Consumption of antibiotics in hospitals.
Antimicrobial stewardship.

Inge C. Gyssens MD PhD
Radboud university medical center, Nijmegen, The Netherlands
Hasselt University, Belgium
Outline

1. Antibiotic use in hospitals
   - Global geographic variations
   - Huge inter-hospital differences, not always explained by case-mix
   - Huge intra-hospital variations, ICU vs psychiatric ward
   - Antimicrobial consumption depends on
     - Cultural factors
     - Socio-economic factors
     - Health regulations
     Sources: ESAC, ESAC-Net, national publications

2. Antimicrobial stewardship
   - why
   - what
   - how: strategies for old drugs, current drugs, new drugs
   - levels: global, national
ANTIBIOTIC USE IN HOSPITALS
Table 4.2. Consumption of antibacterials for systemic use (ATC group J01) in the hospital care sector EU/EEA countries, 1997-2010, expressed as DDD per 1 000 inhabitants and per day.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>2.0</td>
<td>2.0</td>
<td>2.2</td>
<td>2.2</td>
<td>2.2</td>
<td>2.3</td>
<td>2.1</td>
<td>1.9</td>
<td>1.9</td>
<td>1.7</td>
<td>1.9</td>
<td>2.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulgaria</td>
<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
<td>1.4</td>
<td>1.4</td>
<td>1.5</td>
<td>1.5</td>
<td>1.6</td>
<td>1.6</td>
<td>1.7</td>
<td>1.8</td>
<td>1.8</td>
<td>1.8</td>
<td>1.5</td>
</tr>
<tr>
<td>Denmark</td>
<td>8.6</td>
<td>2.4</td>
<td>2.3</td>
<td>2.5</td>
<td>2.1</td>
<td>1.9</td>
<td>1.8</td>
<td>1.6</td>
<td>1.7</td>
<td>1.8</td>
<td>1.8</td>
<td>1.8</td>
<td>1.8</td>
<td>1.8</td>
</tr>
<tr>
<td>Estonia</td>
<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
<td>2.2</td>
<td>2.2</td>
<td>2.2</td>
<td>2.2</td>
<td>2.2</td>
<td>2.2</td>
<td>2.2</td>
<td>2.2</td>
<td>2.2</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td>Finland (a)</td>
<td>3.5</td>
<td>3.7</td>
<td>3.7</td>
<td>3.8</td>
<td>3.9</td>
<td>3.6</td>
<td>3.4</td>
<td>3.5</td>
<td>3.4</td>
<td>3.2</td>
<td>3.2</td>
<td>3.2</td>
<td>3.2</td>
<td>2.8</td>
</tr>
<tr>
<td>France</td>
<td>3.3</td>
<td>3.0</td>
<td>3.1</td>
<td>3.2</td>
<td>2.9</td>
<td>2.8</td>
<td>2.5</td>
<td>2.6</td>
<td>2.3</td>
<td>2.2</td>
<td>2.2</td>
<td>2.2</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td>Greece</td>
<td>2.1</td>
<td>2.1</td>
<td>2.2</td>
<td>2.3</td>
<td>2.2</td>
<td>2.2</td>
<td>2.2</td>
<td>3.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hungary</td>
<td>1.2</td>
<td>1.3</td>
<td>1.5</td>
<td>1.3</td>
<td>1.4</td>
<td>1.4</td>
<td>1.2</td>
<td>1.2</td>
<td>1.3</td>
<td>1.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iceland</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ireland</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latvia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lithuania</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luxembourg</td>
<td>2.0</td>
<td>1.9</td>
<td>2.2</td>
<td>2.2</td>
<td>2.1</td>
<td>2.4</td>
<td>2.4</td>
<td>2.0</td>
<td>2.1</td>
<td>2.1</td>
<td>2.2</td>
<td>2.2</td>
<td>2.2</td>
<td>2.1</td>
</tr>
<tr>
<td>Malta</td>
<td>1.6</td>
<td>2.5</td>
<td>2.6</td>
<td>2.4</td>
<td>1.9</td>
<td>1.7</td>
<td>2.0</td>
<td>1.8</td>
<td>1.4</td>
<td>1.7</td>
<td>1.3</td>
<td>1.4</td>
<td>1.4</td>
<td>2.0</td>
</tr>
<tr>
<td>Netherlands</td>
<td>0.6</td>
<td>0.6</td>
<td>0.7</td>
<td>0.6</td>
<td>0.6</td>
<td>0.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.1</td>
</tr>
<tr>
<td>Norway</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poland</td>
<td>3.0</td>
<td>3.4</td>
<td>2.4</td>
<td>2.4</td>
<td>1.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Portugal (b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.4</td>
</tr>
<tr>
<td>Romania</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.6</td>
</tr>
<tr>
<td>Slovakia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slovenia</td>
<td>0.5</td>
<td>1.6</td>
<td>1.7</td>
<td>1.8</td>
<td>1.7</td>
<td>1.8</td>
<td>1.6</td>
<td>1.7</td>
<td>1.7</td>
<td>1.7</td>
<td>1.7</td>
<td>1.8</td>
<td>1.8</td>
<td>1.7</td>
</tr>
<tr>
<td>Sweden</td>
<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
<td>1.4</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
</tr>
</tbody>
</table>

(a) Finland: data include consumption in remote primary health care centres and nursing homes.
(b) Portugal: data correspond to public hospitals only.
Figure 4.1. Consumption of antibacterials for systemic use (ATC group J01) in the hospital sector in EU/EEA countries, 2010, at group level 3, expressed as DDD per 1,000 inhabitants and per day.

(a) Finland: data include consumption in remote primary health care centres and nursing homes.
(b) Portugal: data correspond to public hospitals only.

Specific or additional recommendations based on ECDC PPS results:

- Report hospital antimicrobial consumption to ESAC-Net in defined daily dose per number of patient-days rather than per number of inhabitants.
National annual surveillance reports at www.swab.nl since 2001

NETHMAP 2012

Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in the Netherlands

MARAN 2012

Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals in the Netherlands
Figure ABuse01. Veterinary therapeutic sales from 1999-2011 (FIDIN, 2012; vertical bars). The line presents the trends in grams of active ingredients used per kg live weight.
Figure 3.4. Use of beta-lactams in hospitals, expressed as DDD/100 patient-days (A) and DDD/100 admissions (B), 1999-2010 (SWAB).
Figure 3.4. Use of beta-lactams in hospitals, expressed as DDD/100 patient-days (A) and DDD/100 admissions (B), 1999-2010 (SWAB).
Intensification of antibiotic use within acute care hospitals in the Netherlands

H. M. Kwint, P. D. van der Linden, M. B. Roukens and S. Natschi* on behalf of SWAB's Working Group on Surveillance of Antimicrobial Use

Figure 2. Variance in total use of antibiotics for systemic use (J01) in Dutch hospitals, 2009: university hospitals (UH) versus large teaching hospitals (LTH) versus general hospitals (GH). (a) Use in DDDS per 100 patient-days. (b) Use in DDDS per 100 admissions.
Conclusion 1

1. Antibiotic use in hospitals
   - Global geographic variations
   - Huge inter-hospital differences not always explained by case-mix
   - Huge intra-hospital variations, Antimicrobial consumption depends on
     - Cultural factors
     - Socio-economic factors
     - Health regulations
   Sources: ESAC, ESAC-Net, national publications

2. Antimicrobial stewardship
   - why, what
   - how: -old drugs, current drugs, new drugs
   - Levels: global, national,
Figure 17. The clinician’s dilemma of empiric therapy.

Antibiotic Resistance

Use of antibiotics with broader spectrum or combination therapy

Increased risk for failure of the empiric therapy

ANTIMICROBIAL STEWARDSHIP
Definition

- The primary goal of a stewardship program is to maximize clinical outcomes while minimizing the unintended consequences of antimicrobial use, such as toxicity, selection of pathogenic organisms, and emergence of resistance.

Dellit et al. SHEA IDSA Guidelines
“The recognition that misuse of antimicrobials affects the society of patients and not just an individual patient by influencing the healthcare setting microflora and risk of transmission of resistant organisms empowered Antimicrobial stewardship development”
Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship

Timothy H. Dellit,1 Robert C. Owens,2 John E. McGowan, Jr.,3 Dale N. Gerding,4 Robert A. Weinstein,5 John P. Burke,6 W. Charles Huskins,7 David L. Paterson,8 Neil O. Fishman,9 Christopher F. Carpenter,10 P. J. Brennan,9 Marianne Billeter,11 and Thomas M. Hooton12

Clinical Infectious Diseases 2007;44:159–77
EDUCATION VS RESTRICTION

Interventions to improve antibiotic prescribing practices for hospital inpatients (Review)
Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
**Antimicrobial stewardship: Interventions**

<table>
<thead>
<tr>
<th>Educational measures and active interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Passive educational measures</strong></td>
</tr>
<tr>
<td>• Developing/updateing local antibiotic guidelines</td>
</tr>
<tr>
<td>• Educational sessions, workshops, local conferences</td>
</tr>
<tr>
<td><strong>Active interventions</strong></td>
</tr>
<tr>
<td>• Clinical rounds discussing cases</td>
</tr>
<tr>
<td>• Prospective audit with intervention and feedback</td>
</tr>
<tr>
<td>• Reassessment of antibiotic prescriptions, with streamlining and de-escalation of therapy</td>
</tr>
<tr>
<td>• Academic detailing, educational outreach visits</td>
</tr>
<tr>
<td><strong>Restrictive measures</strong></td>
</tr>
<tr>
<td>• Limiting number of antibiotics on the hospital formulary</td>
</tr>
<tr>
<td>• Antibiotic order form (compulsory)</td>
</tr>
<tr>
<td>• Automatic stop order</td>
</tr>
<tr>
<td>• Formulary restriction and preauthorization</td>
</tr>
<tr>
<td>• Limiting reporting of susceptibilities by the microbiology laboratory</td>
</tr>
<tr>
<td>• Regulating contacts with the pharmaceutical industry</td>
</tr>
<tr>
<td><strong>Supportive/supplemental measures</strong></td>
</tr>
<tr>
<td>• Multidisciplinary antimicrobial stewardship team</td>
</tr>
<tr>
<td>• Consultancy service (infectious diseases, pharmacy, microbiology)</td>
</tr>
<tr>
<td>• Computer-assisted management program</td>
</tr>
<tr>
<td>• Parenteral to oral conversion</td>
</tr>
<tr>
<td>• Therapeutic drug monitoring service</td>
</tr>
</tbody>
</table>

Pulcini & Gyssens, How to educate prescribers Virulence 2013;4:1-11
Why do educational interventions often fail?

- They come to late! .... in the curriculum

- Changing behaviour is much more difficult than shaping behaviour
Education on prudent antimicrobial use

PATIENTS
- Primary: 9-11 y
- Secondary: 14-15 y

NATIONAL CAMPAIGNS
- Adults: ≥ 16 y

PRESCRIBERS of ANTIBIOTICS
- Undergraduate curriculum: 18-25 y
- Internship/foundation year: 20-25 y
- Professional training: 20-30 y

POSTGRADUATE EDUCATION
- Medical doctors, nurses, midwives, dentists, veterinarians: ≥ 30 y

Pulcini&Gyssens, How to educate prescribers Virulence 2013
Is the “Low-Hanging Fruit” Worth Picking for Antimicrobial Stewardship Programs?

Debra A. Goff, Karri A. Bauer, Erica E. Reed, Kurt B. Stevenson, Jeremy J. Taylor, and Jessica E. West

1Department of Pharmacy, The Ohio State University Wexner Medical Center, 2Division of Infectious Diseases, College of Medicine, and 3Division of Epidemiology, College of Public Health, The Ohio State University, Columbus

J Antimicrob Chemother 2012; 67: 2289–2296

Antibiotic stewardship and early discharge from hospital: impact of a structured approach to antimicrobial management

Formulary restriction and preauthorization requirements for specific agents. Most hospitals have a pharmacy and therapeutics committee or an equivalent group that evaluates drugs for inclusion on the hospital formulary on the basis of considerations of therapeutic efficacy, toxicity, and cost while limiting redundant new agents with no significant additional benefit. Antimicrobial restriction—either through formulary limitation by this method or by the requirement of preauthorization and justification—is the most effective method of achieving the process goal of controlling antimicrobial use.
Example

AUDIT AND FEEDBACK AND FORMULARY RESTRICTION
Quality improvement of surgical prophylaxis in Dutch hospitals: evaluation of a multi-site intervention by time series analysis

Marjo E. E. van Kasteren¹,²*, Judith Mannien³, Bart-Jan Kullberg¹,², Annette S. de Boer³, Nico J. Nagelkerke³, Marja Ridderhof⁴,⁵, Jan C. Wille⁶ and Inge C. Gyssens⁴,⁵

Multi faceted intervention

Table 3. Observed and expected outcomes of quality parameters before and after the intervention

<table>
<thead>
<tr>
<th>Parameter of antibiotic prophylaxis</th>
<th>Observed before intervention, no. inappropriate (total)</th>
<th>%</th>
<th>Observed after intervention, no. inappropriate (total)</th>
<th>%</th>
<th>Expected after intervention, no. inappropriate (total)</th>
<th>%</th>
<th>P value, observed–expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indicated but not administered</td>
<td>51 (1763)</td>
<td>2.9</td>
<td>26 (2050)</td>
<td>1.3</td>
<td>55 (2050)</td>
<td>2.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Antibiotic less effective</td>
<td>88 (1712)</td>
<td>5.1</td>
<td>36 (2024)</td>
<td>1.8</td>
<td>64 (2024)</td>
<td>3.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Antibiotic more toxic</td>
<td>327 (1712)</td>
<td>19.1</td>
<td>241 (2024)</td>
<td>11.9</td>
<td>387 (2024)</td>
<td>19.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Antibiotic more expensive</td>
<td>1275 (1712)</td>
<td>74.5</td>
<td>454 (2024)</td>
<td>22.4</td>
<td>1550 (2024)</td>
<td>76.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Antibiotic broader spectrum</td>
<td>1458 (1712)</td>
<td>85.2</td>
<td>688 (2024)</td>
<td>34.0</td>
<td>1751 (2024)</td>
<td>86.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Antibiotic in therapeutic use</td>
<td>1295 (1712)</td>
<td>75.6</td>
<td>686 (2024)</td>
<td>33.9</td>
<td>1579 (2024)</td>
<td>78.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Antibiotic choice not cefazolin</td>
<td>1646 (1712)</td>
<td>96.1</td>
<td>758 (2024)</td>
<td>37.5</td>
<td>1893 (2024)</td>
<td>93.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Duration exceeding single dose</td>
<td>779 (1699)</td>
<td>44.2</td>
<td>631 (2015)</td>
<td>31.4</td>
<td>944 (2015)</td>
<td>46.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Timing first dose inappropriate</td>
<td>822 (1627)</td>
<td>50.5</td>
<td>779 (1976)</td>
<td>39.4</td>
<td>1024 (1976)</td>
<td>51.8</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Largest effect with the restrictive component of the intervention: the change of antibiotic
Audit and feedback: a picture tells more than a 1000 words..

**Antibiotic for prophylaxis**

- **1st gen cephalosporin**
- **2nd gen cephalosporin**
- **amoxi/clavulanic acid**
- **miscellaneous**

**Timing of prophylaxis**

- **within 30 min before incision**
- **between 2 h-30 min before incision**
- **more than 2 h before incision**
- **after incision**
Now something completely different..

THE DRUG SHORTAGES PROBLEM
Survey on antibiotic shortages in the EU

• Shortages affect the care of critically ill patients

• Shortages lead to the use of more expensive and broad-spectrum or less efficacious substitute agents. These substitutes may further accelerate the emergence and selection of antibiotic resistance

• For instance, replacing piperacillin by piperacillin/tazobactam for susceptible *Pseudomonas spp*, minocycline by tigecycline for methicillin-resistant *Staphylococcus aureus or penicillin* by ceftriaxone for streptococcal infections broadens the spectrum of therapy unnecessarily and increase healthcare costs
Shortage duration ranged from 1 week to 18 months
Another problem affecting prudent use

FORGOTTEN ANTIBIOTICS
Forgotten Antibiotics: An Inventory in Europe, the United States, Canada, and Australia

Céline Pulcini,1 Karen Bush,2 William A. Craig,3 Niels Frimodt-Møller,4 M. Lindsay Grayson,5 Johan W. Mouton,6 John Turnidge,7 Stephan Harbarth,8 Inge C. Gyssens,9,10 and the ESCMID Study Group for Antibiotic Policies

1Centre Hospitalier Universitaire de Nice, Service d’Infectiologie and Université de Nice Sophia-Antipolis, Faculté de Médecine, France; 2Biology Department, Indiana University, Bloomington; 3University of Wisconsin, School of Medicine and Public Health, Madison; 4Department of Clinical Microbiology, Hvidovre Hospital, Copenhagen, Denmark; 5Infectious Diseases Department, Austin Health and Department of Medicine, University of Melbourne, Victoria, Australia; 6Department of Medical Microbiology, Radboud University Nijmegen Medical Centre and Department of Medical Microbiology and Infectious Diseases, Canisius Wilhelmina Hospital, the Netherlands; 7SA Pathology, The University of Adelaide, SA, Australia; 8Geneva University Hospitals and Medical School, Switzerland; 9Department of Medicine, Radboud University Nijmegen Medical Centre and Department of Medical Microbiology and Infectious Diseases, Canisius Wilhelmina Hospital, the Netherlands; and 10Hasselt University, Diepenbeek, Belgium
• A survey was performed in 38 countries among experts including hospital pharmacists, microbiologists and infectious diseases specialists in Europe, the US, Canada and Australia.

• An international expert panel selected systemic antibacterial drugs for their potential to treat infections caused by resistant bacteria or their unique value for specific pathogens or indications.
Benzylpenicillin (Penicillin G)
Phenoxymethylpenicillin (Penicillin V)
Any antistaphylococcal penicillin
Ertapenem
Nitrofurantoin
Cefepime
Teicoplanin
Benzathine benzylpenicillin
Tobramycin
Colistin
Fusidic acid
Trimethoprim
Chloramphenicol
Tobramycin
Ampicillin
Benztaine benzylpenicillin
Teicoplanin
Cefepime
Nitrofurantoin
Ertapenem
Any antistaphylococcal penicillin
Phenoxy methylpenicillin (Penicillin V)
Benzylpenicillin (Penicillin G)

Number of countries where the antibiotic is available (over a total of 38)

- temocillin: 2 countries
- fosfomycin iv: 5 countries
- aztreonam
- colistin
Number of antibiotics available (over a total of 33)
Conclusion 2

1. Antibiotic use in hospitals
   • Global geographic variations
   • Huge inter-hospital differences
   • Huge intra-hospital variations, *not always explained by case-mix*
   • Antimicrobial consumption depends on
     o Cultural factors
     o Socio-economic factors
     o Health regulations
     Sources: ESAC, ESAC-Net, national publications

2. Antimicrobial stewardship
   • why
   • what
   • how: strategies for old drugs, current drugs, new drugs
   • levels: global, national
Questions

• Should we involve the Ministries of Education in national intersectoral coordinating mechanisms on antimicrobial resistance?
• Should we involve Academia for education of students in antimicrobial stewardship principles (the undergraduate curriculum)?
• Should Regulators act against antimicrobial drug shortages?
• Should the access of forgotten antibiotics be facilitated?
• How to preserve the value of newly developed antibiotics in the future?