Vancomycin and Colistin: pharmacokinetics/pharmacodynamics with comments about reasonable uses

Paul M. Tulkens, MD, PhD *

Cellular and Molecular Pharmacology & Centre for Clinical Pharmacy
Louvain Drug Research Institute
Université catholique de Louvain, Brussels, Belgium

http://www.facm.ucl.ac.be

With the support of Wallonie-Bruxelles-International
Contents of the presentation

• Vancomycin
  – origin and why has it been long neglected and then widely used
  – current breakpoints and PK-PD-based dosing recommendations
  – continuous infusion of vancomycin

• Colistin
  – origin and why has it neglected until recently but is now a last resource drug
  – antimicrobial activity, pharmacokinetics/pharmacodynamics
  – synergy
  – what can we expect?
Vancomycin
Vancomycin History

- first isolated in 1953 by Edmund Kornfeld at Eli Lilly & Co.\(^1\) from a soil sample collected in Borneo and produced by *Amycolatopsis orientalis*.

- active against Gram-positive organisms only (size !) and most notably against penicillin-resistant *S. aureus* and *Enterococci* (naturally poorly susceptible to penicillins) by binding to the D-Ala-D-Ala motif in nascent peptidoglycan

- remained for long a rarely used antibiotic because
  - poor oral bioavailability (must be given intravenously for most infections)
  - development of β-lactamase-resistant semi-synthetic penicillins (methicillin and derivatives) that solved the problem of β-lactamase-producing *S. aureus*
  - originally impure forms ("Mississippi mud") causing oto- and nphiototoxicity

- regained increasingly large usage from the mid-80's because of the widespread emergence of MRSA (methicillin-resistant *S. aureus*) that are resistant to all conventional β-lactams (incl. carbapenems)

\(^1\) first company to mass-produce penicillin in the 1940's
Vancomycin: spectrum and resistance

• Broad activity against Gram-positive microorganisms.
  – Staphylococci (\textit{S. aureus, S. epidermidis, S. saprophyticus, S. haemolyticus, S. hominis, S. warneri,} and other coagulase-negative staphylococci)
  – most \textit{Enterococcus faecalis} (variable for \textit{E. faecium})
  – \textit{Streptococcus pneumoniae} and \textit{S. pyogenes}; \textit{S. agalactiae}, group C and group G streptococci,
  – \textit{Listeria monocytogenes}
  – \textit{Bacillus anthracis, B. cereus,} and other \textit{Bacillus} spp.,
  – \textit{Corynebacterium} spp.
  – anaerobes: \textit{Peptostreptococcus} spp., \textit{Actinomyces} spp., \textit{Propionibacterium} spp., \textit{Clostridium} spp. (including \textit{Clostridium difficile} (not \textit{Clostridium ramosum})

• \textit{Lactobacillus} spp., intrinsically vancomycin resistant.

• Clinically important resistance:
  – \textit{S. aureus}: thickening of the cell wall (VISA): MICs increase from 2 to 8-16 mg/L (heteroresistance)
  – \textit{Enterococci} (VRE): acquisition of gene(s) causing a change from D-Ala-D-Ala to D-Ala-D-Lac or D-Ala-D-Ser (usually high MICs)
**Vancomycin and MIC (EUCAST distributions)**

**Vancomycin / Staphylococcus aureus**
EUCAST MIC Distribution - Reference Database 2011-10-08

MIC distributions include collected data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance.

**S. aureus**
(no diff. between MSSA and MRSA)

Limit of the wild type population and EUCAST breakpoint (> is resistant)

VISA

MIC:
Epidemiological cut-off: WT ≤ 2 mg/L

87764 observations (33 data sources)
Clinical breakpoints: S ≤ 2 mg/L, R > 2 mg/L

35.02 ± 4.01
Vancomycin and Dosage

• Original proposals
  – patients with normal renal function \(^1\):
    • 15 mg/kg every 12 h
      (usually rounded up to 1 g / 12 h but … do you always weight 66.6 kg ?)
    • dilute in 100 to 250 mL of 5% glucose or 0.9% NaCl (\(\leq 5\) mg/mL)
    • infuse at 15 mg/min max. (1 g in 60 min)
    • use antihistaminic agent to minimize the incidence of red-man (or red-neck) syndrome
  – patients with renal insufficiency
    • fixed interval (12h):
      Daily dose (mg/kg) = 15.4 x CrCl (mL/min) \(^2\)
    • variable interval:
      Interval = 12 h x (0.86 / [0.689 x Cr Cl + 3.66]) \(^3\)

---

\(^1\) Murray & Nannini, Mandell's Principles and Practice of Infectious Diseases, 7th Ed. Chap. 31
Vancomycin

- **Original proposals**
  - **patients with normal renal function**
    - 15 mg/kg every 12 h (usually rounded up)
    - dilute in 100 to 250 mL of 5% glucose or 0.9% NaCl (≤ 5 mg/mL)
    - infuse at 15 mg/min max.
    - use antihistaminic agent to minimize the incidence of red-man (or red-neck) syndrome
  - **patients with renal insufficiency**
    - fixed interval (12h):
      \[
      \text{Daily dose (mg/kg)} = 15.4 \times \text{CrCl (mL/min)}
      \]
    - variable interval:
      \[
      \text{Interval} = 12 \text{h} \times \left(\frac{0.86}{0.689 \times \text{Cr Cl} + 3.66}\right)
      \]

1. Murray & Nannini, Mandell's Principles and Practice of Infectious Diseases, 7th Ed. Chap. 31
Vancomycin

- Original proposals
  - patients with normal renal function
    - 15 mg/kg every 12 hours (usually rounded up to 1 g / 12 h but ... do you always weight 66.6 kg ?)
    - dilute in 100 to 250 mL of 5% glucose or 0.9% NaCl (≤ 5 mg/mL)
    - infuse at 15 mg/min max.
    - use antihistaminic agent to minimize the incidence of red-man (or red-neck) syndrome
  - patients with renal insufficiency
    - fixed interval (12h):
      - Daily dose (mg/kg) = 15.4 x CrCl (mL/min)
    - variable interval:
      - Interval = 12 h x (0.86 / [0.689 x Cr Cl + 3.66])

FIG. 4. Dosage nomogram for vancomycin in patients with various degrees of renal function. The nomogram is not valid for peritoneal dialysis patients.

1 Murray & Nannini, Mandell’s Principles and Practice of Infectious Diseases, 7th Ed. Chap. 31
Vancomycin and Pharmacodynamics

• Questions:
  – do the "recommended" dosages allow you to obtain an optimized effect?
  – in other words, are the concentrations large enough to fight bacteria that are reported as "susceptible" in microbiology testing (i.e. up to an MIC = 2 mg/L)
  – which concentration do we need to take care of? ($C_{\text{max}}$, $C_{\text{trough}}$, other?)

![Pharmacokinetics](chart1.png)

![Pharmacodynamics](chart2.png)
Vancomycin and Pharmacodynamics

- Vancomycin is an AUC$_{24h}$-MIC dependent antibiotic
Vancomycin – $\text{AUC}_{24h}$ and efficacy

1. In vitro model mimicking the human PK

Vancomycin $AUC_{24h}$ in patients

<table>
<thead>
<tr>
<th>parameter</th>
<th>value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage (mg/kg)</td>
<td>15</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (mg/L)</td>
<td>20-50</td>
</tr>
<tr>
<td>$C_{\text{min}}$ (mg/L) at 12h</td>
<td>5-12</td>
</tr>
<tr>
<td>$AUC_{24h}$ (mg.h/L)</td>
<td>162-783</td>
</tr>
<tr>
<td>(%) prot. binding</td>
<td>55</td>
</tr>
<tr>
<td>$T \frac{1}{2}$ (h) post-distrib.</td>
<td>3-9</td>
</tr>
</tbody>
</table>

Is this variability important?

The answer is: What do YOU need?

modelling by P. Tulkens
Vancomycin – AUC$_{24h}$ and efficacy

1. In vitro model mimicking the human PK

But this is your range! (160-783)

You need at least 400!

Vancomycin – $\text{AUC}_{24h}$ and efficacy

2. In vivo (clinical study)

Pharmacodynamics of Vancomycin and Other Antimicrobials in Patients with *Staphylococcus aureus* Lower Respiratory Tract Infections

*Pamela A. Moise-Broder,¹ Alan Forrest,¹,² Mary C. Birmingham¹ and Jerome J. Schentag¹,²*

1 CPL Associates, LLC, Amherst, New York, USA  
2 University at Buffalo School of Pharmacy and Pharmaceutical Sciences, Buffalo, New York, USA
Vancomycin – $\text{AUC}_{24h}$ and efficacy


Fig. 3. Relationship between clinical and bacteriological responses and two pharmacodynamic indices: $\text{AUC}_{24h}/\text{MIC}$ and $\%T>\text{MIC}$. Each point represents data for one patient. (a) Mean ± SD (median) vancomycin $\text{AUC}_{24h}/\text{MIC}$ values were 655 ± 374 (535) in patients whose infection outcomes were classified as vancomycin treatment successes (cure) and 378 ± 225 (306) in those whose infection outcomes were classified as treatment failures ($p = 0.0029$). (b) Vancomycin serum concentrations were above the MIC 100% of the time in all clinical treatment successes and failures. (c) $\text{AUC}_{24h}/\text{MIC}$ values for vancomycin-treated patients were 951 ± 1432 (593) when $S. \text{aureus}$ was eradicated compared with 405 ± 224 (312) when the organism persisted ($p = 0.0046$). (d) $\%T>\text{MIC}$ was also 100% in all patients whose $S. \text{aureus}$ was eradicated and in all patients who remained culture-positive. $\text{AUC}_{24h}/\text{MIC} = \text{steady-state 24-hour area under the concentration-time curve divided by the minimum inhibitory concentration}; \%T>\text{MIC} = \text{percentage of time that serum concentrations exceed the MIC.}$
Vancomycin – $\text{AUC}_{24h}$ and efficacy

2. In vivo (clinical study) – clinical success

Table IV. Odds ratios for clinical success

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin $\text{AUC}_{24h}/\text{MIC}$ value $\geq 350$</td>
<td>7.19</td>
<td>1.91, 27.3</td>
<td>0.0036</td>
</tr>
<tr>
<td>MSSA as pathogen</td>
<td>3.88</td>
<td>1.10, 14.8</td>
<td>0.0359</td>
</tr>
<tr>
<td>Single lobe involvement</td>
<td>6.32</td>
<td>1.56, 25.6</td>
<td>0.0099</td>
</tr>
<tr>
<td>Baseline serum albumin (per 1 g/dL)</td>
<td>3.73</td>
<td>1.09, 12.8</td>
<td>0.0364</td>
</tr>
<tr>
<td>Baseline $\text{CL}_{\text{CR}}$ (per 1 mL/min)</td>
<td>1.04</td>
<td>1.01, 1.07</td>
<td>0.0154</td>
</tr>
</tbody>
</table>

$\text{AUC}_{24h}/\text{MIC} =$ steady-state 24-hour area under the concentration-time curve divided by the minimum inhibitory concentration; $\text{CL}_{\text{CR}} =$ creatinine clearance; MSSA = methicillin-susceptible Staphylococcus aureus.

Vancomycin – AUC$_{24h}$ and efficacy

![Graph showing the relationship between AUC$_{24h}$/MIC and culture-positive patients over treatment days.]

**Fig. 4.** Time (days of therapy) to bacterial eradication vs vancomycin AUC$_{24h}$/MIC <400 and AUC$_{24h}$/MIC ≥400 illustrated by a Kaplan-Meier survival plot of day of therapy vs the percentage of patients remaining culture-positive on that day. The two AUC$_{24h}$/MIC groups differed significantly ($p = 0.0402$). AUC$_{24h}$/MIC = steady-state 24-hour area under the concentration-time curve divided by the minimum inhibitory concentration.
How to calculate the AUC$_{24h}$?

AUC vs. dose for diff. CL$_{cr}$

$$AUC_{24h} = \frac{D}{[(CL_{CR} \times 0.79) + 15.4] \times 0.06}$$


doses if the MIC = 1 mg/L
How to calculate the $AUC_{24h}$?

$AUC_{24h} / \text{MIC}$ vs. dose for different MIC and $CL_{cr}=90 \text{ mL/min}$

If the MIC reaches 2, you may have problems

How to calculate the AUC$_{24h}$?

AUC$_{24h}$ / MIC vs. dose for diff. MIC and CL$_{cr}$=60 mL/min

A low creatinine clearance helps!

What if you do not know your MIC?

• assume a MIC of 2 mg/L (breakpoint) and check at the level of the population …

• monitor serum concentrations with
  – peak and trough (best to calculate AUC, but …see next slide)
  – through only (and ensure values of 15-20 mg/L !)
    ➔ this will (probably) ensure an AUC/MIC ~ 400

• use a loading dose (25-30 mg/kg)
  – obtain rapidly the peak and the necessary AUC/MIC

• organisms with an MIC ≥ 2 mg/L will be difficult …

Peak and through or through only?

Against through only:
You do not distinguish between abnormal clearance and abnormal $V_d$

$C_{\text{max}} = 30 \text{ mg/L}$  
$t_{1/2} = 3 - 6 - 12 \text{ h}$

$C_{\text{max}} = 15 - 25 - 35 \text{ mg/L}$  
$t_{1/2} = 9 \text{ h}$

Reminder:  
$$C_{\text{max}} = \frac{\text{Dose}}{V_d} \quad \text{and} \quad t_{1/2} = 0.693 \times \frac{V_d}{Cl}$$
Peak and through or through only?

For through only:
Correct peaks are not easy to get...

43 % errors in sampling time
Does "one size" fits all?

**intensive care**: variation in extracellular fluid and renal clearance

---

Does one size fits all?

- **dialysis**: removal of the drug (high flux membranes)
  Caution: vancomycin dialysis is poor ...

Dose adjusted according to:

- trough level before intermittent dialysis
- plasma level at any time (continuous dialysis)
- 6 hours after the end of dialysis

Vancomycin and elderly patients

- age: elderly patients: altered tissue distribution and renal function
  - $V_d \uparrow$
  - clearance $\downarrow$

\[
dose (\text{mg/kg/24 h}) = (0.227 \times \text{Cl}_{\text{CR}}) + 5.67
\]

adapt the dose and the interval as a function of Cl\text{CR}
but this is where peak and trough may be important ...

Dosing intervals of vancomycin as a function of Cl\text{CR}

<table>
<thead>
<tr>
<th>Cl\text{CR} (ml/min per 70 kg)</th>
<th>Dosage interval (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$&gt;65$</td>
<td>8</td>
</tr>
<tr>
<td>40–65</td>
<td>12</td>
</tr>
<tr>
<td>20–39</td>
<td>24</td>
</tr>
<tr>
<td>10–19</td>
<td>48</td>
</tr>
</tbody>
</table>

Rodvold et al. (1988) AAC 32:848-52
Two ways to get better results...

1. Use of more sophisticated algorithms for dose adjustment
   – based on population pharmacokinetic models

*Journal of Antimicrobial Chemotherapy* (2009) 63, 1050–1057
doi:10.1093/jac/dkp085
Advance Access publication 19 March 2009

Development and evaluation of vancomycin dosage guidelines
designed to achieve new target concentrations

A. H. Thomson¹,²*, C. E. Staatz¹,²†, C. M. Tobin³, M. Gall⁴ and A. M. Lovering³

¹Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, Scotland, UK; ²Pharmacy Department, Western Infirmary, NHS Greater Glasgow and Clyde, Glasgow, Scotland, UK; ³Bristol Centre for Antimicrobial Research and Evaluation, Department of Microbiology, Southmead Hospital, Bristol, UK; ⁴Pharmacy Department, Southern General Hospital, NHS Greater Glasgow and Clyde, Glasgow, Scotland, UK
Two ways to get better results…

1. Use of more sophisticated algorithms for dose adjustment
   – based on population pharmacokinetic models

<table>
<thead>
<tr>
<th>Table 4. New vancomycin loading dose guidelines based on the final population model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>Loading dose (mg)</td>
</tr>
</tbody>
</table>
Two ways to get better results…

1. Use of more sophisticated algorithms for dose adjustment
   – based on population pharmacokinetic models

| Table 4. New vancomycin loading dose guidelines based on the final population model |
|-----------------------------------------|-----------------|-----------------|
| CL_{CR} (mL/min) | Dose (mg) | Interval (h) |
| <20 | 500 | 48 |
| 20–29 | 500 | 24 |
| 30–39 | 750 | 24 |
| 40–54 | 500 | 12 |
| 55–74 | 750 | 12 |
| 75–89 | 1000 | 12 |
| 90–110 | 1250 | 12 |
| >110 | 1500 | 12 |

| Table 5. New vancomycin maintenance dose guidelines based on the final population model |
|-----------------------------------------|-----------------|-----------------|
| CL_{CR} (mL/min) | Dose (mg) | Interval (h) |
| <20 | 500 | 48 |
| 20–29 | 500 | 24 |
| 30–39 | 750 | 24 |
| 40–54 | 500 | 12 |
| 55–74 | 750 | 12 |
| 75–89 | 1000 | 12 |
| 90–110 | 1250 | 12 |
| >110 | 1500 | 12 |

CL_{CR} estimate based on the Cockcroft–Gault equation. Higher troughs and lower peaks would be achieved by splitting the total daily dose into three or four equal portions, for example, 1000 mg 8 hourly instead of 1500 mg 12 hourly or 500 mg 6 hourly instead of 1000 mg 12 hourly.
Two ways to get better results...

1. Use of more sophisticated algorithms for dose adjustment
   – based on population pharmacokinetic models

| Table 4. New vancomycin loading dose guidelines based on the final population model |
|---------------------------------|----------------|----------------|
| Loading dose (mg)               | 1000           |                |
| <60                             |                |                |

| Table 5. New vancomycin maintenance dose guidelines based on the final population model |
|---------------------------------|----------------|----------------|
| $\text{CL}_{\text{CR}}$ (mL/min)| Dose (mg)      | Interval (h)   |
| <20                             | 500            | 48             |
| 20–29                           | 500            | 24             |
| 30–39                           | 750            | 24             |
| 40–54                           | 500            | 12             |

A preliminary evaluation of the guidelines indicated that 55% of trough concentrations should be within 10–15 mg/L and 71% within 10–20 mg/L over the first 4 days of therapy and that satisfactory $\text{AUC}_{24}/\text{MIC}$ ratios should be achieved in 87% of patients, assuming an MIC of 1 mg/L.

However, wide variability in the handling of vancomycin between and within patients indicates that monitoring of concentrations is required to ensure that dosage regimens are appropriate for individual patients.
Two ways to get better results…

1. Use of more sophisticated algorithms for dose adjustment
   – based on population pharmacokinetic models
   – based on specific population analysis and Monte-Carlo simulations
Two ways to get better results…

1. Use of more sophisticated algorithms for dose adjustment
   – based on population pharmacokinetic models
   – based on specific population analysis and Monte-Carlo simulations

Figure 3
Cumulative fraction of response against *S. aureus* for several vancomycin daily doses in different ICU population subgroups: (A) For susceptible *S. aureus*; (B) For VISA strains. $\text{CL}_{\text{Cr}}$: Creatinine clearance measured in the ICU setting (ml min$^{-1}$). $\text{CL}_{\text{Cr}} \leq 60$ ml min$^{-1}$ and Age $> 65$ years (—); $\text{CL}_{\text{Cr}} \leq 60$ ml min$^{-1}$ and Age $\leq 65$ years (– –); $\text{CL}_{\text{Cr}} > 60$ ml min$^{-1}$ and Age $> 65$ years (—); $\text{CL}_{\text{Cr}} > 60$ ml min$^{-1}$ and Age $\leq 65$ years (– –)
Two ways to get better results…

1. Use of more sophisticated algorithms for dose adjustment
   – based on population pharmacokinetic models
   – based on specific population analysis and Monte-Carlo simulations

Thus, for vancomycin-susceptible *S. aureus*, an initial 2000 mg day$^{-1}$ dose of vancomycin must only be used for patients with CLCr $<$ 60 ml min$^{-1}$. For better kidney function, the corresponding doses must be increased to 3000 and 3500 mg day$^{-1}$ for aged ($>$65 years) or adult patients, respectively.
Two ways to get better results…

2. Use continuous infusion

- makes monitoring easier (sampling at any time)
- makes calculation of AUC very easy ($C_{ss} \times 24$)

<table>
<thead>
<tr>
<th>number of studies</th>
<th>indications</th>
<th>conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>controlled studies with clinical endpoint</td>
<td>VAP, Gram + osteomyelitis, other serious infections (ICU, open heart surgery)</td>
<td>equivalence (6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>superiority (3)</td>
</tr>
<tr>
<td>9 a</td>
<td>Wysocki 2001; Rello 2005; Hutschala 2009; James 1996; Wysocki 1995; Kitzis 2006; Vuangnat 2004; Boffi 2004; Di Filippo 1998,</td>
<td></td>
</tr>
</tbody>
</table>
A typical example (from France)

Continuous versus Intermittent Infusion of Vancomycin in Severe Staphylococcal Infections: Prospective Multicenter Randomized Study

MARC WYSOCKI,1* FREDERIQUE DELATOUR,2 FRANÇOIS FAURISSON,2 ALAIN RAUSS, YVES PEAN,4 BENOIT MISSET,3 FRANK THOMAS,6 JEAN-FRANÇOIS TIMSIT,7 THOMAS SIMILOWSKI,8 HERVE MENTEC,9 LAURENCE MIER,10 DIDIER DREYFUSS,10
AND THE STUDY GROUP†

Medico-Surgical Intensive Care Unit¹ and Microbiology,² Institut Mutualiste Montsouris, Medico-Surgical Intensive Care Unit, Hôpital Saint-Joseph,³ Medico-Surgical Intensive Care Unit, Hôpital de la Pitié-Salpêtrière, ⁴ Paris, Medico-Surgical Intensive Care Unit, Hôpital V. Dupouy, Argenteuil,⁵ and Medical Intensive Care Unit, Hôpital Louis Mourier, Colombes,⁶ France

Received 28 June 2000/Returned for modification 2 January 2001/Accepted 5 June 2001

AAC 45:2460-2467, 2001

- 119 critically-ill patients with multi-resistant organisms (bacteriaemia, 35%; pneumonia, 45%).
- Microbiologic and clinical outcomes
- Evaluation of safety, pharmacokinetic parameters, ease of dose adjustment, and cost
  - clinical outcomes and safety: equivalent
  - target concentrations (20-25 mg/L – AUC = 480 - 600) obtained more rapidly
  - less samples needed for surveillance of blood levels
  - less variability in AUC₂₄ₙ
  - costs: 23% lower!
Continuous infusion in daily practice…

- **loading dose**

\[ C_t = \frac{\text{Dose}}{V_d} \]

\[ \text{Dose} = C_t \times V_d \]

* The "steady-state" distribution volume (Vdss) of vancomycin varies between 0.39 and 0.97 L/kg

Continuous infusion in daily practice…

• maintenance dose: \( K_o = C_{ss} \times 0.65 \times Cl_{CR} \)

\( \Rightarrow \) Ko = rate of infusion (mg/min

\( \Rightarrow \) Css (mg/L) serum target concentration at steady state

\( \Rightarrow \) ClCR = calculated creatinine clearance (in L/min, based on Cockroft and Gault formula [16])

\( \Rightarrow \) 0.65: correction factor for prediction of vancomycin clearance from calculated creatinine clearance
Continuous infusion in daily practice...

- Maintenance dose: \( K_o = C_{ss} \times 0.65 \times Cl_{CR} \)

Once a bath is at the desired level (i.e., after the loading dose), maintaining this level does not depend upon its volume but on the ratio of tap and drain flows (which must be equal: in = out...).
A few results

concentratie van vancomycine
in functie van de tijd
in patiënten behandeld met continu infuus

monitoring remains important

variabiliteit VAN concentraties tijdens continu infuus
(voorbeelden van typische patiënten)

Ampe et al., in preparation

12-10-2011 WBI - HUP cooperation - Viet Duc Hospital, Hanoi, Vietnam
AUC / MIC distributions ... and MICs

AUC$_{24h}$/MIC distributie

- MIC 2.5-3
- MIC 1.5-2
- MIC $\leq$ 1

low "target attainment" in patients with organisms with MIC $\geq$ 1.5 mg/L

Ampe et al., in preparation
AUC / MIC and success / failures

relation between $AUC_{24h} / MIC$ (E-Test) and clinical efficacy in vancomycin monotherapy (n=19)

Ampe et al., in preparation
Vancomycin: conclusions

1. an old drug put back into service
2. will work for organisms with an MIC up to 2 mg/L
3. but you must
   • use a loading dose
   • optimize the maintenance dose
   • if possible, monitor blood levels AND compare with the MIC
4. use combined therapy for organisms with MIC > 2 mg/L
5. do not forget to detect heteroresistance…
Colistin

or
Colistin

- A cyclic **amphipathic polycationic peptide** with a short aliphatic side chain
- which **interacts with the lipopolysaccharide (LPS)** of the outer membrane of Gram-negative bacteria, triggering a "self-promoted uptake" process
- and **displaces Ca^{++} and Mg^{++}**, which further destabilizes microbial outer membranes and helps conferring more specificity towards procaryotic cells
Colistin History

- Isolated in Japan in 1949 from *Bacillus polymyxa* var. *colistinus* and identified as *polymyxin E* (discovered in 1947 among polymyxins A to E).

- Differs from *polymyxin B* by only one aminoacid (D-Phe replaced by D-Leu)

- Supplied as the
  - methylsulfonate derivative (often called methane sulfonate and also known as *colistimethate sodium*), which is a prodrug that gets spontaneously hydrolyzed into colistin
  - sulfate (*colistine sulfate*) which is more toxic and should no longer be used in the clinics.
Colistin: mg and units …

• Colistin: $10^6$ units are
  – Colistin base: 33.3 mg
  – Colistin sulfate: 50 mg
  – Colistin methane sulfonate (colistimethate): 80 mg

• Polymyxin B: $10^6$ units are
  – Polymyxin base: 100 mg
  – Polymyxin sulfate: 119 mg (but often = 100 mg …)

The true content of commercial preparations and the balance between the E1 and E2 components may vary
Colistin Microbiology
as defined in the late 1960’s

• About 10 x more active against Gram-negative than Gram-positive bacteria
  – inactive against *Burkholderia cepacia*, *Serratia*, *Proteus*, *Bacteroides fragilis* … and most Gram-negative cocci [inherent resistance];
  – synergism with sulfonamides, rifampin (later: beta-lactams, fluroquinolones)

• Bactericidal

• Marked inoculum effect

• Loss of susceptibility of pre-exposed bacteria

• MIC values highly dependent upon technique used (poor diffusion through agar; microdilution is preferred but influence by the inoculum)
Colistin Microbiology: morphological aspects

Figure 2: Schematic representation of the disposition of colistimethate and the colistin generated from it in the body, following administration of colistimethate sodium.

Colistin disposition

Figure 2: Schematic representation of the disposition of colistimethate and the colistin generated from it in the body, following administration of colistimethate sodium

Colistin pharmacokinetics in CF patients after treatment with colistin methane sulfonate

Patients with 160 mg TID ~ 2 x 10^6 Units) for > 2 days
Colistin pharmacokinetics in CF patients after treatment with colistin methane sulfonate

Patients with 160 mg TID (~ 2 x 10^6 Units) for > 2 days
Population pharmacokinetics of colistin in critically-ill patients

Dosage (colistine methane sulfonate [CMS]): 240 mg (3 x 10^6 U) every 8h

CMS
• \( t_{1/2} \approx 2.3 \text{ h} \)

Colistin:
• \( t_{1/2} \approx 14.4 \text{ h} \)
• \( C_{\text{max}} \) (pred.)
  • 1st dose: 0.60 mg/L
  • s.s.: 2.3 mg/L.

Conclusions: Colistin long half-life and insufficient plasma concentrations before steady state suggest the necessity of a loading dose …

Colistin pharmacokinetics: current clinical data

Population Pharmacokinetics of Colistin Methanesulfonate and Formed Colistin in Critically Ill Patients from a Multicenter Study Provide Dosing Suggestions for Various Categories of Patients

S. M. Garonzik,1† J. Li,2† V. Thamlikitkul,3 D. L. Paterson,4 S. Shoham,5 J. Jacob,2 F. P. Silveira,6‡ A. Forrest,1‡ and R. L. Nation2*,‡

School of Pharmacy and Pharmaceutical Sciences, University at Buffalo, SUNY, Buffalo, New York1; Facility for Anti-infective Drug Development and Innovation, Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University, Melbourne, Australia2; Division of Infectious Diseases and Tropical Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand3; The University of Queensland Center for Clinical Research, Royal Brisbane and Women’s Hospital, Brisbane, Australia4; Washington Hospital Center, MedStar Clinical Research Center, Washington, DC5; and Infectious Diseases, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania6

Received 13 December 2010/Returned for modification 13 March 2011/Accepted 28 April 2011

- open-label population PK study (2 centers in US; 1 in Thailand)
- 105 patients (February 2009 - July 2010)
- 12 with HD, 4 with CRRT (3 CVV hemodialysis; 1 CVV hemofiltration)
- physician-selected doses: 75 to 410 mg/day colistin base (2.2 to 12.5 x 10⁶ U)/day
- dosage intervals: 8 to 24 h,
Population pharmacokinetics of CMS and colistin in normal, HD, and CCRT patients

FIG. 3. Representative individual population PK model fits of CMS (A, C, and E) or formed colistin (B, D, and F) in critically ill patients. Panels A and B are representative of a subject not on renal replacement, C and D are representative of a subject on HD, and E and F are representative of a subject on CRRT.
Current dosing recommendations (*): 1 of 3

TABLE 3. Suggested loading dose and daily maintenance doses of CMS

<table>
<thead>
<tr>
<th>Dose</th>
<th>Category of critically ill patient</th>
<th>Dosing suggestions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loading dose</td>
<td>All patient categories</td>
<td>Equation 9:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Loading dose of CBA (mg) = colistin (C_{ss, avg}) target(\times 2.0 \times \text{body wt (kg)}).(^c) See</td>
</tr>
<tr>
<td></td>
<td></td>
<td>caveat in footnote (c). First maintenance dose should be given 24 h later.</td>
</tr>
</tbody>
</table>

* Expressed as mg of colistin base (**) activity (CBA) for various categories of critically ill patients. The suggested maintenance daily dose would commence 24 h after administration of a CMS loading dose.

Example: To target a colistin \(C_{ss, avg}\) of 2.5 mg/liter, a 55-kg patient with a CrCL of 40 ml/min/1.73 m2 would receive a loading dose of 275 mg CBA (***) followed in 24 h by commencement of a maintenance regimen of 225 mg CBA/day in 2 to 3 equally divided doses.

** Colistin \(C_{ss, avg}\) target is expressed in mg/liter. This target should be based on MIC, site, and severity of infection.

*** Use the lower of ideal or actual body weight, expressed in kg. At this time, we suggest caution in the use of a loading dose greater than 300 mg CBA

---

** 33 mg colistine base = 80 mg colistimethate = 1 x 10^6 U
*** 275 mg CBA for loading dose = 8.3 x 10^6 U
### Current dosing recommendations (*): 2 of 3

**TABLE 3.** Suggested loading dose and daily maintenance doses of CMS\(^a\)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Category of critically ill patient</th>
<th>Dosing suggestions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance dose</td>
<td>Not on renal replacement</td>
<td>Equation 10:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Daily dose of CBA (mg) = colistin (C_{ss,avg}^) target(^b) \times (1.50 \times \text{CrCL} + 30)^d )</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recommended dosage intervals based on (\text{CrCL}: &lt;10 \text{ ml/min/1.73 m}^2), every</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 h, 10-70 \text{ ml/min/1.73 m}^2 every 12 (or 8) h, and &gt;70 \text{ ml/min/1.73 m}^2 every</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 (or 8) h. See important caveat in footnote (d).</td>
</tr>
</tbody>
</table>

\(d\) Based upon the population PK analysis for 101 critically ill patients not on continuous renal replacement therapy. Colistin \(C_{ss,avg}\) target expressed in mg/L.

Creatinine clearance (CrCL) expressed in ml/min/1.73 m\(^2\). Although the Jelliffe equation was used to estimate CrCL in this study, other means (e.g., Cockcroft and Gault equation) may be used to estimate CrCL which would then be normalized to a body surface area of 1.73 m\(^2\).

in patients with CrCL values 70 ml/min/1.73 m\(^2\) or when targeting a "high" colistin \(C_{ss,avg}\), both being circumstances where the algorithm may predict daily doses of CBA substantially greater than the current upper limit in the product label.

---

** 33 mg colistine base = 80 mg colistimethate = 1 \(\times 10^6\) U
*** 275 mg CBA for loading dose = 8.3 \(\times 10^6\) U
Current dosing recommendations (*): 3 of 3

**TABLE 3. Suggested loading dose and daily maintenance doses of CMS**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Category of critically ill patient</th>
<th>Dosing suggestions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance dose</td>
<td>Receiving intermittent hemodialysis</td>
<td>Daily dose of CBA on a non-HD day to achieve each 1.0-mg/liter colistin $C_{ss,avg}^{b} = 30$ mg. Supplemental dose of CBA on a HD day: add 50% to the daily maintenance dose if the supplemental dose is administered during the last hour of the HD session, or add 30% to the daily maintenance dose if the supplemental dose is administered after the HD session. Twice-daily dosing is suggested.</td>
</tr>
<tr>
<td></td>
<td>Receiving continuous renal replacement</td>
<td>Daily dose of CBA to achieve each 1.0-mg/liter colistin $C_{ss,avg}^{c} = 192$ mg. Doses may be given every 8-12 h.</td>
</tr>
</tbody>
</table>

* Based upon use of equation 10 and setting CrCL to zero.

f Supplemental dose of CMS to achieve a similar colistin $C_{ss,avg}$ on a HD day as occurs on a non-HD day. It is assumed that the hemodialysis session occurs toward the end of a CMS dosage interval.

g Based on the population PK analysis for 4 critically ill patients receiving continuous renal replacement therapy.

---


** 33 mg colistine base = 80 mg colistimethate = 1 x $10^6$ U

*** 275 mg CBA for loading dose = 8.3 x $10^6$ U
Two typical EUCAST MIC distributions for colistin

**Pseudomonas aeruginosa**
- 3020 observations (11 data sources)
- Clinical breakpoints: S ≤ 4 mg/L, R > 4 mg/L

**Enterobacter aerogenes**
- 214 observations (6 data sources)
- Clinical breakpoints: S ≤ 2 mg/L, R > 2 mg/L

---

EUCAST and CLSI breakpoint is 4mg/L but the \( C_{\text{max}} \) is rarely > than 2 mg/L ... Can you call this a true "susceptibility" breakpoint?
Colistin pharmacodynamics (1)

Time kill curves against *K. pneumoniae* "single dose"

- excellent susceptibility at 2 h...
- but regrowth at 24h if conc. ≤ 16 MIC

**Conclusions:** The data suggest that monotherapy with colistin methanesulfonate, the parenteral form of colistin, and long dosage intervals may be problematic for the treatment of infections caused by multidrug-resistant *K. pneumoniae*, particularly for colistin-heteroresistant strains. Further investigation on combination therapy of colistin with other antibiotics is warranted.

Poudyal et al. JAC 2008; 62:1311-1318
Colistin pharmacodynamics (2)

Population analysis profiles of *K. pneumoniae* isolates

Poudyal et al. JAC 2008; 62:1311-1318
Colistin pharmacodynamics (4)

Time kill curves against *A. baumanii*

- concentration-dependence
- must be 8 x the MIC to become optimal at 4h
- must be 64 x the MIC to avoid regrowth
- modest post-antibiotic effect (see data in paper)

**Conclusions:** These findings suggest that monotherapy with colistin methanesulphonate, the parenteral form of colistin, and long dosage intervals (e.g. 24 h) may be problematic for treatment of infections caused by colistin heteroresistant *A. baumannii.*

Owen et al. JAC 2007; 59:473-477
Colistin pharmacodynamics (5)

In conclusion, the present study demonstrated initial rapid bacterial killing by colistin against susceptible *K. pneumoniae*. However, the concerning findings were a high frequency of colistin heteroresistance, the substantial regrowth within 24 h that occurred even at colistin concentrations up to 64× MIC and no significant colistin PAE. These findings suggest the potential risk that monotherapy with CMS and extended-interval dosage regimens may promote colistin resistance in multidrug-resistant *K. pneumoniae*.

Poudyal et al. JAC 2008; 62:1311-1318
The extent and rate of killing of *P. aeruginosa* by colistin were markedly decreased at high CFUo compared to those at low CFUo.

Colistin pharmacodynamics and resistance (3)

Colistin pharmacodynamics: conclusions

These recent elegant studies confirm what early investigators had already observed, namely that colistin

• Displays a **high and fast bactericidal effect**
  (named today: *concentration-dependent antibiotic*)

  ➔ **A loading dose to reach quickly max. bactericidal effect is essential**

• But that its activity **vanishes after even transient exposure**
  (named today: *heteroresistance and/or persistence of less susceptible isolates, or adaptative resistance*)

  ➔ colistin needs to be **administered several times a day to avoid regrowth**
Colistin synergy: the rationale (1 of 3)

- Gram-negative bacteria have two membranes (OM and IM)
- Antibiotic targets are most often located in the IM or intracellularly
- Most antibiotics must at least pass across the OM to reach their target, which may represent a limiting step
Colistin synergy: the rationale (2 of 3)

- Gram-negative bacteria have also efflux systems defeating the passage of drugs across the OM and explaining the low activity of many antibiotics (intrinsic resistance) and the so-called "adaptative" resistance (aminoglycosides)
Colistin synergy: the rationale (1 of 3)

- Disrupting the OM (as colistin does) will facilitate access of the other antibiotics to their targets
- This may apply EVEN to antibiotics for which the bacteria are resistant (if due to OM impermeability/efflux phenomenon)
Colistin synergy *in vitro* and *P. aeruginosa*

Aoki et al. JAC 2009; 63:534-542

Souli et al. AAC 2009; 2133-2135:
- Synergy / Improved activity if susceptible to both agents or to colistin only
- **Antagonism frequent if colistin-insensitive**
Colistin synergy *in vitro* and *P. aeruginosa*

synergy with doripenem at high inoculum concentration

Bergen et al. AAC Accepts, online: 12 September 2011
Colistin nephrotoxicokinetic is complex…

Figure 2: Schematic representation of the disposition of colistimethate and the colistin generated from it in the body, following administration of colistimethate sodium

Colistin nephrotoxicokinetic is complex...

**Figure 2:** Schematic representation of the disposition of colistimethate and the colistin generated from it in the body, following administration of colistimethate sodium

Colistin nephrotoxicokinetic is complex...

**A) high kidney function**

- Colistimethate
- Non-renal clearance
  - (Hydrolysis)
- Renal clearance

**toxicity may increase**

- intra-urinary hydrolysis into colistin
- Renal clearance
- Non-renal clearance

*Figure 2: Schematic representation of the disposition of colistimethate and the colistin generated from it in the body, following administration of colistimethate sodium*

Colistin nephrotoxicokinetic is complex...

B) Low kidney function

Figure 2: Schematic representation of the disposition of colistimethate and the colistin generated from it in the body, following administration of colistimethate sodium

FIG. 1. The distribution of serum creatinine levels on the first day of colistin treatment (START), at the peak value (MAX), and at the end of colistin treatment (END) in all studied patients (A), in the group of patients with normal baseline creatinine values (B), and in the group of patients with abnormal baseline creatinine values (C). The horizontal lines within the boxes represent the median creatinine baseline value at the first day of colistin treatment.

Kasiakou et al. AAC 2005; 49:3136-3146
A recent prospective clinical study

Effectiveness and safety of colistin: prospective comparative cohort study

Mical Paul\textsuperscript{1,2}, Jihad Bishara\textsuperscript{1,2}, Ariela Levcovich\textsuperscript{1,2}, Michal Chowers\textsuperscript{2,3}, Elad Goldberg\textsuperscript{1,2}, Pierre Singer\textsuperscript{2,4}, Shaul Lev\textsuperscript{2,4}, Perla Leon\textsuperscript{5}, Maria Raskin\textsuperscript{1,2}, Dafna Yahav\textsuperscript{2,6} and Leonard Leibovici\textsuperscript{2,6}

\textsuperscript{1}Unit of Infectious Diseases, Rabin Medical Center, Beilinson Hospital, Petach Tikva, Israel; \textsuperscript{2}Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel; \textsuperscript{3}Unit of Infectious Diseases, Meir Medical Center, Kfar Saba, Israel; \textsuperscript{4}Intensive Care Unit, Rabin Medical Center, Beilinson Hospital, Petach Tikva, Israel; \textsuperscript{5}Department of Anesthesiology, Rabin Medical Center, Beilinson Hospital, Petach Tikva, Israel; \textsuperscript{6}Department of Medicine E, Rabin Medical Center, Beilinson Hospital, Petach Tikva, Israel

*Corresponding author. Unit of Infectious Diseases, Rabin Medical Center, Beilinson Hospital, Petach Tikva, 49100, Israel. Tel: +972-3-9377512; Fax: +972-3-9377513; E-mail: paulm@post.tau.ac.il

Received 6 January 2010; returned 14 January 2010; revised 9 February 2010; accepted 12 February 2010

Background: Colistin has re-entered clinical use by necessity. We aimed to assess its effectiveness and safety compared with newer antibiotics.

colistimehate: 6–9 MU (million units) divided in 3 doses/day (if hemodialysis: 1–2 MU twice daily) if Gram (-) carbapenem resistant vs. beta-lactams (if susceptible)

Conclusions: The need for colistin treatment is associated with poorer survival. Adjusted analyses suggest that colistin is less effective and more toxic than \(\beta\)-lactam antibiotics.
if colistin is your last option …

- a repeated dosage of 150 mg colistimethate (2 x 10^6 U or 66 mg colistin base) every 8h is probably the best option … but more may be needed (see slide 58) …

- A loading dose (additional 2 to 4 x 10^6 U at first dose; total 4 to 6 x 10^6 U and perhaps up to 8-9 [see slide 57]) is essential …

- Never use it in monotherapy … (meropenem, doripenem, … even if non-susceptible)

- Test for susceptibility on a repeated fashion …

- Monitor the renal function and adjust by decreasing the dose and prolonging the interval …

- Remember that this is a last resource drug which should be put back on the shelf as soon as possible … and should not have left in the first place!
Disclosures and slides availability

Financial support from

• the Belgian *Fonds de la Recherche Scientifique* (and other federal and regional funding agencies) for basic research on pharmacology and toxicology of antibiotics and related topics and for support to a PhD fellow (D. Das)

• the Université catholique de Louvain for support to E. Ampe (vancomycin studies)

• the Belgian Public Federal Service "Public Health" for "Appropriate antibiotic use" studies in General Practice

• Research grant from Bophar Pharmaceuticals B.V., importer of colistimethate in Belgium (from Forest Pharmaceuticals UK)

http://www.facm.ucl.ac.be