Can TDM-guided therapy reduce antimicrobial resistance?

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Articles published on beta-lactam TDM

Search = “beta-lactam therapeutic drug monitoring”
Can TDM-guided therapy reduce resistance?

1. TDM-guided therapy is many things, and “resistance” is diverse

2. Antibiotic exposure and development of resistance

3. What is the evidence that TDM guidance could reduce resistance?
   – Imipenem and *Pseudomonas*
Part 1: What is TDM-guided therapy and what could it have to do with resistance?
TDM guidance is just a means to an end

- Therapeutic drug monitoring (TDM) of antibiotics is not the intervention; it’s just a facilitator

- TDM of some antibiotics is primarily to protect against toxicity (e.g., aminoglycosides)
TDM guidance is just a means to an end

• TDM of **glycopeptides** and **beta-lactam antibiotics** is at least partially to protect against subtherapeutic levels
  – TDM for these drugs would lead to more robust dosing
  – The people who like TDM guidance also like **shorter durations**
    • **GO HARD [AND] GO HOME**
    • **HIT HARD AND HIT FAST**
  – The people who like TDM guidance also like **continuous infusions**
  – So, as such, could TDM guidance reduce resistance?
The three pharmacokinetic indices
Time-dependent antibiotics: what actually happens in sick patients

Time-dependent antibiotics: what actually happens in sick patients

Concentration of antibiotics

Time

TDM would try to avoid this: either by guiding higher doses or continuous infusions

MIC

MIC

MIC

MIC
Time-dependent antibiotics: what actually happens in sick patients

- Higher dosing
- Continuous infusion (with loading dose)
Part 2: Antibiotic exposure & the development of resistant strains
What happens when antibiotic levels are below the MIC

CAVEAT: one MIC is a very imperfect measure!
What happens when antibiotic levels are below the MIC

- More and more *in vitro* evidence that sub-MIC antibiotic concentrations select for resistance

- Emergence of resistant *Salmonella typhimurium* with very low-level streptomycin concentrations

- *E. coli*: Very low concentrations select for “selfish” resistance (efflux pumps) and higher concentrations for “cooperative” resistance (beta-lactamase)

Gullberg et al., PLoS Pathogens 2011; 7:e1002158; Bottery et al., Antimicrob Ag Chemother 2016; 60 (4)
The good news: these studies are \textit{in vitro}

- There are fitness costs to these mutations
  - In the clinic, these mutant strains do not always dominate
  - Once the selection pressure is removed, some reversion to wild-type predominance

- The example of imipenem...
Imipenem and the intestinal microbiota

• Imipenem
  – Wide-spectrum, intravenous-only, small molecule that
    • Rapidly distributes to the periphery
    • Is renally cleared
    • *Does not appreciably transit the gut*
Impact of Imipenem/Cilastatin Therapy on Normal Fecal Flora

The impact of parenteral imipenem/cilastatin therapy on the bowel flora of six patients was evaluated. Stool samples were collected before and during therapy and qualitative and quantitative bacteriologic studies were performed. Imipenem had no effect on total microorganism counts. Two patients acquired Candida albicans during therapy, and three patients acquired Proteus species. Pseudomonas species in one patient acquired resistance. Imipenem appears to have a relatively modest effect on the bowel flora and apparently does not readily induce resistance in the resident flora as compared with other agents.

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Imipenem and the intestinal microbiota

Unexpected persistence of extended-spectrum β-lactamase-producing Enterobacteriaceae in the faecal microbiota of hospitalised patients treated with imipenem

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Grall et al., Int J Antimicrob Ag 2017; 50: 81-87

Culture & metagenomics
Imipenem and the intestinal microbiota

“The most important result of this study is that ESBL-E did not disappear during imipenem treatment, even though they were susceptible with MICs similar to those of non-ESBL-E. Carriage rates remained very high during treatment, suggesting intestinal concentrations of imipenem below the MIC of these strains.

“Another striking result is that the patients’ microbiota changed minimally on imipenem treatment.”
In contrast, ceftriaxone...

- Ceftriaxone
  - Larger molecule, also IV only, but:
  - 35 – 45% of its excretion is biliary!
Ceftriaxone and intestinal exposure

Massive Increase, Spread, and Exchange of Extended Spectrum β-Lactamase–Encoding Genes Among Intestinal Enterobacteriaceae in Hospitalized Children With Severe Acute Malnutrition in Niger

Paul-Louis Woerther,² Cécile Angebault,¹ Hervé Jacquier,¹⁵ Henri–Charles Hugede,³ Ann–Carole Janssens,⁴ Sani Sayadi,⁴ Assiya El Mniaï,¹ Laurence Armand–Lefèvre,¹² Etienne Ruppé,¹² François Barbier,¹² Laurent Raskine,⁵ Anne-Laure Page,⁴ Nathalie de Rokemoire,⁴ and Antoine Andremont¹²

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Ceftriaxone and intestinal exposure

• 55 malnourished children enrolled

• All treated with antibiotics (80% with ceftriaxone)

• Of patients who were \( bla_{\text{CTX-M}} \) negative at admission, 94% became positive by discharge (median 8 days later)
Ceftriaxone and intestinal exposure

Amplification of Antimicrobial Resistance in Gut Flora of Patients Treated with Ceftriaxone

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Meletiadis et al., Antimicrob Ag Chemother 2017; 61 (11)
Ceftriaxone and intestinal exposure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. of patients with amplification$^a$</th>
<th>% of patients with amplification$^a$</th>
<th>Fisher exact test P value</th>
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<tbody>
<tr>
<td>Treatment duration</td>
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<td></td>
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<tr>
<td>$&gt;$14 days</td>
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<td>69</td>
<td>0.0019</td>
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<tr>
<td>$\leq$14 days</td>
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<tr>
<td>$fC_{max} \geq 29.3^{b}$</td>
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<td>63</td>
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<td>$fC_{max} &lt; 29.3^{b}$</td>
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<tr>
<td>$fAUC_{0-24} \geq 221.9^{b}$</td>
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<tr>
<td>$fAUC_{0-24} &lt; 221.9^{b}$</td>
<td>4</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

$^a$“Yes” for amplification was assigned to patients with a maximum $bla_{CTX-M}/16S$ rRNA ratio that was $>20\%$ higher than the initial $bla_{CTX-M}/16S$ rRNA ratio.

$^b$These cutoff values were derived from CART analysis for patients treated with ceftriaxone for $\leq$14 days. Steady-state $fC_{max}$ and $fAUC_{0-24}$ were estimated using the population pharmacokinetic model of ceftriaxone.
Development of resistance depends on exposure

- So TDM-guided **imipenem** therapy may do little to decrease the emergence of *Enterobacteriaceae* resistance

- But there may be a role for TDM guidance of other antibiotics to reduce resistance in the intestinal microbiota
Part 3: What is the evidence that TDM guidance could reduce resistance?
Back to imipenem

• “So TDM-guided imipenem therapy would likely do little to decrease the emergence of *Enterobacteriaceae* resistance...”

• But what about organisms that are *not* primarily in the gut?
**Pseudomonas aeruginosa**

- Thrives in moist, aerobic environments
  - Found most commonly in the respiratory and urinary tracts

- Several mechanisms of antibiotic resistance
  - Efflux pumps
  - Modification of antibiotics (e.g., beta-lactamases) or of antibiotic targets (e.g., topoisomerase)
  - Modification of porins (OprD loss \(\rightarrow\) imipenem resistance)

Pai et al., *Antimicrob Ag Chemother* 2001; 45 (2) 480–484
The evidence: can TDM guidance decrease resistance?

• *Pseudomonas aeruginosa* resistance to carbapenem antibiotics is on the rise

• We examined the transition from imipenem susceptibility to resistance among *P. aeruginosa* strains detected in hospitalised patients
Imipenem concentrations & emergence of *Pseudomonas* resistance

- Single-center, retrospective cohort

- Adult patients hospitalized at Geneva University Hospital:
  - Undergoing any imipenem TDM
  - Having at least one *Pseudomonas* + clinical culture
Imipenem concentrations & emergence of *Pseudomonas* resistance

• Outcomes:
  – Incidence of emergence of an imipenem-resistant *Pseudomonas aeruginosa* (IRP) strain
  – Minimum plasma concentrations of patients with and without IRP
  – Time between initiation of imipenem and emergence of resistance
Imipenem concentrations & emergence of *Pseudomonas* resistance

- 67 patients had imipenem TDM and a *Pseudomonas* + clinical isolate
  - Mean age 63 years (SD ±16)
  - 49 (73%) were men
  - 32 (48%) required intensive care
  - 34 (51%) were surgical patients
- 45 (67%) had an imipenem-susceptible *Pseudomonas* (ISP) strain to start
Imipenem concentrations & emergence of \textit{Pseudomonas} resistance

• In 16/45 (36\%), an imipenem-\textbf{resistant} strain emerged during or shortly after imipenem therapy

• Median time between the susceptible strain and the resistant strain was \textbf{32 days} (IQR 16 – 44)
The duration of antibiotic therapy matters – a lot

- Patients with emergence of imipenem resistance had significantly more days of imipenem

- Median 11 days (IQR 5-20) vs 5 (IQR 3-7), p = .044

- But most clinicians won’t see the “switch” to resistant *Pseudomonas* (median time = 32 days)

*Probability of being colonized or infected with an imipenem-resistant *Pseudomonas* strain as a function of duration of imipenem therapy.*
“Subtherapeutic” levels also matter

- Patients with emergence of imipenem resistance trended toward lower plasma levels of imipenem

- Mean minimum concentration 3.97 mg/l (SD ±3.85) vs. 5.31 mg/l (SD ±5.36)

- Early TDM and dose adjustment might have prevented emergence of resistant strains
Conclusions

• TDM guidance is diverse in its goals and effects
• There is as yet little clinical evidence for a direct impact on resistance emergence
• Its effects would be indirect:
  – Duration:
    • Shorten overall durations & thus selection pressure
  – Higher doses:
    • Reduce subtherapeutic levels (and thus resistant-strain escape)
  – Continuous infusion:
    • Reduce inter-dose troughs (and thus resistant-strain escape)
Thank you!