What makes an antibiotic the right antibiotic?

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Disclosures

Industry support for work on investigational compounds from
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• GSK
• Melinta Therapeutics ²
• The Medicine Company ³
• MerLion Pharmaceuticals
• Trius Therapeutics ⁴
• Debiopharm

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Influenced by my participation to the
• Belgian Drug Reimbursement Committee (CRM/CTG; up to 2006)
• *EUCAST* steering committee (2008-2010) and General Assembly (current)
• the Governance Body of *DRIVE-AB* (2014-2017)
  (an EU programme aiming at (re)designing the economic framework of the discovery, development and commercialization processes for new antibiotics)

¹ merged in 2017 with and renamed as Melinta Therapeutics
² formerly RibX Pharmaceuticals; world rights holder for delafloxacin (with license to Menarini for EU and other countries)
³ antibiotic portfolio acquired by Melinta Therapeutics in 2018
⁴ acquired by Cubist (2014), which was then acquired by Merck (2016)
Chapter 17: Principles of Anti-infective Therapy
George M. Eliopoulos
Robert C. Moellering Jr.*

"In choosing the appropriate antimicrobial agent for therapy for a given infection, a number of factors must be considered.

• First, the identity of the infecting organism must be known or, at the very least, it must be possible to arrive at a statistically reasonable guess as to its identity on the basis of clinical information.

• Second, information about the susceptibility of the infecting organism, or likely susceptibility, must be as accurate as possible.

• Finally, a series of factors specific to the patient who is being treated (and his/her disease) must be considered to arrive at the optimal choice of antimicrobial agent. "

Here are the questions …

When choosing an antibiotic, do we know

1. for the organism
   – its identity and whether it is causal or not
   – its susceptibility to and the main key properties of the proposed antibiotic

2. for the patient
   – the antibiotic effectiveness in the specific disease
   – how to dose the antibiotic appropriately
   – how to prevent / avoid patient- and drug-related side effects

3. for Society
   – how to prevent emergence of resistance
   – how to get "value for money"

Please, think about what YOU would answer!
Possible answers for the organism …

When choosing an antibiotic, do we know

1. for the organism
   - its identity and whether it is causal or not?

If sample(s) is (are) available, use of all "possible" techniques

- Gram stain and direct microscopy examination…
- rapid immunological and molecular techniques…
- culture and identification (galleries / MALDI-TOF)…
- quantitative cultures

caution: garbage in – garbage out

If no sample is available… we must use "bacteriological statistics"

- likelihood to cause a specific infection
- endogenous and/or environmental presence

caution: possible surprizes
When choosing an antibiotic, do we know

1. for the organism
   - its susceptibility to the proposed antibiotic

Susceptibility

• are *in vitro* methods predictive (and which ones to use) ?

• which interpretive criteria ?
Implementation of EUCAST breakpoints, January 2018

% Laboratories
- >50%
- 10-50%
- <10%
- No information

Map showing the percentage of laboratories implementing EUCAST breakpoints by country.
Possible answers for the organism …

When choosing an antibiotic, do we know
1. for the organism
   - its susceptibility to the proposed antibiotic

Epidemiological studies are critical for global antibiotic policy…

Figure 3.26. *Staphylococcus aureus*. Percentage (%) of invasive isolates with resistance to meticillin (MRSA), by country, EU/EEA countries, 2016


National Surveillance of Methicillin-Resistant *Staphylococcus aureus* in China Highlights a Still-Evolving Epidemiology with 15 Novel Emerging Multilocus Sequence Types

Meng Xiao,* He Wang,* Ying Zhao,* Lei-Li Mao,* Mitchell Brown,† Yun-Song Yu,‡ Matthew V. N. O’Sullivan,¶ Fanrong Kong,¶ Ying-Chun Xu*†

Department of Clinical Laboratory, Peking Union Medical College Hospital and Graduate School, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, China; Centre for Infectious Diseases and Microbiology Laboratory Services, Westmead Hospital, Westmead, New South Wales, Australia; Marie Bashir Institute for Infectious Diseases and Biosecurity, University of Sydney, Sydney, Australia; Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang Province, China

Possible answers for the organism …

When choosing an antibiotic, do we know

1. for the organism
   – the main key properties of the proposed antibiotic against the identified (or likely) target(s)

Spectrum and mode / extent of action
• narrow or wide spectrum ?
• bactericidal or bacteriostatic (MIC / MBC)…

Long and hot debates …
Possible answers for the organism …

When choosing an antibiotic, do we know

1. for the organism
   – the main key properties of the proposed antibiotic against the identified (or likely) target(s)

Spectrum and mode / extent of action

• the molecular parameters that differentiate drugs …
From linezolid to tedizolid: what the structure tells us

**Linezolid (LZD)**

**Tedizolid (TZD)**

**Substantial differences that DO impact on**
- **intrinsic activity** *(more potent)*
- activity against **LZD-resistant strains**
- **half-life** *(longer)*

- acetamido vs. free -OH
- pyridinyl replacing the morpholinyl
- additional methyl-tetrazolyl
Possible answers for the organism …

When choosing an antibiotic, do we know

1. for the organism
   - the main key properties of the proposed antibiotic against the identified (or likely) target(s)

Spectrum and mode / extent of action

• activity against persisters, small colony variants, intracellulars, biofilms …

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Lewis et al, Nat Rev Microbiol. 2007; 5:48-56
When choosing an antibiotic, do we know

1. for the organism
   - the main key properties of the proposed antibiotic against the identified (or likely) target(s)

Spectrum and mode / extent of action

- activity against persisters, small colony variants, intracellulars...

Possible answers ...


Lewis et al, Nat Rev Microbiol. 2007; 5:48-56
When choosing an antibiotic, do we know

2. for the patient
   - the antibiotic effectiveness in the specific disease?

Are potent *in vitro* antibiotics always potent *in vivo*? …

The daptomycin story…

Inhibition of Daptomycin by Pulmonary Surfactant: In Vitro Modeling and Clinical Impact

Jared A. Silverman, Lawrence I. Mordin, Andrew D. G. VanPraagh, Tongchuan Li, and Jeff Alder
Cubist Pharmaceuticals, Lexington, Massachusetts

The lipopeptide daptomycin has been approved for use in skin and skin-structure infections but has failed to meet statistical noninferiority criteria in a clinical trial for severe community-acquired pneumonia. Daptomycin exhibited an unusual pattern of activity in pulmonary animal models: efficacy in *Staphylococcus aureus* hematogenous pneumonia and inhalation anthrax but no activity against *Streptococcus pneumoniae* in simple bronchial-alveolar pneumonia. Daptomycin was shown to interact in vitro with pulmonary surfactant, resulting in inhibition of antibacterial activity. This effect was specific to daptomycin and consistent with its known mechanism of action. This represents the first example of organ-specific inhibition of an antibiotic.


clinical demonstration is essential!

cautions with off-label use …
Antibiotic poor penetration can explain many difficulties...

Vancomycin Penetration

CNS: <10%

Sternal bone¹: 57%
Heart valve⁴: 12%

Lung tissue²: 17%–24%

Bone⁵: 7%–13%

Epithelial lining fluid³: 18%

Fat⁴: 14%
Muscle⁴: 9%

Possible answers for the patient …

When choosing an antibiotic, do we know

2. for the patient
   – how to dose the antibiotic appropriately?

This is where the PK/PD guys came in (Stockholm, 1989)
A simple *in vitro* comparison

- bacteria in broth
- increasing concentrations (multiples of MIC)
- measure of the change in CFUs over time

**Fast and concentration-dependent**

**Slow and time-dependent**

PK parameters governing the activity of antibiotics

- $C_{\text{max}} / \text{MIC}$
- $fT > \text{MIC}$
- $\text{AUC}_{24h} / \text{MIC}$

Diagram:
- Concentration vs. time (h)
- Key points:
  - $C_{\text{max}}$
  - $fT > \text{MIC}$
  - $\text{AUC}_{24h}$

Time (h):
- 0
- 6
- 12
- 18
- 24

MIC
How to determine which PK parameter is critical?

- If you fractionate the daily dose, you change $C_{\text{max}}$ without changing $AUC_{24h}$.
How to determine which PK parameter is critical?

- If you increase the dose without change of schedule, you increase BOTH $C_{\text{max}}$ and $AUC_{24h}$.

\[ AUC_{24h} = \frac{\text{Dose}_{24h}}{\text{Clearance}} \]

$AUC_{24h}$ is proportional to the dose.
The 3 main patterns of antibiotic PK/PD properties
(W.A. Craig, 2000; revised in 2003)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>PK/PD Parameter</th>
<th>What to do?</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-lactams</td>
<td>time &gt; MIC</td>
<td>stay &gt; MIC as needed</td>
</tr>
<tr>
<td>Macrolides, oxazolidinones,</td>
<td>AUC&lt;sub&gt;24h&lt;/sub&gt; / MIC</td>
<td>give a sufficient total daily dose</td>
</tr>
<tr>
<td>vancomycin…</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinolones</td>
<td>peak / MIC and</td>
<td>obtain a peak and aim for a sufficient total</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>AUC&lt;sub&gt;24h&lt;/sub&gt; / MIC</td>
<td>daily dose</td>
</tr>
</tbody>
</table>

What should you strive for?

- **Maximal effect**: $E_{\text{max}}$
- **E_min**: Minimal effect
- **E_{50\%}**: Concentration at 50% effect
- Intercept: $\ln EC_{50} - 2$
- Slope: $E_{\text{max}}/4$

**Concentration**

$$\text{% of maximum effect}$$

$$\text{ln C [ng/ml]}$$
If you select a β-lactam …

- cefotaxime
- neutropenic mice
- *K. pneumoniae*
- lung infection

100 % - Maximal effect
Fig. 2.6  Change in $\log_{10}$ CFUs/thigh over 24 h for various Enterobacteriaceae following treatment with multiple fluoroquinolones in neutropenic mice. Redrawn from data in Andes and Craig (2002)
Breakpoint setting: the EUCAST way

Fig. 3.4 Summary of the process of setting PK/PD breakpoints by EUCAST (Mouton et al. 2012)
Toxicodynamics: what drives linezolid toxicity…

![Graph showing the relationship between linezolid $C_{\text{min}}$ and the probability of platelet reduction.](image)

**Fig. 16.13** Linezolid $C_{\text{min}}$ and logistic regression model for thrombocytopenia (Pea et al. 2012), reproduced with permission. The symbols refer to the $C_{\text{min}}$ observed over time in each patient with (top) or without (bottom) thrombocytopenia. The continuous line represents the result of the logistic regression model. The vertical broken line identifies the $C_{\text{min}}$ value predicting 50 % probability of thrombocytopenia.

When choosing an antibiotic, do we know

2. for the specific patient
   – how to prevent / avoid patient- and drug-related side effects

**Aminoglycosides** are concentration-dependent and need to be given once-daily both for increased efficacy and possible reduction of toxicity

![Graph showing concentration-time profile comparison of conventional q8h intermittent dosing versus the once-daily daily administration technique](image)
When choosing an antibiotic, do we know

2. for the specific patient
   – how to prevent / avoid patient- and drug-related side effects

Aminoglycosides are concentration-dependent and need to be given once-daily for increased efficacy and possible reduction of toxicity.
Answers for the patient …

When choosing an antibiotic, do we know
2. for the specific patient
   – how to prevent / avoid patient- and drug-related side effects

Choosing the appropriate drug derivative can be rewarding…

Tedizolid (TZD) vs. linezolid (LZD) safety:
Platelet counts
Pooled Phase 3 Studies

DeAnda et al. Integrated results from 2 phase 3 studies comparing tedizolid phosphate 6 days vs. linezolid 10 days in patients with ABSSSI. Poster presented at: 53rd Interscience Congress on Antimicrobial Agents and Chemotherapy (ICAAC); September 10-13, 2013; Denver, CO. (L-203).
Here are the questions …

When choosing an antibiotic, do we know

3. for the society
   – how to prevent emergence of resistance?
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This is probably a most difficult challenge because
• resistance genes are already present in nature (resistome)
• bacteria quickly adapt to new environments (mutation/selection)

When choosing an antibiotic, do we know

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- resistance genes are already present in nature (resistome)
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Fig. 1 The antibiotic resistome gene flow in environments, human, and animals. We propose that the antibiotic resistome gene flow is “from the natural environments” and “to the natural environments.” The natural environments are the reservoirs for antibiotic resistome. The original ARGs in environmental bacteria can be captured by human or animal pathogens and gradually evolved under the antibiotic selection pressure and become qualified. These ARGs or ARG-bearing bacteria are then disseminated back to the natural environments due to the human activities in producing and using antibiotics. In most cases, the ARGs are more easily transferred within respective ecological niches (the natural environments, and the human- and animal-associated environments). This resistance gene flow scenario is not very applicable to antibiotic resistance caused by chromosomal mutation.
MIC may increase during treatment!

Change in MIC of antibiotics used in empiric antipseudomonal therapy (nosocomial pneumonia; intensive care units) towards the isolate identified before onset of therapy (D0) vs. the last isolate (DL) collected from the same patient and with clonal similarity with the first isolate. Differences were analyzed using both raw and log₂ transformed data and found significant by both non-parametric (Wilcoxon matched pair test) and parametric (two-tailed paired t-test) analysis.

Optimization may prevent emergence of resistance

Determining β-lactam exposure threshold to suppress resistance development in Gram-negative bacteria

Vincent H. Tam1*, Kai-Tai Chang1, Jian Zhou1, Kimberly R. Ledesma1, Kady Phe1, Song Gao1, Françoise Van Bambeke2, Ana María Sánchez-Díaz3, Laura Zamorano4, Antonio Oliver4 and Rafael Cantón3

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Simulation of serum concentration levels (hollow fibers model)
Optimization may prevent emergence of resistance

To prevent emergence of resistance, $C_{\text{min}}$ of β-lactams must stay $> 4 \times \text{MIC}$ (mean), which commands higher dosages...


Figure 2. Typical bacterial profiles for WT P. aeruginosa. Placebo control (a). Ceftazidime at 500 mg every 8 h ($C_{\text{min}}$/MIC = 2.9) (b). Ceftazidime at 3000 mg every 8 h ($C_{\text{min}}$/MIC = 7.7) (c). Data are shown as mean ± SD.

Figure 3. Drug exposures ($C_{\text{min}}$/MIC) stratified by outcomes. Each data point represents a hollow-fibre infection model experiment. The most significant threshold ($C_{\text{min}}$/MIC ≥ 3.8) is depicted by the horizontal broken line.
Appropriately dosed antibiotics may avoid resistance creep

*S. pneumoniae* susceptibility to moxifloxacin in Belgium

* Moxifloxacin was introduced in Belgium in 2001 and became the almost only fluoroquinolone used for RTI since 2004

From data of a national collection
- Non invasive respiratory tract infections
- Similar results in 2008 for a collection of *S. pneumoniae* from clinically-confirmed CAP (n=132)

- Surveys from the Belgian Scientific Institute for Public Health for *S. pneumoniae* from community isolates (n=156 in 1999 and 312 in 2014)
- Data available yearly for 1999 through 2014 at [http://www.iph.fgov.be](http://www.iph.fgov.be)

Vanhoof et al. 19th ECCMID, Helsinki, 2009
Ceyssens et al. 35th RICAI, Paris, 2015
Why no resistance of *S. pneumoniae* to moxifloxacin?

Clinical doses of moxifloxacin exceeded the fAUC/MIC resistance breakpoint against wild-type *S. pneumoniae*, whereas those of levofloxacin (500 and 750 mg) were associated with first- and second-step mutations.

Additionally, moxifloxacin breakpoints were significantly lower (*P* < 0.002) than those of gatifloxacin.

The order of resistance development determined from fAUC/MIC breakpoints was levofloxacin > moxifloxacin = gemifloxacin, which may be related to structural differences within the class.
What differentiates fluoroquinolones?

Results with *S. pneumoniae*

Would this cause less emergence of resistance?
Pharmacokinetics and “resistance” breakpoint vs. MIC

Levofloxacin: 500 mg 1X/day
- AUC [(mg/l)xh] = 47
- peak [mg/l] = 5
- \( \text{MIC}_{\text{max}} \approx 0.5 \)

Moxifloxacin: 400 mg 1X/day
- AUC [(mg/l)xh] = 48
- peak [mg/l] = 4.5
- \( \text{MIC}_{\text{max}} \approx 0.5 \)

Maximal MIC to avoid selection of resistance:
- AUC/MIC = 100
- peak/MIC = 10

% of strains

MIC data: EUCAST MIC distributions (wild type)
PK data: US and EU labelling (typical values)
The risk for resistance to fluoroquinolones … the MPC!

Time after administration

MPC: moxifloxacin vs levofloxacin

MPC: moxifloxacin

\[ \text{MPC}_{90} \]

\[ \text{MIC}_{90} \]

~10 x the median MIC (0.125 mg/L)

Levofloxacin

\[ \text{MPC}_{90} \]

\[ \text{MIC}_{90} \]

~10 x the median MIC (1 mg/L)

Plasma drug concentration (\(\mu g/ml\))

Time post-administration (hr)
What about the recommendations for CAP?

Recommendation:

- Aminopenicillin ± macrolide\[^a,b\]
- Aminopenicillin/β-lactamase inhibitor\[^a\] ± macrolide\[^b\]
- Non-antipseudomonal cephalosporin
- Cefotaxime or ceftriaxone ± macrolide\[^b\]
- Levofloxacin\[^a\]
- Moxifloxacin\[^a,c\]
- Penicillin G ± macrolide

\[^a\]Can be applied as sequential treatment using the same drug.
\[^b\]New macrolides preferred to erythromycin.
\[^c\]Within the fluoroquinolones, moxifloxacin has the highest antipneumococcal activity.

In patients at risk of GNEB, particularly strains with ESBL, but without risk (or after exclusion of) of \textit{P. aeruginosa}, ertapenem may be used.
Here are the questions …

When choosing an antibiotic, do we know

3. for Society
   – how to get "value for money"?
How do you score the cost of a treatment?

- **Cost ++**
  - Zone of interest for the supplier
- **Efficacy --**
  - Zone with no interest
  - Zone for the cost-minimizer addict
- **Cost --**
  - Zone of interest for the purchaser
- **Efficacy ++**
Scoring the cost of treatments

Costs: an example for vancomycin (always intravenous)

- **Medical costs**
  - ordering and acquiring the drug (generic)
  - storage in the hospital pharmacy
  - preparing the infusion (nurse's time and material)
  - infusion to the patient (twice daily) (nurse's time and material)
  - collecting and handling blood samples for monitoring (nurse's time)
  - laboratory serum level assay (cost and time)
  - maintaining the patient in the hospital for at least 10 days (daily cost)
  - managing nephrotoxicity (~ 5-10% of all patients)

- **Non-medical costs**
  - patient's absence from home for at least 10 days (need of external help)
  - patient's absence from work for at least 10 days (productivity loss)

The drug acquisition price of the generic vancomycin is only a small part of the total treatment cost !!!
Switching to a short course with an oral form with similar efficacy?

- **Medical costs**
  - ordering and acquiring the drug (branded drug)
  - storage in the hospital pharmacy
  - preparing the infusion (nurse's time and material)
  - infusion to the patient (twice daily) (nurse's time and material)
  - collecting and handling blood samples for monitoring (nurse's time)
  - laboratory serum level assay (cost and time)
  - maintaining the patient in the hospital for at least 10 days (daily cost)
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- **Non-medical costs**
  - patient's absence from home for at least 10 days (need of external help)
  - patient's absence from work for at least 10 days (productivity loss)

The treatment cost can be substantially reduced with an oral drug…

offsetting the increased drug acquisition cost (branded)
What you wish to avoid …

A short personal view…

- insusceptibility
- emerging resistance
- toxicity
- cost
and what you may be looking for …

appropriate spectrum

insusceptibility

emerging resistance

toxicity

simple efficient dosing

fast oral switch and shorter treatments

reduced side effects

cost

A short personal view…
Last words: strive for quality *

Many antibiotics are available as generics!

For the patient
- lower cost
- availability

For Society
- Social Security savings

For the patient
- API purity ?
- excipients ?
- PK equivalence ?
- PD equivalence ?
- fake drugs !

For Society
- cost of analysis !
- innovation loss ?

* based on previous presentations: see http://www.facm.ucl.ac.be/facm-conferences.htm

API: Active Pharmaceutical Ingredient
PK: Pharmacokinetic
PD: Pharmacodynamic
It's all a problem of balance and compass