Antimicrobial Stewardship Programme: When, Why and How?

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Basic Principles of Antibiotic Therapy

- Timely
- Appropriate
- Apply PK/PD parameters
- De-escalate
- Stop as soon as possible

Deresinski S. Clin Infect Dis 2007;45:S177
Opal SM, et al. JAMA 2009;302:2367
Delay in Antimicrobial Therapy Increases Mortality

Mortality (%) vs. Appropriateness of Therapy

- Rello et al
- Alvarez-Lerma
- Ibrahim et al
- Luna et al
- Garnacho-Montero et al
- Vallés et al

Is Antibiotic Development Dying?

New Antibiotics Approved by the FDA

- 1983-1987: 16
- 1993-1997: 10
- 1998-2002: 8
- 2008-2012: 2

Figure 1  Dates of discovery of distinct classes of antibacterial drugs

Illustration of the "discovery void." Dates indicated are those of reported initial discovery or patent.

Adapted from Silver 2011 (1) with permission of the American Society of Microbiology Journals Department.
Barriers for New Antibiotics

• Scientific
  - Hard to find new antibiotics, especially vs. Gram (-)s
  - Hard to find new classes of antibiotics
  - Superiority trials are not feasible

• Regulatory
  - Hard to get a licence from the FDA
  - Rules repeatedly changed

• Financial
  - Antibiotics not very profitable
Future Hopes…

![Emergency sign with text: 174 KM AHEAD](image)
43% withdrawn between 1983-2009
New Antibiotics Currently in Clinical Development

- Cadazolide (Actelion)
- Carbavance (Medicines)
- Ceftolozone/tazobactam (Cubist), Approved
- Ceftazidime/Avibactam (AstraZeneca), Approved
- Delafloxacin (Melinta)
- Eravacycline (Tetraphase)
- Plazomicin (Achaogen)
- Surotomycin (Cubist)
In Total…

• 37 new antibiotics in development
  – Not all to resistant bacteria
  – 11, Phase I
  – 18, Phase II
  – 7, Phase III

• Historically 60% that enters Phase III will be approved

• At least 23 antibiotics designated as ‘qualified ID products’
  – If approved, will get FDA exclusivity

Antibiotic Stewardship in Europe
A pan-European survey to investigate antibiotic policy criteria in 170 hospitals from 32 countries

<table>
<thead>
<tr>
<th></th>
<th>North n=19 (%)</th>
<th>West n=55 (%)</th>
<th>South n=40 (%)</th>
<th>SE n=13 (%)</th>
<th>CE n=43 (%)</th>
<th>Total n=170 (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital has a DTC</td>
<td>19 (100)</td>
<td>53 (98)</td>
<td>27 (68)</td>
<td>9 (69)</td>
<td>38 (88)</td>
<td>146 (86)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital has a written formulary</td>
<td>16 (84)</td>
<td>51 (94)</td>
<td>23 (59)</td>
<td>5 (42)</td>
<td>36 (84)</td>
<td>131 (77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Written formulary lists restricted ABs</td>
<td>7 (39)</td>
<td>36 (71)</td>
<td>21 (78)</td>
<td>7 (78)</td>
<td>32 (82)</td>
<td>103 (61)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hospital has a written AB policy</td>
<td>15 (79)</td>
<td>39 (72)</td>
<td>18 (46)</td>
<td>3 (25)</td>
<td>22 (54)</td>
<td>97 (57)</td>
<td>0.003</td>
</tr>
<tr>
<td>Hospital has an AB committee</td>
<td>14 (74)</td>
<td>30 (57)</td>
<td>17 (45)</td>
<td>4 (31)</td>
<td>24 (56)</td>
<td>89 (52)</td>
<td>0.12</td>
</tr>
<tr>
<td>Prescription improvement is a strategic goal</td>
<td>8 (44)</td>
<td>32 (59)</td>
<td>17 (45)</td>
<td>5 (46)</td>
<td>25 (61)</td>
<td>87 (51)</td>
<td>0.50</td>
</tr>
<tr>
<td>No AB committee or AB policy in place</td>
<td>2 (5)</td>
<td>7 (19)</td>
<td>13 (35)</td>
<td>6 (16)</td>
<td>9 (24)</td>
<td>37 (22)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Antibiotic Stewardship in Europe

• 57% European hospitals have a written antibiotic policy
  – 20% teaching hospitals do not

• Hospitals in Northern and Western Europe are most likely to have antibiotic committees

• Policies and practices relating to antibiotic stewardship vary considerably across Europe

## Comparison of Antibiotic Stewardship Situation in 3 Countries

<table>
<thead>
<tr>
<th></th>
<th>UK</th>
<th>France</th>
<th>US</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of hospitals</strong></td>
<td>2412</td>
<td>Appr. 2500</td>
<td>Appr. 5723</td>
</tr>
<tr>
<td><strong>Main driver</strong></td>
<td>↓ Resistance</td>
<td>↓ HAIs</td>
<td>Improve patient outcomes</td>
</tr>
<tr>
<td><strong>Legislation</strong></td>
<td>2008 law mandates AS practices</td>
<td>ASP since 2002 Performance indicators 2007</td>
<td>Only in California since 2008. VA hospitals since 2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Financial penalty</td>
<td></td>
</tr>
<tr>
<td><strong>Infrastructure</strong></td>
<td>IDs manage</td>
<td>Antibiotic advisor w/wo ID training</td>
<td>IDs and ID pharmacists</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Local strategies</strong></td>
<td>Start Smart-Then Focus program</td>
<td>National guidance and local implement.</td>
<td>Varies to local facilities</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Hospitals monitor outcomes</td>
<td>Annual public reports, R rates are monitored</td>
<td>Mixed data monitored. Most Ab expenditures</td>
</tr>
</tbody>
</table>

Core Elements of Hospital Antibiotic Stewardship Programs-I

• **Leadership commitment**
  – Human, financial, IT resources

• **Accountability**
  – A leader reporting an executive or committee

• **Drug expertise**
  – Pharmacist leader

• **Action**
  – Implementing at least one action
    • i.e. antibiotic time-out after 48h

Core Elements of Hospital Antibiotic Stewardship Programs-II

- **Tracking**
  - Monitor processes and impact on patients
- **Reporting**
  - Regular reports to doctors and nurses
- **Education**

Two Extremes in Antibiotic Utilization

- Limit use to minimize resistance
  - Preserve for future use
  - Contain expenditures
  - Ignores future innovations

- Concern for underuse
  - Ignore resistance
  - Assume there will always be new antibiotics
  - Fails to recognize possibility that future may not keep pace with resistance

McKellar MR, Fendrick AM. Clin Infect Dis 2014;59(S3):S104
Yin and Yang

- Everything has two opposing poles
- Each pole has the opposite inside
- But, they are
  - Complementary
  - Interconnected
  - Interdependent

*Taijitu*

‘Diagram of the supreme ultimate’
Global Antibiotic Consumption 2000-2010

- Global consumption increased 36% in 71 countries
  - BRICS accounted for 76%
- Consumption increased
  - 45% for carbapenems
  - 13% polymyxins

Consumption of Antibiotics in 2010 by Year of Launch and Price

Laxminarayan R. Science 2014;345:1299
Total Antibiotic Use in Eastern Europe, 2011

Penicillin Use in Eastern Europe, 2011

UK Ciprofloxacin Resistance in Gonococci

Cipro abandoned as first line therapy 2002-4

% resistant

00 01 02 03 04 05 06 07 08

UK Grasp surveys; http://www.hpa.org.uk
Slide: Courtesy of DM Livermore
Falling Sulphonamide Use in UK

Scrips per annum, UK x 10^4

Year

Enne et al. Lancet 2001; 357:1325
Slide: Courtesy of DM Livermore
## % Resistance in Disuse Antibiotics

<table>
<thead>
<tr>
<th></th>
<th>1991</th>
<th>1999</th>
<th>2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulphonamide</td>
<td>39.7</td>
<td>46.0</td>
<td>45.5</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>33.9</td>
<td>34.3</td>
<td>41.2</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>20.2</td>
<td>15.3</td>
<td>7.9</td>
</tr>
</tbody>
</table>

Bean et al. JAC 2006;56:962
Slide: Courtesy of DM Livermore
Antibiotic Stewardship
A British Example

Use of iv-im Cephalosporins & Quinolones

↑ ▲ ▲ ▲

C. difficile
100s to >50,000

↓ ▼ ▼ ▼ ▼

use of Cephalosporins
>80%

↑ ▲ ▲ ▲ ▲

use of Pip-tazo

↓ ▼ ▼ ▼ ▼

C. difficile
>50,000 to 14,689

Mid-1980s-2006

From 1990s to 2007-2008

2004-2009

2012-2013

Additional Results...

- **Expected**
  - Cephalosporin and quinolone R stabilized in *E. coli* and decreased in *Klebsiella* and *Enterobacter* spp.

- **Somewhat expected**
  - No increase in pip-tazo resistance

- **Unexpected**
  - Increase in carbapenamase-producing Enterobacteriaceae
    - Highly-R to pip-tazo, MIC >128 mg/L
    - Less R to carbapenems

Pharmacological Properties of Antibiotics

- Cmin (trough)
- MIC
- T > MIC

Dosing interval

PK/PD ratio =

- 50% f T > MIC
- 100% f T > MIC

DALI: Defining Antibiotic Levels in ICU patients

- 384 patients in 68 hospitals in 10 countries
- 10 beta-lactams antibiotics including meropenem
- 248 patients treated for infection
  - 16% did not achieve 50% $f \text{T}>\text{MIC}$
  - 32% less likely to have (+) outcome
  - (+) outcome was associated with increasing 50% and 100% $f \text{T}>\text{MIC}$

Achievement of PK/PD Targets in Critically Ill Patients

% achievement

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>50% f T&gt;MIC</th>
<th>100% f T&gt;MIC</th>
<th>50% f T&gt;4XMIC</th>
<th>100% f T&gt;4XMIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefepime 6 g</td>
<td>78.6</td>
<td>50</td>
<td>78.6</td>
<td>71.4</td>
</tr>
<tr>
<td>Ceftriaxone 2 g</td>
<td>97</td>
<td>93.9</td>
<td>93.9</td>
<td>87.9</td>
</tr>
<tr>
<td>Piperacillin, 12 g</td>
<td>80.6</td>
<td>48.9</td>
<td>67</td>
<td>30.3</td>
</tr>
<tr>
<td>Meropenem 3 g</td>
<td>95</td>
<td>68.8</td>
<td>69.7</td>
<td>41.6</td>
</tr>
</tbody>
</table>

Duration of antibiotics in FUO: Evidence & Recommendations

- Discontinue iv empirical antibacterials after ≥ 72h
  - If patient has been afebrile ≥ 48h and is **stable**
  - Irrespective of neutrophil count or **expected** duration of neutropenia **B11**

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Joshi et al., Am J Med 1984
Jones et al., J Pediatr 1994
Cornelissen et al., Clin Infect Dis 1995
Horowitz et al., Leuk Lymphoma 1996
Santolaya et al., Clin Infect Dis 1997
Lehmbecher et al., Infection 2002
Chen et al., Scand J Infect Dis 2004
Slobbe et al., Eur J Cancer 2009
Duration of therapy in documented infections

Continue targeted antibiotics for clinically- or microbiologically- documented infection

- Until infection is microbiologically eradicated &
- Until all clinical signs of infection are resolved
- At least 7 days, of which at least 4 days afebrile

References:
Eggimann et al., J Antimicrob Chemother 1993
Cometta et al., Antimicrob Agents Chemother 1995
Cordonnier et al., Clin Infect Dis 1997
Biron et al., J Antimicrob Chemother 1998
Elting et al., J Clin Oncol 2000
Feld et al., J Clin Oncol 2000
Giamarello et al., Antimicrob Agents Chemother 2000
Viscoli et al., Clin Microbiol Infect. 2002
Sanz et al., J Antimicrob Chemother 2002
Tamura et al., Am J Hematol 2002
Cometta et al., Clin Infect Dis 2003
Raad et al., Cancer 2003

4th European Conference on Infections in Leukemia
Early Cessation of Empirical Therapy in Patients with Neutropenia and FUO

January 2010-June 2014
283 neutropenia episodes (214 pts)

80 (28%) Inf. documented
203 (72%) FUO

8 (4%) Died under tx
4 remained neutropenic
163 (%80) Defervesced & survived up to 10 months
32 (16%) Fever reappeared in median 5 days (1-23)
10 (6%) Died after 23d-10m

Korucu B & Akova M. Unpublished
Outcome in 32 Episodes with Relapsed Fever

32 episodes
6 d median tx (5-22 d)
5 d median after defervesced (1-23 d)

20 (63%) relapsed as FUO
No mortality

12 (37%) relapsed as documented infection

2 died (6%)
- CR-Kp bacteremia
- Inv. aspergillosis

10 (94%) survived up to a year

Korucu B & Akova M. Unpublished
The Role and Place of ESCMID in Global Antimicrobial Resistance
The European Committee on Antimicrobial Susceptibility Testing - EUCAST

EUCAST is a standing committee jointly organized by ESCMID, ECDC and European national breakpoint committees. EUCAST deals with breakpoints and technical aspects of monocentric in vitro antimicrobial susceptibility testing and functions as the breakpoint committee of EMA and ECDC. EUCAST does not deal with antibiotic policies, surveillance or containment of resistance or infection control. The Steering Committee is the decision making body. It is supported by a General Committee with representatives from European and other countries, FESCI and ISC. The Steering Committee also consults on EUCAST proposals with experts within the fields of infectious diseases and microbiology, pharmaceutical companies and susceptibility testing device manufacturers.

EUCAST has a subcommittee on antifungal susceptibility testing. Subcommittees on: expert rules for antimicrobial susceptibility testing, antimicrobial susceptibility testing of antifungals and on methods for detection of: resistance mechanisms of clinical and/or epidemiological importance have completed their tasks and have been disbanded.

Most antimicrobial MIC breakpoints in Europe have been harmonised by EUCAST. Breakpoints for new agents are set as part of the licensing process for new agents through EMA. EUCAST breakpoints are available in devices for automated susceptibility testing but with some limitations, depending on the system. A disk diffusion susceptibility test method calibrated to EUCAST MIC breakpoints is also available.

EUCAST invites anyone with an interest in antimicrobial agents in general and antimicrobial breakpoints in particular to contact EUCAST, ESCMID or one of the National Breakpoint Committees.

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European Committee for Infection Control (EUCIC)

Infection control and preventive measures: an ESCMID priority

Healthcare-associated infections (HAIs) are a leading cause of morbidity and mortality worldwide. Therapy is becoming ever more difficult because of the increasing rate of antimicrobial resistance among common HAI pathogens. Over the last decade, multidrug-resistant bacteria have been implicated in severe invasive infections and their occurrence has increased steadily. Patients are starting to see the rate of HAI and antibiotic resistance as an important indicator of quality of care.

After presenting the first European Guidelines on infection control in Berlin, intended to reduce the spread of multidrug-resistant bacteria in hospitalised patients, ESCMID is going to increase its influence and involvement in infection control. A new ESCMID Committee for Infection Control was formed at the beginning of 2014 and had its kick-off meeting in March 2014.

Major goals will be:
- to harmonise infection control and preventive measures in all European countries and to reduce morbidity and mortality related to HAI.
- Development of new educational tools as well as specific guidelines and expert opinion with ‘real life’ applicability are a major focus.
- Research will be coordinated through dedicated networking.
Central Asian and Eastern European Surveillance on Antimicrobial Resistance (CAESAR)

The CAESAR (Central Asian and Eastern European Surveillance of Antimicrobial Resistance) network is a joint initiative of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), the Dutch National Institute for Public Health and the Environment (RIVM) and WHO/Europe, to survey, contain and prevent emergence and spread of antibiotic resistance in the European Region.

The aim of CAESAR is to gradually set up a network of national AMR surveillance systems in all countries of the Region that are not part of the AMR surveillance network EARS-Net of the European Commission, coordinated by the European Centre for Disease Prevention and Control (ECDC). In order to enable comparison of data in the whole Region, the methodology of EARS-Net will be used in close collaboration with ECDC. This would enable joined reports of antibiotic resistance for all 53 countries based on the same standards and methodologies in the future.

This project is an important step in the implementation of the European strategic action plan on antibiotic resistance (WHO EURO) that was adopted by the Regional Committee 61 in Baku, Azerbaijan, September 2011.

For any questions, regarding participation, manuals, methodology and planned activities regarding CAESAR please contact Danilo Lo Fo Wong or Nienke van de Sande.

European strategic action plan on antibiotic resistance
Working document of the sixty-first session of the WHO Regional Committee for Europe

European Society of Clinical Microbiology and Infectious Diseases (ESCMID)
Dutch National Institute for Public Health and the Environment (RIVM)
European Centre for Disease Prevention and Control (ECDC)
Antibiotic resistance surveillance network extended throughout European Region
# New Treatment Paradigm for Severe Infections

<table>
<thead>
<tr>
<th>Old</th>
<th>New</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start with narrow spectrum</td>
<td>Get it right first time De-escalate</td>
</tr>
<tr>
<td>Cost-efficient low dose</td>
<td>Hit hard up front</td>
</tr>
<tr>
<td>Low doses = less side effects</td>
<td>Low dose → resistance</td>
</tr>
<tr>
<td>Long courses ≥2 weeks</td>
<td>Seldom &gt;7-days</td>
</tr>
</tbody>
</table>

Determination...
Hope...
Think and plan carefully...
And accomplish...
Thank you...