Antibiotic policy and Microbiological vigilance: “why, who, how?”

F. Van Bambeke and Paul M. Tulkens
Pharmacologie cellulaire et moléculaire
Louvain Drug Research Institute & Centre de Pharmacie clinique
Université catholique de Louvain
Brussels, Belgium

Based on the Belgian expérience and on material kindly provided by
• Pharm. Caroline Briquet, Groupe de Gestion de l’antibiothérapie,
  Cliniques univ. St Luc, Bruxelles, Belgium
• Dr C. Rossi, infectiologue - hygiéniste, CHU Ambroise Paré, Mons, Belgium
• Dr C. Potvliege, microbiologiste – hygiéniste, CHU Tivoli, La Louvière, Belgium
• Prof. H. Goossens, microbiologist and "creator" of the Belgian Antibiotic Policy Coordination
  Committee", Antwerp, Belgium
• Prof. A. Simon, microbiologiste – hygiéniste, Clin. univ. St-Luc, Bruxelles, Belgium
• Dr A. Apisarnthanarak, Division of Infectious Diseases, Thammasat University Hospital, Thailand.

1 member of the Association for the Prudent Use of Antibiotics (APUA: http://www.apua.org)
But before that, where are you from?

The medical campus of the Université catholique de Louvain

The Cellular and Molecular Pharmacology Group

slides are available on www.facm.ucl.ac.be → Lectures
And what do you do in Belgium?

- Cellular pharmacokinetics
- Cellular pharmacodynamics
- Antibiotic toxicity
- Novel bacterial targets
- Resistance
- Clinical applications

Antibiotics: from molecules to man
Our laboratory has a long-lasting experience in the training foreign graduate fellows

- group leaders
- post-docs
- doctoral fellows
- students

in 2011
And also experience in academic partnerships
In this context, we had for 2 years and half a very active Vietnamese post-doctoral fellow

- supported first by the programme "Research in Brussels" of the "Région Bruxelloise" (in 2007)
- and then by the "Fonds de la Recherche Scientifique" (in 2008-2009)
And he was successful…

Prix "AORIC" remis à Paris, France, pour le meilleur travail d'antibiothérapie expérimentale

Intracellular Activity of Antibiotics in a Model of Human THP-1 Macrophages Infected by a *Staphylococcus aureus* Small-Colony Variant Strain Isolated from a Cystic Fibrosis Patient: Pharmacodynamic Evaluation and Comparison with Isogenic Normal-Phenotype and Revertant Strains

Hoang Anh Nguyen, Olivier Denis, Anne Vergison, Anne Theunis, Paul M. Tulkens, Marc J. Struelens, and Françoise Van Bambeke

Université Catholique de Louvain, Louvain Drug Research Institute, Unité de Pharmacologie Cellulaire et Moléculaire, and Hôpital Erasme, Department of Microbiology, Laboratoire de Référence MRSA-Staphylococques, Hôpital des Enfants Reine Fabiola, Département de Maladies Infectieuses Pédiatiques, and CHU Saint Pierre-Huober/CHU Brugmann, Département Interhospitalier de Dermatologie, Université Libre de Bruxelles, Brussels, Belgium
very successful…

Prix "AORIC" remis à Paris, France, pour le meilleur travail d'antibiothérapie expérimentale
Based on what he learned in Belgium, the following seemed possible at UPH and Hanoi …

• **Launching clinical pharmacy in Vietnam…**
  – Creating a strong basis for Pharmacokinetics/Pharmacodynamics of antibiotics in Vietnamese hospitals and at the University of Pharmacy
  – Creating a "Drug Information Center" for the country
  – Creating the basis for a strong Pharmacoeconomy group
  – helping to address the "antibiotic crisis" in Vietnam (but also present in other Asian Countries)
Now, Belgium is by no means perfect…

*P. aeruginosa* from HAP / VAP patients in 6 hospitals in Belgium

![Graphs showing the percentage of strains at EUCAST breakpoint](image)

MIC (mg/L: 0.0156 to 512 mg/L)

*Riou et al, IJAA 2010, 36:513-522*
Belgium is certainly not perfect…

Consumption of Antibiotics in the Community


Other (J01 classes)
Sulfonamides and trimethoprim (J01E)
Quinolones (J01M)
Macrolides, lincosamides, and streptogramins (J01F)
Tetracyclines (J01A)
Cephalosporins and other beta-lactams (J01D)
Penicillins (J01C)
Inorderly use of antibiotics causes major problems!

Is this car all right here?

Chaotic traffic somewhere around

Which way should I go?
Antimicrobial resistance is a major problem in hospitals …

Factors that may increase antimicrobial resistance in hospitals.

Greater severity of illness of hospitalized patients
More severely immunocompromised patients
Newer devices and procedures in use
Increased introduction of resistant organisms from the community
Ineffective infection control and isolation practices and compliance
Increased use of antimicrobial prophylaxis
Increased empiric polymicrobial antimicrobial therapy
High antimicrobial usage per geographic area per unit time

NOTE. Modified from McGowan JE Jr.

You can act upon these parameters by a rational policy of use!

But what can we do ?

• Local
  – organism isolation (efficiency)
  – susceptibility pattern and reporting
  – Antibiotic Management Team
  – Isolation and Hygiene

• Regional/National
  – resistance and antibiotic consumption data
  – setting up guidelines
  – coordination
Organism isolation
Organism isolation

- "No organism isolated" means the doctor is blind …
- Setting of pro-active programme to improve isolation success
  - local team (nursing) training for correct sampling
  - fast delivery to the laboratory
  - enough personnel and means to handle the daily load and apply the most appropriate technique
  - record success / failures by ward and main suspected infection and compare
    - with literature data
    - other hospitals
    - over time

  **to detect low level of performance and indentify the causes**
Organism isolation

Examples of techniques for success *

• Abcesses
  – Aspirate of pus or fluid in anaerobic transport vial is preferred; swabs usually have insufficient material for Gram stain and culture.
  – Clean surface of closed abscess with 70% alcohol; collect specimens at margins of abscess.
  – Aspirates in anaerobic transport tubes are acceptable for aerobic and anaerobic bacterial, fungal, and mycobacterial cultures.
  – Specify location of abscess for optimal processing; provide all other pertinent information (e.g., surgical infection, trauma, bite wound).

• Catheter
  – Intravascular: Remove aseptically, cut at least a 2-inch segment from tip, and place segment in sterile container. Transport rapidly to prevent drying out.

• Skin Lesion
  – Scrape skin at active edge of lesion; avoid blood. Place in sterile petri dish; biopsy may be more definitive than swabs of lesion. Transport swabs in transport media to prevent drying out; specify specific organism if one is suspected (e.g., dermatophyte, Sporothrix, Mycobacterium, etc.).

* from Mandel's Principles and Practice of Infectious Diseases, 7th Edition, Elsevier
Organism isolation

Examples of techniques for success

• **Sputum, expectorated**
  – Have patient rinse or gargle with water to remove excess oral flora; instruct patient to cough deeply and expectorate secretions from lower airways; collect and transport in a sterile container.
  – Collect 1 mL for bacterial culture; 5 mL or more for mycobacterial culture and molds.
  – Presence of abundant epithelial cells is indicative of contamination with oral flora; a contaminated specimen is unacceptable for routine bacterial culture, but can be processed for mycobacteria or molds.

• **Urine (midstream)**
  – Instruct women to hold labia apart, discard the first portion of voided urine, and collect a midstream portion in a sterile container.
  – Instruct men to retract the foreskin, discard the first portion of voided urine, and collect a midstream portion in a sterile container.
  – Collect first voided urine for *Chlamydia trachomatis* and *N. gonorrhoeae* tests.
  – Keep refrigerated and transport to laboratory promptly, or submit in urine tube with boric acid to prevent overgrowth of contaminating organisms.
  – Cleansing before voiding does not consistently improve the quality of the specimen; however, if the patient is unable to provide a proper specimen, cleansing and supervised collection may be necessary.
Susceptibility pattern and reporting
Susceptibility pattern and reporting

• Follow the techniques proposed by annually reviewed standards (CLSI, EUCAST, CA-SFM, BSAC, …) but with a critical eye and if appropriate to where you are

• Use reporter antibiotics to increase your diagnostic abilities (e.g. norfloxacin to detect efflux)

• Use automated systems but check for the quality of their answer (heteroresistance will be poorly detected)

• Keep track of the real MIC as much as possible for difficult cases, and compare values with those of the wild type distribution and with breakpoints

• Use E-test and microdilution when needed (e.g., detection of heteroresistance)

• Report MICs for (i) epidemiological surveys; (ii) any difficult case (with appropriate comment to the prescriber)
Looking at local hospital MIC distributions…

*P. aeruginosa* from HAP / VAP patients in 6 hospitals in Belgium

![Graph showing MIC distributions for piperacillin/tazobactam](chart.png)
Going from the lab to the ward

• Does your microbiologist discuss infection cases in ICU with you?

1. Each case
2. Few cases
3. Upon asking
4. Never

"We’ve considered every potential risk except the risks of avoiding all risks."
Addressing the questions you always wanted to ask ...

- Does your microbiologist gives MIC of antibiotics apart from sensitivity in ICU infections?
  
  1. Each case
  2. Few cases
  3. upon asking
  4. Never

No, MIC is not the acronym for "Minimal Interest to the Clinician"!
Looking at local regional MIC distributions…

% of isolates (n=249)

MIC (mg/L)

isolates collected from confirmed cases of CAP from Belgium

amoxicillin

wild type

EUCAST

CLSI

Lismond et al. 19th ECCMID 2009, Helsinki, Finland; and submitted for publication
And making decisions....

Based on "target attainment rates" approaches, we can show that the dose of 0.5 g 3 x/day will be almost perfect in Belgium...
### 5. Pharmacodynamics

<table>
<thead>
<tr>
<th></th>
<th>Enterobacteriaceae</th>
<th>Streptococcus pneumoniae</th>
<th>Haemophilus influenzae</th>
</tr>
</thead>
<tbody>
<tr>
<td>%T&gt;MIC for 2 log drop: exp</td>
<td>35 – 45</td>
<td>35 – 45</td>
<td>35 – 45</td>
</tr>
<tr>
<td>%T&gt;MIC from clinical data</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
</tbody>
</table>

**References**

- Craig WA et al. 33rd ICAAC 1993; Abstract 86
- MacGowan AP. *Clin Microbiol Infect* 2004: 52: 6-11

Amoxicillin EUCAST rationale document: Target attainment rate*

Depending on the dose and schedule, you may cover bacteria with MIC from 0.5 to 8 mg/L.

But, where are YOU and what do YOU need?

* for $fT > \text{MIC} = 40\%$

Graph prepared from data in http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Rationale_documents/Amoxicillin_rationale_Nov2010_v_1.0.pdf
Performing longitudinal surveys

S. pneumoniae susceptibility to moxifloxacin in Belgium

From data of a national collection

- Non invasive respiratory tract infections
- similar results in 2008 for a collection of S.penumoniae from clinically-confirmed CAP)

- Surveys from the Belgian Scientific Institute for Public Health for S. pneumoniae from community isolates (n=156 in 1999 and 448 in 2008)
- Data available yearly for 1999 through 2008
- http://www.iph.fgov.be

Antibiotic Management team
Milestones in Belgium

- 1997: « package deal » for antiobioprophylaxis in surgery
- 1998: Copenhagen conference « the microbial threat »
- 1999: launching of a Belgian Antibiotic Policy Coordination Committee
- 2001: European conference on AB use in Europe, Brussels, Belgium
- 2002: Pilot projects of antibiotic policy control groups in a few hospitals

3 major papers describing the role of an antibiotic policy committee:

**JAMA. 1996 Jan 17, 275(3): 234-40.**

Strategies to Prevent and Control the Emergence and Spread of Antimicrobial-Resistant Microorganisms in Hospitals. A challenge to hospital leadership.

Goldman DA, Weinstein RA, Wenzel RP, Tablan OC, Duma RJ, Savides TP, Schlosser J, Martone WJ.

Department of Medicine, Children's Hospital, Boston, Mass 02115, USA.

**Infect Control Hosp Epidemiol. 1997 Apr;18(4):275-81.**


Wadsworth Research, Pearl Fryar, NY 10665, USA.


Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship.


Harborview Medical Center and the University of Washington, Seattle, USA.
Antibiotic Management team

Multidisciplinary team ...

Infectious diseases MD

microbiologist

Clinical pharmacist trained in ID

MD from departments using antibiotics

pharmacist

hygienist
History project

• October 2002  ASTs in 37 acute care hospitals
  (Financing: Royal Decree 25 April 2002)

• July 2006  ASTs in 61 acute care hospitals
  (Financing: Royal Decree 10 November 2006)

• July 2007  acute care hospitals and chronic care hospitals with >150 beds
  (Financing: Royal Decree 19 June 2007)
  (Tasks: Royal decree 12 February 2008)
Position within the hospital organigram

Direction médicale

Comité Médico-pharmaceutique
Formulaire thérapeutique hospitalier

Comité d'hygiène hospitalière
Prévention des IH
Épidémiologie de la résistance
Suivi des IH

Groupe de gestion des AB
GGA

DGA
Rapports au Groupe des antibiotiques

Délégué à la Gestion de l’Antibiothérapie
• de 1 à 4 DGA selon les hôpitaux
• formation de base du DGA:
  – interniste - pneumologues,
  – biologistes-cliniciens, microbiologistes
  – ou pharmaciens hospitaliers.
• Formation complémentaire de 2 ans

Unités
Traitements antibiotiques
Priority tasks

• **Mandatory interventions**
  – Hospital formularium

• **Required interventions**
  – Guidelines
  – Local epidemiology

• **Priority interventions**
  – Evaluation of consumption
  – Link between consumption and epidemiology
  – Providing advice about antibiotic use
  – Limitation and control of antibiotic usage
  – Staff education
  – Annual report for the commission coordinating antibiotic policy
A. How to set up an antibiotic policy control group?

1. Clearly establish the main goals of the working group.
   → improve antibiotic usage (efficacy AND security)
   → reduce the cost without altering quality of care

2. Convince the medical direction of the need
   → self-supported by cost savings
     and improving of quality of care

3. Examine the local situation
   → number and type of beds
   → number and type of hospital stays
   → type of activities (surgery, ICU, oncology, …)
Financial support

• Annual budget of 3 609 208 euro (federal funding for antibiotic managers)

• According to number of beds

• Range: 10 000- 81 700 euro per hospital
A. How to set up an antibiotic policy control group?

4. Determine human resources that are needed
   ... and available

5. Describe the current situation

6. Establish a working plan for YOUR hospital
**Proactive core strategies**

- Prospective audit of AB use with direct intervention and feedback to prescriber (A-I)

- Formulary restriction and preauthorization requirements for specific agents (A-II)
Supplemental strategies

• Education (A-III)
• Guidelines and clinical pathways (A-I)
• Streamlining/de-escalation of empirical therapy (A-II)
• Parenteral to oral conversion (A-I)
• Dose optimization (A-II)
• Antimicrobial order forms (B-II)
• Combination therapy (C-II)
• Antimicrobial cycling (C-II)
C. How should this group act in practice?

1. « Face to Face » interventions

- Prospective and direct interaction between the prescriptor and the infectiologist/clinical pharmacist and feed-back
- Des-escalation (if empirical treatment) based on lab data
- Dose adaptation
- IV-Oral switch

⇒ Very efficient to reduce inappropriate usage!
C. How should this group act in practice?

2. Formularium

- list of antibiotics that are available in the hospital
- list of « reserved » antibiotics (broad spectrum) with specific modalities of use

⇒ Very efficient to reduce consumption!
C. How should this group act in practice?

3. At the level of the laboratory
   - modalities of sample collection
     why, when, how?
   - data interpretation
     criteria used
     colonisation vs infection
     sample quality
   - testings
     antibiograms vs MIC
     which antibiotics to test?
   - epidemiology
     how often?
     which type of sample?
C. How should this group act in practice?

4. At the level of the pharmacy

- **consumption data** (per ward)

- **detailed evaluation of specific antibiotics**
  - carbapenems
  - fluoroquinolones
  - glycopeptides

- **tables to improve antibiotic use**
  - dose
  - compatibilities and storage interactions, …
C. How should this group act in practice?

5. Education

• guidelines

• analysis and feedback of data (resistance and consumption)

   Should be accompanied by active interventions to be efficient
C. How should this group act in practice?

6. Evaluation

• compliance to guidelines

• reasons for non-observance

Propose new measures to improve at the next round!
Evaluation of impact

- Process measure: antimicrobial use (B-III)
- Outcome measure: resistance patterns (B-III)
3. Antibiotic formulary and guidelines

• Antibiotic formulary:
  96.3% of the acute care hospitals

• Guidelines for empirical and etiological antibiotic therapy:
  91.7% of the acute care hospitals

• Guidelines for antibiotic prophylaxis:
  98.2% of the acute care hospitals
Successes and Difficulties of the antibiotic management teams

- accepted as a reference in the hospital for
  - evaluation of consumption
  - prescription habits
  - detection of inappropriate use
  - reminding of guidelines

- Diffusion of information
- Communication
- Data availability
- unlinked softwares (laboratory vs pharmacy)
- Heaviness of evaluation
Isolation and Hygiene
Isolation and Hygiene

- Overpopulation must be avoided and/or corrected for
- Patients with multi-resistant organisms must be promptly diagnosed and isolated (with specific personnel)
- Cohorting is an useful approach to avoid dissemination while minimizing the costs and personnel burden
- Sound and consistent disinfection procedures must be enforced (hand washing, medical materials, plants and fruits from external and internal sources, …)
Isolation and Hygiene: the problem

avoid those
Isolation and Hygiene: knowing what you have

Results from recent European prevalence surveys

Belgium was 6 % in 2007
Hygiene: the most simple but most effective measure

Hand Hygiene (HH) is the most simple and effective measure to prevent healthcare associated infections.

Does everyone in your hospital agree???
Hand hygiene must be comprehensive
Hand hygiene must be comprehensive
Hand hygiene must be comprehensive
The hand hygiene campaigns in Belgium

- During 1 month
  - Invitation to participate
  - Measurement of HH indicators
- 1 month later and for 1 month
  - Awareness Campaign + press conference
- 1 month later and for 1 month
  - Measurement of HH indicators
- 9 months later
  - Post-campaign
- National Feedback session

First campaign: 2005
Second campaign: 2006-2007
Third campaign: 2008-2009
Fourth campaign: 2010-2011
Measurement of HH compliance: Gold standard

- Direct (overt or covert) observation
- By trained observers (IC practitioner or reference nurses for hospital hygiene)
- Standardised observation grid
- Observation period of 30 minutes, 24/24h, 7/7d
- Minimum 150 opportunities for HH per unit
- At least intensive care units
- Same methodology before and after campaign
Results are obtained sequentially …

<table>
<thead>
<tr>
<th>Campaign</th>
<th>Messages</th>
<th>Participation</th>
<th>Hand hygiene compliance %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&gt;80%</td>
<td>Before campaign</td>
</tr>
<tr>
<td>2005</td>
<td>Just Do It</td>
<td></td>
<td>48</td>
</tr>
<tr>
<td>2006-2007</td>
<td>Do It correctly</td>
<td></td>
<td>53</td>
</tr>
<tr>
<td>2008-2009</td>
<td>Without jewels and with appropriate use of gloves</td>
<td></td>
<td>58</td>
</tr>
<tr>
<td>2010-2011</td>
<td>Doctor, don’t forget, it works and you have a role model</td>
<td></td>
<td>63</td>
</tr>
</tbody>
</table>
Incidence of healthcare associated MRSA in Belgian hospitals 1994-2009

Antibiotic use management teams

MRSA new guidelines

1st Camp 2005

2d Camp 2007

3d Camp 2009

National surveillance MRSA, Bea Jans
Surveillance of ESBL-producing *Enterobacter aerogenes* in Belgian hospitals

**Graph:**
- **Proportion d'E.a., ESBL+**
- **Incidence d'E.a., ESBL+**

<table>
<thead>
<tr>
<th>Year</th>
<th>Proportion</th>
<th>Incidence</th>
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<tbody>
<tr>
<td>2002/12</td>
<td>2.3</td>
<td>36.6</td>
</tr>
<tr>
<td>2003/1</td>
<td>2.2</td>
<td>34.9</td>
</tr>
<tr>
<td>2003/2</td>
<td>1.9</td>
<td>29.2</td>
</tr>
<tr>
<td>2004/1</td>
<td>2.3</td>
<td>37.9</td>
</tr>
<tr>
<td>2004/2</td>
<td>2.1</td>
<td>31</td>
</tr>
<tr>
<td>2005/1</td>
<td>2.4</td>
<td>37.5</td>
</tr>
<tr>
<td>2005/2</td>
<td>2.6</td>
<td>41.5</td>
</tr>
<tr>
<td>2006/1</td>
<td>2.1</td>
<td>30.7</td>
</tr>
<tr>
<td>2006/2</td>
<td>2.5</td>
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</tr>
<tr>
<td>2007/1</td>
<td>1.6</td>
<td>31</td>
</tr>
<tr>
<td>2007/2</td>
<td>1.7</td>
<td>31</td>
</tr>
<tr>
<td>2008/1</td>
<td>1.4</td>
<td>25.5</td>
</tr>
<tr>
<td>2008/2</td>
<td>1.3</td>
<td>1.3</td>
</tr>
</tbody>
</table>

- Decrease in proportion / incidence of ESBL+ *E. aerogenes* since 2006/2
- No difference in incidence by hospital nbr of bed size
- 2.5 fold higher incidence in hospitals with DMS >9 days

**Notes:**
- BAPCOC effect? (Implementation of GGA)
- Hand hygiene
- National campagnes?
- BICS guidelines for infection control of MRSA in hospitals?

ISP/WIV report 2008/2

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11/10/2011  WBI - HUP cooperation - Bach Mai Hospital, Hanoi, Vietnam
Can isolation / hygiene be applied in a country of limited resources?

Resource-full
- Molecular epidemiology
- Environmental culture
- Active Surveillance
- Enhanced environmental cleaning
- Enhanced isolation precaution
- Antibiotic management

Resource-Limited
- Stratified unit specific infection rate
- Line listing and/or case-control study (identify common source outbreak)
- Implement emergency measure for highly alert pathogen
- Initial environmental culture (per finding from line listing)
- Modified Active Surveillance
- Enhanced isolation precaution
- Environmental cleaning
- Antibiotic management program

PDR-Acinetobacter baumannii: Can it be controlled?
Anucha Apisarnthanarak, MD, Division of Infectious Diseases, Thammasat University Hospital, Thailand
Presented at the 8th International Symposium on Antibiotic Resistance (ISAR), Seoul, Korea, April 2011
Hand Hygiene Compliance Rate in Thailand

Year 2006-2007

Percent

Pre-contact/procedure
Post-contact/procedure
After touching pt care item

Intervention
Urinary Tract Infection Intervention

CA-UTI rates/1000 FC-days

- Inappropriate catheter-days 83%
- Total length of hospitalization 68%
- Cost of hospitalization/patient 57%

Creating cohort area to limit transmission of *PDR-A. baumannii* in a medical unit

- October 2007, first case of *PDR-A. baumannii* was detected in a medical unit. The nurse to patient ratio was 1:8 in this medical unit.

- IC measured were implemented within 24 hours including 1) enhanced contact isolation, 2) ASCs, 3) environmental cleaning, 3) enhanced hand hygiene program

- During period 1 (4-28 October), 6 cases of *PDR-A. baumannii* were detected by ASCs; infection and colonization rate 2.4/1000 patient-days & acquisition rate 6/1000 patient-days.

Regional / National activities
Regional / National activities

- Antibiotic consumption data
  - global
  - per hospital with feedback and comparisons

- Guidelines
  - for general practice → guide sent to all GP's
  - for hospital: through Scientific Societies with the help of the Ministry of Health and the Social Security

- Centers for <pathogen> (*Pneumococci*, *Pseudomonas*, *Staphylococci*, …)
  - reference centers for clinical microbiology laboratories (identification, novel resistance mechanisms, alerts…)
  - stable collections for evaluation of novel (or "come back") antibiotics