Colistin: pharmacokinetics/pharmacodynamics: an update

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Contents of the presentation

- colistin : a reminder
- antimicrobial activity
- pharmacokinetics/pharmacodynamics
- toxicodynamics
- current use and perspectives
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or

?
What is (exactly) colistin in its active form?

- 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**²⁺ **and Mg**²⁺, which further destabilizes microbial outer membranes and helps conferring more specificity towards procaryotic cells
Colistin and its prodrug

**Active compound - polycationic**

\[ \text{Fatty acid} \xrightarrow{(\alpha)\text{L-Dab}} \text{L-Thr} \xrightarrow{(\alpha)\text{L-Dab}} (\alpha,\gamma)\text{L-Dab} \]

- \( \gamma-\text{NH}_2 \)
- \( \gamma-\text{NH}_2 \)

**Prodrug – inactive – blocked aminogroups**

\[ \text{Fatty acid} \xrightarrow{(\alpha)\text{L-Dab}} \text{L-Thr} \xrightarrow{(\alpha)\text{L-Dab}} (\alpha,\gamma)\text{L-Dab} \]

- \( \gamma-\text{NH} \)
- \( \gamma-\text{NH} \)

Colistin methane sulfonate - colistimethate

- Must be hydrolyzed to act -- has a lesser toxicity and a faster elimination -- conversion is spontaneous in aqueous media … and complicates PK studies

*Li et al. AAC 2003; 47:1364-1370 – Bergen et al. AAC 2006; 1953-1958*
Colistin: conversion from the prodrug

- CMS → Colistin

Occurs in vitro and in vivo in aqueous media

- critical for activity
- need for specific assay and careful sample handling (PK/PD studies)
- colistin sulfate should be used for in vitro susceptibility testing
Colistin: mg and units …

<table>
<thead>
<tr>
<th>International units (IU)</th>
<th>Colistin base activity (CBA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Mio IU = 80 mg CMS = 30 mg CBA</td>
<td>240 mg CBA = 400 mg CMS</td>
</tr>
<tr>
<td>2 Mio IU = 160 mg CMS = 60 mg CBA</td>
<td>2 Mio IU = 160 mg CMS = 60 mg CBA</td>
</tr>
<tr>
<td>3 Mio IU = 240 mg CMS = 90 mg CBA</td>
<td>3 Mio IU = 240 mg CMS = 90 mg CBA</td>
</tr>
</tbody>
</table>

Common daily dose: 9 Mio IU (270 mg CBA) ~                      Common daily dose: 5 mg/kg/day (300 mg CBA = 10 Mio IU)
Colistin around the world
Colistin: mg and units: what about Vietnam?

240 mg CBA = 400 mg CMS
2 Mio IU = 160 mg CMS = 60 mg CBA
3 Mio IU = 240 mg CMS = 90 mg CBA

Common daily dose: 5 mg/kg/day (300 mg CBA = 10 Mio IU)
Contents of the presentation

- colistin: a reminder
- antimicrobial activity
- pharmacokinetics/pharmacodynamics
- toxicodynamics
- current use and perspectives

The absence of new antibiotics has led to a growing reliance on older, more toxic drugs such as colistin, but resistance to these is already arising. ChiroACCESS Mini-review, 27 April 2011; http://www.chiroaccess.com
Colistin Microbiology: lysis of bacteria

Colistin microbiology

• 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 most antibiotics (increase in their penetration)

• 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, sticking on plastic)
Issues in testing susceptibility to colistin

- CMS is a prodrug → test colistin sulfate
- Colistin is a mixture of colistin A and B
  - USP standard: colistin B
  - Sigma reagent colistin A
- Activity depends on calcium concentration
- Colistin sticks to plastic ...
  - Do not add any detergent to avoid adsorption, this effect is taken into account since MIC have been determined in plastic plates for PK/PD measures
- Colistin in agar: do not use, as calcium content not optimally controlled in MHagar; poor diffusion
Do all the methods tell you the same thing?

**TABLE 1** Summary of colistin susceptibility test methods used in phase I and phase II of the study

<table>
<thead>
<tr>
<th>Test(^a)</th>
<th>Method reference</th>
<th>Description</th>
<th>Test medium(^b) (manufacturer)</th>
<th>Inoculum(^c)</th>
<th>Study phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>CLSI M07 (12)</td>
<td>In-house prepared AD plates</td>
<td>MHA (BBL)</td>
<td>0.5 McFarland suspension diluted in sterile saline to obtain 10^4 CFU/spot</td>
<td>II</td>
</tr>
<tr>
<td>BMD</td>
<td>CLSI M07 (12)</td>
<td>In-house prepared BMD panels in untreated polystyrene microplates</td>
<td>CAMHB (Difco)</td>
<td>0.5 McFarland suspension diluted in sterile water to obtain 3 × 10^5 to 5 × 10^5 CFU/ml</td>
<td>II</td>
</tr>
<tr>
<td>BMD-T</td>
<td>Modification of CLSI M07 (12)</td>
<td>In-house prepared BMD panels in untreated polystyrene microplates</td>
<td>CAMHB (Difco)</td>
<td>0.5 McFarland suspension diluted in sterile water ± 0.02% polysorbate 80 to obtain 3 × 10^5 to 5 × 10^5 CFU/ml; final polysorbate 80 concn, 0.002%</td>
<td>I &amp; II</td>
</tr>
<tr>
<td>TDS</td>
<td>CLSI M07 (12)</td>
<td>In-house prepared tube dilution in borosilicate tubes washed with Micro-90</td>
<td>CAMHB (Difco)</td>
<td>0.5 McFarland suspension diluted in CAMHB to obtain 3 × 10^5 to 5 × 10^5 CFU/ml</td>
<td>I</td>
</tr>
<tr>
<td>Etest</td>
<td>bioMérieux package insert</td>
<td>Agar gradient diffusion</td>
<td>MHA (BBL); MHA (Remel); MHA (Hardy)</td>
<td>0.5 McFarland suspension</td>
<td>I</td>
</tr>
<tr>
<td>TREK GNXF</td>
<td>TREK package insert</td>
<td>Dried MIC panel</td>
<td>Sensititre cation-adjusted Mueller-Hinton broth with TES buffer</td>
<td>0.5 McFarland suspension diluted in deionized water to obtain 3 × 10^5 to 5 × 10^5 CFU/ml</td>
<td>II</td>
</tr>
</tbody>
</table>

\(^a\) AD, agar dilution; BMD, broth microdilution; BMD-T, broth microdilution with 0.002% polysorbate 80; TDS, broth macrotube dilution.

\(^b\) MHA, Mueller-Hinton agar; CAMHB, cation-adjusted Mueller-Hinton broth; TES, N-tris(hydroxymethyl)methyl 2-aminopropanesulfonic acid.

\(^c\) The initial suspension of the organism was prepared in normal saline for all testing, with the exception of TREK GNXF, for which the suspension was prepared in deionized water.
Do all the methods tell you the same thing?

<table>
<thead>
<tr>
<th>Isolate no.</th>
<th>Organism</th>
<th>Phase I (n = 107)</th>
<th>Phase II (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>BMD-T</td>
<td>TDS</td>
</tr>
<tr>
<td>1*</td>
<td>A. baumannii</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>A. baumannii</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>A. baumannii</td>
<td>&gt;8</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>A. baumannii</td>
<td>8</td>
<td>&gt;16</td>
</tr>
<tr>
<td>5</td>
<td>A. baumannii</td>
<td>&gt;8</td>
<td>16</td>
</tr>
<tr>
<td>6</td>
<td>A. baumannii</td>
<td>&gt;8</td>
<td>16</td>
</tr>
<tr>
<td>7</td>
<td>A. baumannii</td>
<td>&gt;8</td>
<td>16</td>
</tr>
<tr>
<td>7A</td>
<td>A. baumannii</td>
<td>2</td>
<td>4*c</td>
</tr>
</tbody>
</table>

*In vitro* evaluation of colistin susceptibility is fraught with complications, due in part to the inherent cationic properties of colistin. In addition, no reference method has been defined against which to compare the results of colistin susceptibility testing. This study systematically evaluated the available methods for colistin MIC testing in two phases. In phase I, colistin MICs were determined in 107 fresh clinical isolates of multidrug-resistant (MDR) Gram-negative bacilli (GNB) by broth microdilution with polysorbate 80 (BMD-T), broth macrodilution (TDS), and the Etest. In phase II, 50 of these isolates, 10 of which were colistin resistant, were tested in parallel using BMD-T, TDS, agar dilution, broth microdilution without polysorbate 80 (BMD), and the TREK Gram-negative extra MIC format (GNXF) Sensititre. The Etest was also performed on these 50 isolates using Mueller-Hinton agar (MHA) from three different manufacturers. Colistin MIC results obtained from the five methods were compared to the MIC results obtained using BMD-T, the method that enables the highest nominal concentration of colistin in the test medium. Essential agreement ranged from 34% (BMD) to 83% (TDS), whereas categorical agreement was >90% for all methods except for BMD, which was 88%. Very major errors (VMEs) (i.e., false susceptibility) for the Etest were found in 47 to 53% of the resistant isolates, depending on the manufacturer of the MHA that was used. In contrast, VMEs were found for 10% (n = 1) of the resistant isolates by BMD and 0% of the isolates by the TDS, agar dilution, and Sensititre methods. Based on these data, we urge clinical laboratories to be aware of the variable results that can occur when using different methods for colistin MIC testing and, in particular, to use caution with the Etest.

## Current EUCAST and CLSI breakpoints

<table>
<thead>
<tr>
<th>species</th>
<th>EUCAST</th>
<th>CLSI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S ≤</td>
<td>R &gt;</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Acinetobacter</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

PK/PD validation still in process…suggest to use epidemiological cut-off
Two typical EUCAST MIC distributions for colistin

Colistin / Pseudomonas aeruginosa
EUCAST MIC Distribution - Reference Database 2013-10-24

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

MIC
Epidemiological cut-off WT ≤ 4 mg/L

4217 observations (12 data sources)
Clinical breakpoints: S ≤ 4 mg/L, R > 4 mg/L

Resistance!
Two typical EUCAST MIC distributions for colistin

Colistin / Enterobacter aerogenes
EUCAST MIC Distribution - Reference Database 2013-10-24

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

MIC (mg/L)

% microorganisms

≤ 0.002 0.004 0.006 0.008 0.010 0.012 0.015 0.020 0.025 0.030 0.040 0.050 0.060 0.070 0.080 0.090 0.100 0.110 0.120 0.130 0.140 0.150 0.160 0.170 0.180 0.190 0.200 0.210 0.220 0.230 0.240 0.250 0.260 0.270 0.280 0.290 0.300 0.310 0.320 0.330 0.340 0.350 0.360 0.370 0.380 0.390 0.400 0.410 0.420 0.430 0.440 0.450 0.460 0.470 0.480 0.490 0.500 0.510

Resistance!

MIC
Epidemiological cut-off: WT ≤ 2 mg/L
Clinical breakpoints: S ≤ 2 mg/L, R > 2 mg/L

215 observations (7 data sources)
Two typical EUCAST MIC distributions for colistin

Colistin / Acinetobacter baumannii
EUCAST MIC Distribution - Reference Database 2013-10-24

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

MIC (mg/L)

% microorganisms

≤ 0.002  0.004  0.006  0.008  0.010  0.012  0.015  0.020  0.025  0.05  1  2

Resistance!

MIC

Epidemiological cut-off - 152 observations (7 data sources)
Clinical breakpoints: S ≤ 2 mg/L, R > 2 mg/L
### Key antimicrobial resistance patterns for the 12 monitored nations in the APAC RRS region

<table>
<thead>
<tr>
<th>Nation (no. of sites/no. of strains)</th>
<th>(26 sites; 5,053 strains)</th>
<th>ESBL (%)</th>
<th>CARB-R (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Klebsiella spp.</th>
<th>P. aeruginosa</th>
<th>COL/TIG&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia (6/1,136)</td>
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<tr>
<td>Hong Kong (1/237)</td>
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<tr>
<td>India (5/915)</td>
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<tr>
<td>Indonesia (1/175)&lt;sup&gt;f&lt;/sup&gt;</td>
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<tr>
<td>Japan (4/398)&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>South Korea (2/462)</td>
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<tr>
<td>Malaysia (1/239)</td>
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<tr>
<td>New Zealand (2/477)</td>
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<tr>
<td>Philippines (1/195)&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Singapore (1/251)</td>
<td></td>
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<tr>
<td>Taiwan (1/137)</td>
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<tr>
<td>Thailand (2/431)&lt;sup&gt;f&lt;/sup&gt;</td>
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<td></td>
</tr>
<tr>
<td>All (26/5,053)</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

<sup>a</sup> CARB-R percentage for Klebsiella spp. and P. aeruginosa

<sup>b</sup> COL/TIG indicates the resistance rate to colistin and tigecycline
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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 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 methane sulfonate
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
• \( t_{1/2} \approx 2.3 \) h,

Colistin:
• \( t_{1/2} \approx 14.4 \) 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 regeneration depends on the brand!

Comparison of PK profile in rats for 4 brands

Pharmacokinetic parameters of CMS and formed colistin in rats (n=4)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>X-GEN (USA)</th>
<th>Paddock (USA)</th>
<th>Atlantic (Thailand)</th>
<th>Forest (UK)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formed colistin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$t_{1/2}$ (min)$^a$</td>
<td>108.0 ± 57.2</td>
<td>68.9 ± 12.0</td>
<td>107.2 ± 13.5</td>
<td>45.3 ± 10.0</td>
</tr>
<tr>
<td>$C_{max}$ (mg/L)</td>
<td>0.49 ± 0.035</td>
<td>0.44 ± 0.10</td>
<td>0.62 ± 0.075</td>
<td>0.47 ± 0.053</td>
</tr>
<tr>
<td>AUC$_{0-180min}$ (mg·min/L)</td>
<td>65.4 ± 6.81</td>
<td>40.5 ± 10.6</td>
<td>77.8 ± 9.54</td>
<td>42.4 ± 12.0</td>
</tr>
<tr>
<td>ratio of AUC$_{0-180min}$ of colistin to CMS (%)$^b$</td>
<td>2.73 ± 0.41</td>
<td>1.68 ± 0.35</td>
<td>3.29 ± 0.43</td>
<td>1.98 ± 0.58</td>
</tr>
</tbody>
</table>

He et al, JAC (2013) 68: 2311-17
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


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

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 10^6 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: Loading dose of CBA (mg) = colistin ( C_{ss,avg} ) target ( \times 2.0 \times \text{body wt (kg)} ). See caveat in footnote c. First maintenance dose should be given 24 h later.</td>
</tr>
</tbody>
</table>

a 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 m\(^2\) 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.

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

c 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 colistin base = 80 mg colistimethate = 1 \times 10^6 U
*** 275 mg CBA for loading dose = 8.3 \times 10^6 U
Current dosing recommendations (*): 2 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>
</table>
| Maintenance dose | Not on renal replacement            | Equation 10: Daily dose of CBA (mg) = colistin $C_{ss,avg}$ target$^b \times (1.50 \times CrCL + 30)$.d
|               |                                    | Recommended dosage intervals based on CrCL: <10 ml/min/1.73 m², every 12 h, 10-70 ml/min/1.73 m² every 12 (or 8) h, and >70 ml/min/1.73 m² every 12 (or 8) h. See important caveat in footnote 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 m². 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 m².

in patients with CrCL values 70 ml/min/1.73 m² 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 colistin base = 80 mg colistimethate = 1 x 10⁶ U
*** 275 mg CBA for loading dose = 8.3 x 10⁶ U
**Current dosing recommendations (**): 3 of 3**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Category of critically ill patient</th>
<th>Dosing suggestions</th>
</tr>
</thead>
</table>
| Maintenance dose              | Receiving intermittent hemodialysis                                             | Daily dose of CBA on a non-HD day to achieve each 1.0-mg/liter colistin $C_{ss,avg}$ target$^b = 30$ mg$^e$.  
Supplemental dose of CBA on a HD day$^f$: 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. |
|                               | Receiving continuous renal replacement                                         | Daily dose of CBA to achieve each 1.0-mg/liter colistin $C_{ss,avg}$ target = 192 mg.$^g$  
Doses may be given every 8-12 h.                                                                                                                                               |

$^e$ 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.

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** 33 mg colistine base = 80 mg colistimethate = 1 x 10$^6$ U  
*** 275 mg CBA for loading dose = 8.3 x 10$^6$ U
Colistin pharmacodynamics in vitro

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. 24h) may be problematic for treatment of infections caused by colistin heteroresistant *A. baumannii.*

Owen et al. JAC 2007; 59:473-477
Colistin pharmacodynamics in vitro

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 $64 \times \text{MIC}$ 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
Colistin and inoculum effect

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

Population analysis of *P. aeruginosa* after exposure to colistin modeling:

5 mg/kg divided in 3 admin. (TID)

5 mg/kg in one admin (qD)

---

**Conclusions:** No difference in overall bacterial kill was observed when the recommended maximum daily dose was administered at 8, 12 or 24 h intervals. However, the 8 hourly regimen appeared most effective at minimizing emergence of resistance.
Colistin pharmacodynamics in vitro: 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 pharmacodynamics in vivo

Tigh infection model - Pseudomonas

Activity is depending on the free AUC $\rightarrow$ optimize the daily dose

An application in humans: Asian study in Thailand

Polymyxin Use in Clinical Practice in Asia

Visanu Thamlikitkul, MD
Division of Infectious Diseases & Tropical Medicine
Faculty of Medicine Siriraj Hospital,
Mahidol University, Bangkok, Thailand

First International Conference on polymyxins, Prato, Italy, 2013
An application in humans: Asian study in Thailand

Polymyxin Use in Thailand

- PK study in 103 Thai patients
- Colistin dosing regimens were computed from PK data
  ✓ Colistin MIC Distribution XDR non-fermenters from 103 Thai Patients: $\text{MIC}_{50} = 0.5$, $\text{MIC}_{90} = 1$
  ✓ PK/PD Targets: $C_{\max} \sim 2.5$ and $\text{AUC}/\text{MIC} \sim 50$
An application in humans: 
Asian study in Thailand

CMS Dosing (Colistin Base Activity) before 2011

- Manufacture’s Recommendation
  - Sr. Cr 0.7 - 1.2 100 - 150 mg q 12 h (5mg/kg/d)
  - Sr. Cr 1.3 - 1.5 75 - 115 mg q 12 h (2.5-3.8mg/kg/d)
  - Sr. Cr 1.6 - 2.5 100 - 150 mg q 24 h (2.5mg/kg/d)
  - Sr. Cr 2.6 - 4 100 - 150 mg q 36 h (1.5mg/kg/d)
- The Sanford Guide to Antimicrobial Therapy
  - Cr. Clearance* > 50 ml/min 160 mg q 12 h
  - Cr. Clearance* 10 - 50 ml/min 160 mg q 24 h
  - Cr. Clearance* < 10 ml/min 160 mg q 36 h

* Cockcroft & Gault equation

- Empiric Therapy 30%
- Combination Therapy 70%
- Median Duration Colistin 10 days
An application in humans: Asian study in Thailand

Suggested Colistin Dosing Regimens since March 2011

<table>
<thead>
<tr>
<th>Cr. Clearance* (ml/min)</th>
<th>Loading Dose (mg)</th>
<th>Maintenance Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50</td>
<td>300</td>
<td>150 q 12 h or 100 q 8 h</td>
</tr>
<tr>
<td>41 – 50</td>
<td>300</td>
<td>150 q 12 h or 75-100 q 8 h</td>
</tr>
<tr>
<td>31 – 40</td>
<td>300</td>
<td>75 - 100 q 12 h</td>
</tr>
<tr>
<td>21 – 30</td>
<td>300</td>
<td>75 q 12 h or 150 q 24 h</td>
</tr>
<tr>
<td>11 – 20</td>
<td>300</td>
<td>100 q 24 h</td>
</tr>
<tr>
<td>≤ 10</td>
<td>150</td>
<td>75 q 24 h</td>
</tr>
</tbody>
</table>

Acute RRT 150 100 q 24 h

* Cockcroft & Gault equation
An application in humans: Asian study in Thailand

CMS & Colistin Levels at Steady State in 103 Thai patients
An application in humans: Asian study in Thailand

Effectiveness of Suggested Dosing Regimens

<table>
<thead>
<tr>
<th></th>
<th>Probability of Target Attainment (PTA) for GNB with</th>
<th>CFR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC=0.25</td>
<td>MIC=0.5</td>
</tr>
<tr>
<td>D1</td>
<td>0.99</td>
<td>1.00</td>
</tr>
<tr>
<td>SS</td>
<td>1.00</td>
<td>0.95</td>
</tr>
<tr>
<td>SD</td>
<td>0.98</td>
<td>0.99</td>
</tr>
<tr>
<td>AD</td>
<td>0.96</td>
<td>0.98</td>
</tr>
<tr>
<td>MD</td>
<td>0.95</td>
<td>0.99</td>
</tr>
<tr>
<td>GD</td>
<td>0.98</td>
<td>0.99</td>
</tr>
</tbody>
</table>

CFR = Cumulative Fraction of Response
D1 = Day 1
SS = Steady State
SD = Suggested Dosing
AD = Actual Dosing
MD = Manufacture Dosing
GD = Sanford Guide Dosing
An application in humans: Asian study in Thailand

Effectiveness of Suggested Dosing Regimens

<table>
<thead>
<tr>
<th>MIC</th>
<th>Probability of Target Attainment (PTA) for GNB with</th>
<th>CFR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3%</td>
<td>48%</td>
</tr>
<tr>
<td>------</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>MIC=0.25</td>
<td>D1</td>
<td>SS</td>
</tr>
<tr>
<td>SD</td>
<td>0.99</td>
<td>1.00</td>
</tr>
<tr>
<td>AD</td>
<td>0.88</td>
<td>0.99</td>
</tr>
<tr>
<td>MD</td>
<td>0.96</td>
<td>0.98</td>
</tr>
<tr>
<td>GD</td>
<td>0.95</td>
<td>0.99</td>
</tr>
</tbody>
</table>

*CFR = Cumulative Fraction of Response
D1 = Day 1
SD = Suggested Dosing
MD = Manufacture Dosing
SS = Steady State
AD = Actual Dosing
GD = Sanford Guide Dosing*
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 (3 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**

\[ \text{Viable cell count (log}_{10} \text{ cfu/mL)} \]

\begin{align*}
(a) \quad \text{colistin alone at increas. conc.} & \quad \text{Time after infection (h)} \\
(b) \quad \text{colistin at fixed conc. (1 x MIC) plus 0.5 MIC of} & \\
\text{none} & \\
\text{cipro} & \\
\text{amikacin} & \\
\text{imipenem rifampicin} &
\end{align*}

Aoki et al. JAC 2009; 63:534-542
Is it used in the clinics?

Survey performed in 2011 (284 respondents from 56 different countries)

Response to what drugs are used for combination therapy with colistin.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Never</td>
</tr>
<tr>
<td>Carbapenem</td>
<td>24.5</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>41.3</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>47.4</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>51.9</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>49.3</td>
</tr>
<tr>
<td>Fluoroquinolone</td>
<td>52.8</td>
</tr>
<tr>
<td>Fosfomycin</td>
<td>81.5</td>
</tr>
<tr>
<td>Minocycline</td>
<td>81.1</td>
</tr>
<tr>
<td>Other&lt;sup&gt;a&lt;/sup&gt;</td>
<td>64.3</td>
</tr>
</tbody>
</table>

<sup>a</sup> Other includes cephalosporins, trimethoprim/sulfamethoxazole, glycopeptide, linezolid and doxycycline.

Wertheim et al, Journal of Global Antimicrobial Resistance (Epub)
Is it used in the clinics?

Ongoing clinical trials are evaluating the interest of combinations in practice

**Example: NIH-10065:**
colistin/placebo vs colistin/imipenem for MDR Gram-negative bacilli

- HAP/VAP, bloodstream infections
- primary outcome: mortality at day 28
- secondary outcomes: bacterial eradication & toxicity

→ **objectives**
- efficacy of the combination?
- risk of resistance?
- relationship between plasma level, microbiological eradication and toxicity
- relationship between in vitro synergism and clinical outcomes?
Contents of the presentation

• colistin: a reminder
• antimicrobial activity
• pharmacokinetics/pharmacodynamics
• toxicodynamics
• current use and perspectives
Colistin gross toxicology

• Colistin methanesulfonate is about 50 to 100 X less toxic in LD$_{50}$ evaluations than colistine sulfate

• Renal toxicity (polymyxin B << other polymyxins)
  – Up to 20 % of patients in early trials
  – Occurs after 4 days of treatment
  – Acute tubular necrosis (can progress after drug discontinuation)
  – Related to overdosage (obese ! Oliguric renal failure if doses higher than recommended are used)

• Neurotoxicity:
  – Giddiness, numbness, paresthesia, peripheral neuropathy
  – Confusion, coma, psychosis at large doses
  – Neuromuscular blockade (paralysis) related to doses but other contributing factors
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

Renal clearance

Colistimethate

Non-renal clearance (Hydrolysis)

intra-urinary hydrolysis into colistin

Renal clearance

Colistin

Non-renal clearance

toxicity may increase

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 nephrotoxicity

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
Contents of the presentation

• colistin: a reminder
• antimicrobial activity
• pharmacokinetics/pharmacodynamics
• toxicodynamics
• current use and perspectives
Meta-analysis of 13 published studies
[by Mical Paul; Tel Aviv University, Israël]

IV colistin vs comparators - mortality in sepsis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Odds Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Odds Ratio IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betrosian 2008 J Infect</td>
<td>0.512824</td>
<td>0.857296</td>
<td>2.8%</td>
<td>1.67 [0.31, 8.96]</td>
</tr>
<tr>
<td>Rigatto 2013 Infection</td>
<td>1.360977</td>
<td>0.51843</td>
<td>7.6%</td>
<td>3.90 [1.41, 10.77]</td>
</tr>
<tr>
<td>Kallel 2007 Int CM</td>
<td>0.4796</td>
<td>0.4027</td>
<td>12.6%</td>
<td>1.62 [0.73, 3.56]</td>
</tr>
<tr>
<td>Oliveira 2008 (polyB) JAC</td>
<td>0.7275</td>
<td>0.3561</td>
<td>16.1%</td>
<td>2.07 [1.03, 4.16]</td>
</tr>
<tr>
<td>Kvitko 2011 (polyB) JAC</td>
<td>0.6471</td>
<td>0.3017</td>
<td>22.4%</td>
<td>1.91 [1.06, 3.45]</td>
</tr>
<tr>
<td>Paul 2011 JAC</td>
<td>0.3646</td>
<td>0.23</td>
<td>38.6%</td>
<td>1.44 [0.92, 2.26]</td>
</tr>
</tbody>
</table>

Total (95% CI) 100.0% 1.79 [1.35, 2.36]

Heterogeneity: Chi² = 3.44, df = 5 (P = 0.63); I² = 0%
Test for overall effect: Z = 4.06 (P < 0.0001)

Adjusted OR 1.79 (95% CI 1.35-2.36)

First International Conference on polymyxins, Prato, Italy, 2013
Meta-analysis of 13 published studies

[by Mical Paul; Tel Aviv University, Israël]

IV colistin vs comparators – mortality in pneumonia

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Odds Ratio IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betrosian 2008 J Infect</td>
<td>0.512824</td>
<td>0.857296</td>
<td>9.9%</td>
<td>1.67 [0.31, 8.96]</td>
</tr>
<tr>
<td>Paul 2011 JAC</td>
<td>0.165514</td>
<td>0.328477</td>
<td>67.7%</td>
<td>1.18 [0.62, 2.25]</td>
</tr>
<tr>
<td>Rigatto 2013 Infection</td>
<td>1.376244</td>
<td>0.571904</td>
<td>22.3%</td>
<td>3.96 [1.29, 12.15]</td>
</tr>
</tbody>
</table>

Total (95% CI)

- Heterogeneity: Chi² = 3.37, df = 2 (P = 0.19); I² = 41%
- Test for overall effect: Z = 1.74 (P = 0.08)

Adjusted OR 1.60 (95% CI 0.94-2.72)
Meta-analysis of 13 published studies

[by Mical Paul; Tel Aviv University, Israël]

IV colistin vs inappropriate antibiotics - mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Colistin Events</th>
<th>Comparator Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qureshi 2012 AAC</td>
<td>5</td>
<td>4</td>
<td>9</td>
<td>15.6%</td>
<td>0.28 [0.04, 2.09]</td>
</tr>
<tr>
<td>Lim 2011 J Korean med</td>
<td>11</td>
<td>15</td>
<td>26</td>
<td>37.3%</td>
<td>0.88 [0.33, 2.34]</td>
</tr>
<tr>
<td>Koomanachai 2007 Int J</td>
<td>36</td>
<td>12</td>
<td>48</td>
<td>47.1%</td>
<td>0.21 [0.06, 0.82]</td>
</tr>
</tbody>
</table>

Total (95% CI)

<table>
<thead>
<tr>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>123</td>
<td>60</td>
<td>100.0%</td>
<td>0.47 [0.23, 0.96]</td>
</tr>
</tbody>
</table>

Total events 52 31

Heterogeneity: $\chi^2 = 3.15$, $df = 2$ ($P = 0.21$); $I^2 = 37\%$

Test for overall effect: $Z = 2.07$ ($P = 0.04$)

OR 0.47 (95% CI 0.23-0.96)
Meta-analysis of 13 published studies

[by Mical Paul; Tel Aviv University, Israël]

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Colistin Events</th>
<th>Comparator Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.4.1 Non-matched</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garnacho-Montero 2003 CID</td>
<td>5</td>
<td>21</td>
<td>6</td>
<td>14</td>
<td>0.42 [0.10, 1.79]</td>
</tr>
<tr>
<td>Hachem 2007 AAC</td>
<td>7</td>
<td>31</td>
<td>14</td>
<td>64</td>
<td>1.04 [0.37, 2.92]</td>
</tr>
<tr>
<td>Kržiko 2011 (polyB) JAC</td>
<td>5</td>
<td>45</td>
<td>6</td>
<td>88</td>
<td>1.71 [0.49, 5.94]</td>
</tr>
<tr>
<td>Lim 2011 J Korean med</td>
<td>10</td>
<td>20</td>
<td>10</td>
<td>35</td>
<td>2.50 [0.80, 7.84]</td>
</tr>
<tr>
<td>Oliveira 2008 (polyB) JAC</td>
<td>18</td>
<td>69</td>
<td>21</td>
<td>81</td>
<td>1.01 [0.49, 2.10]</td>
</tr>
<tr>
<td>Paul 2011 JAC</td>
<td>26</td>
<td>168</td>
<td>17</td>
<td>244</td>
<td>2.44 [1.28, 4.67]</td>
</tr>
<tr>
<td>Reina 2005 Int CM</td>
<td>0</td>
<td>55</td>
<td>0</td>
<td>130</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Rigatto 2013 Infection</td>
<td>9</td>
<td>45</td>
<td>4</td>
<td>22</td>
<td>1.13 [0.30, 4.16]</td>
</tr>
<tr>
<td>Rios 2007 Eur Resp</td>
<td>0</td>
<td>31</td>
<td>0</td>
<td>20</td>
<td>Not estimable</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>485</strong></td>
<td><strong>698</strong></td>
<td></td>
<td><strong>96.4%</strong></td>
<td><strong>1.45 [1.02, 2.07]</strong></td>
</tr>
</tbody>
</table>

Total events: 80

Heterogeneity: $\chi^2 = 7.74$, df = 6 ($P = 0.26$); $I^2 = 23$
Test for overall effect: $Z = 2.06$ ($P = 0.04$)

1.4.2 Matched

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Colistin Events</th>
<th>Comparator Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betrosian 2008 J Infect</td>
<td>5</td>
<td>15</td>
<td>2</td>
<td>13</td>
<td>2.75 [0.43, 17.49]</td>
</tr>
<tr>
<td>Durakovic 2011 Intern Med</td>
<td>3</td>
<td>26</td>
<td>0</td>
<td>26</td>
<td>7.89 [0.39, 160.91]</td>
</tr>
<tr>
<td>Kallel 2007 Int CM</td>
<td>0</td>
<td>60</td>
<td>0</td>
<td>60</td>
<td>Not estimable</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>101</strong></td>
<td><strong>99</strong></td>
<td></td>
<td><strong>3.6%</strong></td>
<td><strong>3.95 [0.84, 18.48]</strong></td>
</tr>
</tbody>
</table>

Total events: 8

Heterogeneity: $\chi^2 = 0.35$, df = 1 ($P = 0.55$); $I^2 = 0$
Test for overall effect: $Z = 1.75$ ($P = 0.08$)

Overall toxicity: 15 % (12 studies)
Ongoing clinical trials

- Efficacy: vs carbapenems

- Combinations: with carbapenems
  - rifampin
  - fosfomycin

- Inhalation: IV vs IV+ inhalation for VAP/HAP

- Prevention of toxicity by ascorbic acid
If colistin had to be submitted for registration today …

A few problems…

- **Pharmaceutical aspects:**
  - uncertainties about the composition and strengths of the medicinal product offerings

- **Microbiology:**
  - High risk of failures by loss of bacterial susceptibility (regrowth and development of resistance)

- **Preclinical safety:**
  - Uncertain and incomplete animal safety testing

- **Preclinical assessment of efficacy:**
  - Incomplete and often unconvincing pharmacokinetics/pharmacodynamic parameters

- **Clinical safety:**
  - Uncertainties about the true human nephrotoxic potential and definite risk of emergence of resistance

- **Clinical effectiveness:**
  - incomplete clinical development
if colistin is your last option …

• A repeated dosage of 3 Mio IU = 240 mg CMS = 90 mg CBA) every 8h is probably the best option …
• A loading dose (6-9 Mio IU = 480-720 mg CMS = 160-240 mg CBA) 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 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](http://www.facm.ucl.ac.be)

all slides are available there

click on "Advanced Courses"