Comparative studies with antibiotics: Why should we change the rules?

Paul M. Tulkens, MD, PhD
Cellular and Molecular Pharmacology
& Centre for Clinical Pharmacy
Louvain Drug Research Institute,
Université catholique de Louvain,
Brussels, Belgium
What its all about?

- We are in real need of novel antibiotics… but …
  - most clinical studies with new compounds aim at equivalence or non-inferiority, failing to meet clinicians’ expectations and regulatory requirements for novelty.
  - In parallel, safety issues are becoming an increasingly worrying hurdle for manufacturers
  - Pricing make antibiotic unattractive

- What are the possible solutions?
The antibiotic crisis *

* A pictorial view using 4 paintings of Van Gogh (who stayed briefly in Belgium when moving from Holland to France) and with selected Belgian and International data…
Are antibiotics following a path to madness?

discovery in soil bacteria and fungi

1928 - …
Are antibiotics following a path to madness?

and then we all saw the blooming tree of semi-synthetic and totally synthetic antibiotics

1950 – 1980 …
Are antibiotics following a path to madness?

and the US General Surgeon told us that the fight was over

1970 …
Are antibiotics following a path to madness?
Extent of resistance of *P. aeruginosa* (International data – EUCAST breakpoints)

The hidden risk of therapy (at the corner of your street …)

In vivo development of antimicrobial resistance in *Pseudomonas aeruginosa* strains isolated from the lower respiratory tract of Intensive Care Unit patients with nosocomial pneumonia and receiving antipseudomonal therapy

Mickaël Riou\(^a,1\), Sylviane Carbonnelle\(^a,2\), Laëtitia Avrain\(^a,\textit{b}\), Narcisa Mesaros\(^a,3\), Jean-Paul Pirnay\(^c\), Florence Bilocq\(^c\), Daniel De Vos\(^c,\textit{d}\), Anne Simon\(^e\), Denis Piérard\(^f\), Frédérique Jacobs\(^g\), Anne Dediste\(^h\), Paul M. Tulkens\(^a,\textit{*}\), Françoise Van Bambeke\(^a\), Youri Glupczynski\(^i\)

\(^a\) Unité de Pharmacologie Cellulaire et Moléculaire & Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium  
\(^b\) Coris BioConcept, Gembloux, Belgium  
\(^c\) Laboratory for Molecular & Cellular Technology, Queen Astrid Military Hospital, Neder-over-Heembeek, Brussels, Belgium  
\(^d\) Department of Molecular and Cellular Interactions, Vrije Universiteit Brussel, Brussels, Belgium  
\(^e\) Laboratoire de Microbiologie, Cliniques Universitaires St-Luc, Brussels, Belgium  
\(^f\) Laboratorium voor Microbiologie, Universitair Ziekenhuis Brussel, Brussels, Belgium  
\(^g\) Clinique des Maladies Infectieuses, Hôpital Erasme, Brussels, Belgium  
\(^h\) Laboratoire de Microbiologie, Centre Hospitalier Universitaire Saint-Pierre, Brussels, Belgium  
\(^i\) Laboratoire de Microbiologie, Cliniques Universitaires UCL de Mont-Godinne, Yvoir, Belgium
**Question #1: are you effective?**

<table>
<thead>
<tr>
<th></th>
<th>No. of patients</th>
<th>No. of adequate antibiotics/total</th>
<th>% (no.) of patients with adequate therapy (EUCAST)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy</td>
<td>26</td>
<td>1/1</td>
<td>57.7 (15)</td>
</tr>
<tr>
<td>2 antibiotics</td>
<td>14</td>
<td>2/2</td>
<td>71.4 (10)</td>
</tr>
<tr>
<td>3 antibiotics</td>
<td>13</td>
<td>3/3</td>
<td>38.5 (5)</td>
</tr>
<tr>
<td>4 antibiotics</td>
<td>1</td>
<td>3/4</td>
<td>100 (1)</td>
</tr>
</tbody>
</table>

**Message #1: many patients receive ineffective antibiotics**
Question #2: do you remain effective while treating?

- D0: initial isolate
- DL: last isolate obtained
- Individual values with geometric mean (95% CI)
- S (lowest line) and R (highest line) EUCAST breakpoints

* p < 0.05 by paired t-test (two-tailed) and Wilcoxon non-parametric test

a p < 0.05 by Wilcoxon non-parametric test only

Note: stratification by time between D0 and DL gave no clue (too low numbers)

Message #2: for all antibiotics, we see global increases of MIC during treatment
Question #3: Can you still treat patients?

- In North-America / Western Europe", we may still work with available antibiotics but we are reaching the limit…

  A well known Belgian politician…
  - heart attack during his holidays (in Europe) …
  - transfer to hospital Intensive Care Unit
  - nosocomial pneumonia …
  - dying a few days later (multi-resistant organism)

- The situation becomes hopeless in several other countries for hospitals (Russia, Vietnam, …) and, for some countries, even in the community…
Resistance IS a problem …

Has the era of untreatable infections arrived?

David M. Livermore*

Antibiotic Resistance Monitoring and Reference Laboratory, Health Protection Agency Centre for Infections, 61 Colindale Avenue, London NW9 5EQ, UK

- The choices of effective therapies is narrowing dangerously for several important pathogens
- Good faith people try acting by
  - Rationalizing the choice among the remaining ones
  - Optimizing those "remaining antibiotics"
  - decreasing the inappropriate use of antibiotics whenever possible and improving hygiene with close follow-up of the epidemiology
The problem is the lack of new compounds…

The drying pipeline?
The drying pipeline ? (1)

- Everyone speaks about the reduction in the number of new antibiotics… What is your reality ?

New antibiotics introduced in the Belgian market since 2000 in ATC code J01

- J01A tetracyclines……………….. 1 (tigecycline [Pfizer])
- J01B phenicols ………………….. 0
- J01C β-lactams (penicillins)……… 0
- J01D other β-lactams …………. 1 (doripenem [Janssen-Cilag])
- J01E sulfamides/trimethoprim:… 0
- J01F macrolides/linc./streptog.: 1 (telithromycin [Sanofi])
- J01G aminoglycosides………….. 0
- J01M quinolones………………….. 1 (moxifloxacin [Bayer])
- J01R associations:……………….. 0
- J01X others:………………………. 1 (linezolid [Pfizer])

Which of these molecules do YOU wish in your hospital ?
Drying pipeline? (2)

Antibiotics in ATC code J01 and with EMA approval but not available in Belgium

- J01A tetracyclines..................0
- J01B phenicols.......................0
- J01C β-lactams (penicillins).......0 (sulbactam [Pfizer])
- J01D other β-lactams..............1 (ertapenem [MSD])
- J01E sulfamides/trimethoprim:....0
- J01F macrolides/linc./streptogr.:1 (quinupristin/dalfopristin)
- J01G aminoglycosides.............0
- J01M quinolones.................0
- J01R associations:...............0
- J01X others:......................2 (daptomycin [Novartis])
  (telavancin [Astellas])

* in at least one EU country since 2000 and with at least some advantages/differences with comparators
Drying pipeline? (3)

New antibiotics in ATC code J01 and in the pipeline/waiting for EMA approval *

- J01A tetracyclines..................1 → amadacycline (PTK 0796)
- J01B phenicols .....................0
- J01C β-lactams (penicillins).......0
- J01D other β-lactams ..............3 → ceftobiprole, ceftaroline
- J01E sulfamides/trimethoprim:....0 → iclaprim
- J01F macrolides/linc./streptogr.:1 → cethromycin
- J01G aminoglycosides.............0 → plazomycin (ACHN-490)
- J01M quinolones....................0 → several...
- J01R associations:...................0 → avibactam (+ cephalosporins)
- J01X others:..........................2 → oritavancin, dalbavancin

* not an exhaustive list
Drying pipeline? (4)

New molecules in preclinical/early clinical development *

- New oxazolidinones (tedizolid, radezolid …) active against LZD\textsuperscript{R} strains
- New aminoglycosides active against AMG\textsuperscript{R} strains (including arm) (**)
- New fluroquinolones active against MRSA (including CIP\textsuperscript{R} strains)
- New gyrase inhibitors active against CIP\textsuperscript{R} Gram(-) bacteria (**)
- New pleuromutilins (active against Gram + bacterial)
- New anti-MRSA carbapenems
- New lipopeptides (not affected by lung surfactant)
- New polymyxins derivatives (potentially less toxic)
- New dual target gyrase inhibitors (new target)
- ...

This is what you find by attending ICAAC ...

* not an exhaustive list
** DOD/NIH program
So, what are the hurdles?

• Discovery!
  – More efforts must be made with both public and private funding

• Clinical development
  – We must strive to efforts that are really meaningful
    (but this may command a smaller market … see hereunder)

• Registration
  – Provisional registration must be warranted for really innovative
    compounds (at phase II level) if helping to solve unmet medical
    needs
  – Safety issues must remain of paramount importance but should
    not deter honest efforts (no drug is harmless !)
So, what are the hurdles?

- **Discovery!**
  - More efforts must be made with both public and private funding

Today, several new antibiotic programs are financed by the US DOD …

But NIH (and EU…) programs are catching up…
So, what are the hurdles?

• Clinical development!
  – Phases I and phase II are reasonable
  – The major weakness is in phase III

• Currently, phase III studies are "controlled" (i.e. with a comparator) as per Regulatory Authorities requests…

• Almost all antibiotic therapies are still initiated empirically (i.e. without documentation of the causative organism)

• For ethical reasons, the comparator must be active

• Therefore, most if not all studies follow a "non-inferiority" design
An example with daptomycin…

- Original molecule with a novel mode of action!

- **Very bactericidal (membrane destabilization; no need of proteinaceous receptor !) and potent (MIC *S. aureus* = 0.5mg/L)**

- Spare eucaryotic cells because they lack phosphatidylglycerol (critical for binding to Gram(+) membranes)
An example with daptomycin…

- Phase III studies: 1. skin & skin structures infections

Table 12. Clinical Success Rates by Infecting Pathogen in the cSSSI Trials (Population: Microbiologically Evaluable)

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Success Rate n/N (%)</th>
<th>CUBICIN</th>
<th>Comparator*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methicillin-susceptible <em>Staphylococcus aureus</em> (MSSA)†</td>
<td>170/198 (86%)</td>
<td>180/207   (87%)</td>
<td></td>
</tr>
<tr>
<td>Methicillin-resistant <em>Staphylococcus aureus</em> (MRSA)†</td>
<td>21/28 (75%)</td>
<td>25/36     (69%)</td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
<td>79/84 (94%)</td>
<td>80/88     (91%)</td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus agalactiae</em></td>
<td>23/27 (85%)</td>
<td>22/29     (76%)</td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus dysgalactiae subsp. equisimilis</em></td>
<td>8/8 (100%)</td>
<td>9/11      (82%)</td>
<td></td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em> (vancomycin-susceptible only)</td>
<td>27/37 (73%)</td>
<td>40/53     (76%)</td>
<td></td>
</tr>
</tbody>
</table>

* Comparator: vancomycin (1 g IV q12h) or an anti-staphylococcal semi-synthetic penicillin (i.e., nafcillin, oxacillin, cloxacillin, or flucloxacinillin; 4 to 12 g/day IV in divided doses).
† As determined by the central laboratory.
An example with daptomycin...

- Look at the phase III studies: 2. endocarditis

### Table 13. Success Rates at Test of Cure in the *S. aureus* Bacteremia/Endocarditis (ITT)

<table>
<thead>
<tr>
<th>Population</th>
<th>Success Rate</th>
<th>Difference: CUBICIN – Comparator (Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N (%)</td>
<td>CUBICIN 6 mg/kg Comparator</td>
</tr>
<tr>
<td>Overall</td>
<td>53/120 (44%)</td>
<td>48/115 (42%)</td>
</tr>
<tr>
<td>Baseline Pathogen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methicillin-susceptible <em>S. aureus</em></td>
<td>33/74 (45%)</td>
<td>34/70 (49%)</td>
</tr>
<tr>
<td>Methicillin-resistant <em>S. aureus</em></td>
<td>20/45 (44%)</td>
<td>14/44 (32%)</td>
</tr>
<tr>
<td>Entry Diagnosis§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite or Possible Infective Endocarditis</td>
<td>41/90 (46%)</td>
<td>37/91 (41%)</td>
</tr>
<tr>
<td>Not Infective Endocarditis</td>
<td>12/30 (40%)</td>
<td>11/24 (46%)</td>
</tr>
<tr>
<td>Final Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncomplicated Bacteremia</td>
<td>18/32 (56%)</td>
<td>16/29 (55%)</td>
</tr>
<tr>
<td>Complicated Bacteremia</td>
<td>28/60 (43%)</td>
<td>23/61 (38%)</td>
</tr>
<tr>
<td>Right-Sided Infective Endocarditis</td>
<td>8/19 (42%)</td>
<td>7/16 (44%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncomplicated Right-Sided Infective Endocarditis</td>
<td>3/6 (50%)</td>
<td>1/4 (25%)</td>
</tr>
<tr>
<td>Complicated Right-Sided Infective Endocarditis</td>
<td>5/13 (39%)</td>
<td>6/12 (50%)</td>
</tr>
<tr>
<td>Left-Sided Infective Endocarditis</td>
<td>1/9 (11%)</td>
<td>2/9 (22%)</td>
</tr>
</tbody>
</table>

* Comparator: vancomycin (1 g IV q12h) or an anti-staphylococcal semi-synthetic penicillin (i.e., nafcillin, oxacillin, cloxacillin, or flucoxacinilin; 2 g IV q4h), each with initial low-dose gentamicin.

† 95% Confidence Interval  ‡ 97.5% Confidence Interval (adjusted for multiplicity)
§ According to the modified Duke criteria*  ¶ 99% Confidence Interval (adjusted for multiplicity)
An example with daptomycin…

- As a result, in a major EU country …

Daptomycine (Cubicin®): Infections graves à GRAM positif : Aucun avantage et des troubles musculaires

Is this what discovery was promising?
Solving the problem of "uninteresting phase III studies"?

- Address a real problem … and look for the **correct target** (the bacteria)
  - Look for infections caused by multi-resistant RESISTANT organisms (or organisms you cannot fight with available antibiotics)
    (infections need NOT be necessarily severe…)

- Run the study in a **non-controlled fashion**
  - By definition, you cannot have a comparator if you aim at resistant organisms

- Target your study for non-inferiority against **historical controls**
  - Control = same type of infection caused by the same organisms but when it was still susceptible to the best-in-class antibiotic at that time

- By definition, **you will be superior** since the "control antibiotic" will not longer be acceptable.
Why not avoiding phase III altogether?

- Provisional registration could be warranted for really innovative compounds at phase II level if helping to solve unmet medical needs (and be accepted for that)!

---

**New antimicrobials are required to demonstrate non-inferiority to a licensed control. This can require hundreds, even thousands of patients across a development programme. Requirements for evidence of efficacy in phase III might be reconsidered. It should be further discussed whether it might be preferable to relax the currently tight requirements for active comparator trials, so that less stringent demonstration of non-inferiority could be acceptable (especially) if absolute efficacy is clearly established (i.e. versus placebo).**
Why not avoiding phase III altogether?

- Provisional registration could be warranted for really innovative compounds at phase II level if helping to solve unmet medical needs (and be accepted for that)!

---

Exploring options for new and effective antibiotic treatments

- Reviewing existing options to **promote development of new antibiotics to treat multi-resistant bacteria including adaptation of clinical guidance documents**, consideration of the balance between the amount of prior data needed with enhancing post-marketing surveillance, use of orphan legislation, etc.
What about safety?

- Registration: old scheme
  - Progression through phase I – II – III ...
  - Until reaching the number of patients required for safety ...

![Diagram showing phases of clinical trials with progression from preclinical to phase III, indicating patient numbers: n ~ 50, n ~ 300, N ~ 6000.](image-url)
How to combine this with safety?

- Registration: proposed new scheme
  - Provisional registration at phase II level (solving the unmet medical need)
  - Continue evaluation through commercialization until reaching a number of patients equivalent to a phase III to get full registration
But there us still another problem?

- Discovery **IS** difficult…
- Preclinical development **IS** challenging…
- Clinical development and registration are **not easy** …
- **But, will you recoup your investment?**

This is a main part of the problem (in our current situation)
Why is economy important?

• Can you work without support? …
  – You need investors
  – Those will ask some return at some point…
  – And none ignores what is a ROI

This is what every economist will tell you (and you know it!)
Let us take a simple comparison …

- Pricing
  - Antibiotics are cheap…
  - And now, the Belgian pharmacist must deliver the cheapest one (generic)…
  - Why would Industry make an effort?

Allow me to take a simple example…

- **Pneumonia (> 60 years)**
  - Levofloxacin high dose: < 200 € / 10 days
  - Survival of many years

- **Breast cancer (> 50 years)**
  - Trastusumab: > 20,000 € / year
  - Survival of a few years
This may be saving lives … but at which price?


Ipiлимумаб monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study.


Ludwig Center for Cancer Immunotherapy, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA. wolchokj@mskcc.org

- gain in lifetime over dose (phase II trial)
- price of a reimbursed treatment: 77,000 euros/year

Figure 2: Kaplan-Meier estimate for overall survival, by treatment arm
Do you remember having seen this?

Penicillin saves lives (in 1944)!

It is no longer true!

The Emerging Threat of Untreatable Gonococcal Infection

Gail A. Bolan, M.D., P. Frederick Sparling, M.D., and Judith N. Wasserheit, M.D., M.P.H.

Gonorrhea, which disproportionately affects marginalized populations, is the second most commonly reported communicable disease in the United States. Over the past 3 years, the gonococcus has shown decreased susceptibility to our last line of antimicrobial defense.