tedizolid</td>
</tr>
</tbody>
</table>
## 30-day in-hospital mortality; MSSA bacteraemia

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>Number of patients</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>naf/cef only</td>
<td>38</td>
<td>3% (1/38)</td>
</tr>
<tr>
<td>vanc plus naf/cef</td>
<td>135</td>
<td>7% (10/135)</td>
</tr>
<tr>
<td>vanc only</td>
<td>94</td>
<td>20% (19/94)</td>
</tr>
</tbody>
</table>

(chi-square test for trend p<0.01)

### Association

<table>
<thead>
<tr>
<th>Association</th>
<th>Adjusted hazard ratio and 95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receipt of nafcillin or cefazolin vs. vancomycin alone</td>
<td>0.21 (0.09, 0.47)</td>
</tr>
<tr>
<td>Switch from vancomycin to nafcillin or cefazolin vs. remaining on vancomycin alone</td>
<td>0.31 (0.10, 0.95)</td>
</tr>
</tbody>
</table>

Schweizer et al. BMC Infectious Diseases 2011; 11:279.
Ceftaroline fosamil: 1st licensed MRSA ceph

ZINFORO™: Administered as Prodrug

Prodrug: ceftaroline fosamil

- Increases solubility
- Phosphono amino group

Active metabolite: ceftaroline

- Rapid biotransformation in plasma
- β-lactamase stability
- Oxime group
- Gram-negative penetration, & transpeptidase activity prevents cell wall synthesis
- 1,2,4-thiadiazole ring
- Carboxyl group zwitterion (negative charge)
- Pyridine ring zwitterion (positive charge)
- Anti-MRSA activity
- 1,3-thiazole ring
### Competition of ceftaroline for PBP2’ of MRSA

<table>
<thead>
<tr>
<th>MIC (mg/L) without 2% NaCl</th>
<th>MIC (mg/L) with 2% NaCl</th>
<th>IC₅₀ (mg/L)</th>
<th>CPT</th>
<th>OXA</th>
<th>CRO</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>0.5–1</td>
<td>0.16 ± 0.04</td>
<td>PBP2α -</td>
<td></td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>128</td>
<td>408 ± 6</td>
<td></td>
<td>OXA</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>&gt;128</td>
<td>677 ± 53</td>
<td></td>
<td>CRO</td>
<td></td>
</tr>
</tbody>
</table>

- Moisan *et al.*, *JAC* 2010; 65: 713–716
**In vitro** activity of ceftaroline fosamil and comparators against staphylococci & streptococci

<table>
<thead>
<tr>
<th></th>
<th>MSSA (334)*</th>
<th>MRSA (119)*</th>
<th>β-haemolytic streptococci (201)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MIC (mg/L)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ceftaroline</strong></td>
<td>0.12-1</td>
<td>0.25-2</td>
<td>≤0.004-0.12</td>
</tr>
<tr>
<td><strong>Vancomycin</strong></td>
<td>1-4</td>
<td>≤0.5-4</td>
<td>0.5-1</td>
</tr>
</tbody>
</table>

### Summary

The *in vitro* activity of ceftaroline fosamil against Gram-positive isolates from the 2008 BSAC Bacteraemia Surveillance Programme in the UK and Ireland.

Biek D et al. ECCMID 2011 BSAC Poster
**CANVAS 1 and 2: study design**

- Phase III, multicentre, randomised, double-blind, comparative with identical methods
- Multinational: USA, Latin America, EU, non-EU Europe

**Patients**
- (n=1396)
- aged ≥18 yr with cSSTI
- requiring at least 5 days of IV antimicrobial therapy

**1:1 randomisation**

**Ceftaroline fosamil**
- 600 mg IV q12h
- (400 mg q12h for moderate renal impairment)
- (n=693)

**Vancomycin 1 g IV q12h**
- + aztreonam 1g IV q12h
- (n=685)

**End of treatment (EOT)**

- 21–35 days after EOT
- 8–15 days after EOT

**10% non-inferiority design**

- TOC (Test of cure)
- LFU (Late follow-up)

OPAT allowed if specific conditions met
No oral step-down therapy

# CANVAS 1 & 2: Baseline patient characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>MITT population, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ceftaroline fosamil (N=693)</td>
</tr>
<tr>
<td>Age, years, median (range)</td>
<td>48.0 (18-93)</td>
</tr>
<tr>
<td>Gender, N (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>444 (64.1)</td>
</tr>
<tr>
<td>Race, N (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>506 (73.0)</td>
</tr>
<tr>
<td>Non White</td>
<td>62 (8.9)</td>
</tr>
<tr>
<td>Other / unknown</td>
<td>125 (18.0)</td>
</tr>
<tr>
<td>BMI, kg/m², median (range)</td>
<td>26.9 (14.1-74.1)</td>
</tr>
<tr>
<td>Diabetes mellitus, N (%)</td>
<td>122 (17.6)</td>
</tr>
<tr>
<td>PVD, N (%)</td>
<td>93 (13.4)</td>
</tr>
<tr>
<td>Bacteraemia, N (%)</td>
<td>29 (4.2)</td>
</tr>
</tbody>
</table>

BMI, Body mass index, PVD, peripheral vascular disease

CANAAS 1 & 2: infection types

Type of infection at baseline (MITT population)

LE, lower extremity

### CANVAS 1 & 2: ceftaroline fosamil clinical efficacy

#### CANVAS 1 & 2 integrated analysis selected baseline isolates at TOC

<table>
<thead>
<tr>
<th>Organism</th>
<th>ME population [n/N(%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ceftaroline fosamil (N=693)</td>
</tr>
<tr>
<td><strong>Gram-positive</strong></td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>352/378 (93.1)</td>
</tr>
<tr>
<td>MSSA</td>
<td>212/228 (93.0)</td>
</tr>
<tr>
<td>MRSA</td>
<td>142/152 (93.4)</td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
<td>56/56 (100)</td>
</tr>
<tr>
<td><em>Streptococcus agalactiae</em></td>
<td>21/22 (95.5)</td>
</tr>
<tr>
<td><strong>Gram-negative</strong></td>
<td></td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>20/21 (95.2)</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>17/18 (94.4)</td>
</tr>
</tbody>
</table>

Better diagnosis to improve stewardship

Biomarkers to indicate bacterial infection

- **Procalcitonin raised in bacterial infection**
  - Use to guide which patients need antibiotics
- **Multiple trials, 3500 patients, 30-80% saving on antibiotics**
- **Caveats**
  - Consequence for treatment outcomes not always studied
  - Mostly validated in pneumonia
  - Surgery or trauma may ‘falsely’ raise levels

Reinhart, Hartog *Int J Antimicrob Agents* 2010; 36 Suppl 2:S17
Diagnostics to improve stewardship
Procalcitonin trial, Royal Hampshire Hospital

- 99 Medical Admissions Unit (MAU) patients; also 42 ICU patients with 87 procalcitonin tests

- Procalcitonin results within 90 min of request

- Antibiotics withheld in 52/99 MAU cases and on 42/87 ICU occasions based on low procalcitonin
  - 6 MAU patient died: deaths NOT infection related
  - 5 ICU patients died with infection, all receiving antibiotics
Accelerating microbiology
Potential to revolutionise stewardship

Now…. and for the past 60 years

Meanwhile the patient is on empirical $R_x$
May be inappropriate --- or unnecessarily broad
Accelerating microbiology
Potential to revolutionise stewardship & therapy

Future….

PCR on specimen
Recognise key pathogens and a few resistances

… some systems available

Next generation sequencing
Comprehensive pathogen and resistance detections

….under development

Potential to deliver results in 6h, benefitting individual patient and stewardship…. but much work still to do

Strategy of antibiotic stewardship
Start Smart, then Focus

• Immediate $R_x$ in severe infection
  - Specimens sent for microbiology

• Empiric therapy steered by local guidelines

• Treatment refined based on microbiology results
  - Stop, move to narrow spectrum, oral or OPAT

• Document and audit; continuous improvement

UK Dept Health: 'Start Smart, then Focus
Future of antibiotic stewardship

Personalised therapy

- Biomarkers to distinguish patients with bacterial infection
- Molecular microbiology to identify pathogens and resistances
  - PCR and next generation sequencing
- Many challenges but huge potential