Use of nephrotoxic antibiotics in the critically ill

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Leuven - Belgium
Infections in ICU: recent trends

Increased resistance rates amongst gram-pos and gram-neg organisms (Streptococcus pneumoniae, MRSA, VRE, multidrug-resistant Pseudomonas and Acinetobacter, ESBL- and carbapanemase-producing Enterobacteriaceae) against multiple currently available antibiotics

E  = Enterococcus faecium
S  = Staphylococcus Aureus
K  = Klebsiella
A  = Acinetobacter baumanii
P  = Pseudomonas aeruginosa
E  = Enterobacter species
Risk factors for MDR pathogens

- previous antibiotic exposure
- admission from long-term care
- hospital stay > 4 days
- colonization or previous infection with MDR organisms
- advanced underlying disease (dialysis, structural lung disease, malnutrition ...)
- care in ICU
- presence of indwelling catheters, endotracheal tube, tracheostomy, ...
MDR pathogens may result in inadequate initial antibiotic therapy associated with increased morbidity/mortality.
MDR pathogens

Few new antibacterials in the pipeline, especially for gram-negatives

“bad bugs, no drugs”

→ correct use of currently available antibiotics
→ renewed interest in older more toxic antibiotics (colimycin, aminoglycosides, ...
Correct use of antibiotics

• “right drug at the right time”
• adequate early empiric therapy, eventually a combination of drugs to ensure activity against all likely pathogens (risk factors for MDR pathogens, local ecosystem, ...)
• “Right dose” PK/PD

• de-escalate
• limit duration (7-10d)
• antibiotic stewardship
Last resorts for MDR infections

- Aminoglycosides
- Colistin
### MDR Pseudomonas US data

>7000 isolates from 80 US centers

<table>
<thead>
<tr>
<th>Antimicrobial Agent</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt;</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt;</th>
<th>CLSI&lt;sup&gt;3&lt;/sup&gt;</th>
<th>EUCAST&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>%S</td>
<td>%I</td>
</tr>
<tr>
<td>MDR isolates</td>
<td>15%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftazidime-avibactam</td>
<td>4</td>
<td>16</td>
<td>82.1</td>
<td>-</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>32</td>
<td>&gt;32</td>
<td>27.6</td>
<td>16.0</td>
</tr>
<tr>
<td>Cefepime</td>
<td>16</td>
<td>&gt;16</td>
<td>26.5</td>
<td>39.5</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>&gt;64</td>
<td>&gt;64</td>
<td>15.5</td>
<td>34.0</td>
</tr>
<tr>
<td>Meropenem</td>
<td>8</td>
<td>&gt;8</td>
<td>21.4</td>
<td>18.1</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>&gt;4</td>
<td>&gt;4</td>
<td>21.3</td>
<td>12.3</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>&gt;4</td>
<td>&gt;4</td>
<td>14.8</td>
<td>14.6</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>4</td>
<td>&gt;8</td>
<td>51.1</td>
<td>10.3</td>
</tr>
<tr>
<td>Amikacin</td>
<td>8</td>
<td>32</td>
<td>87.1</td>
<td>5.0</td>
</tr>
<tr>
<td>Colistin</td>
<td>1</td>
<td>2</td>
<td>99.1</td>
<td>0.6</td>
</tr>
<tr>
<td>XDR isolates</td>
<td>9%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftazidime-avibactam</td>
<td>8</td>
<td>32</td>
<td>75.8</td>
<td>-</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>32</td>
<td>&gt;32</td>
<td>18.9</td>
<td>16.0</td>
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<tr>
<td>Cefepime</td>
<td>16</td>
<td>&gt;16</td>
<td>14.3</td>
<td>42.0</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>&gt;64</td>
<td>&gt;64</td>
<td>5.7</td>
<td>34.4</td>
</tr>
<tr>
<td>Meropenem</td>
<td>8</td>
<td>&gt;8</td>
<td>7.6</td>
<td>17.6</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>&gt;4</td>
<td>&gt;4</td>
<td>10.2</td>
<td>12.2</td>
</tr>
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<td>&gt;4</td>
<td>&gt;4</td>
<td>4.2</td>
<td>14.2</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>&gt;8</td>
<td>&gt;8</td>
<td>38.1</td>
<td>11.5</td>
</tr>
<tr>
<td>Amikacin</td>
<td>8</td>
<td>&gt;32</td>
<td>83.2</td>
<td>6.2</td>
</tr>
<tr>
<td>Colistin</td>
<td>1</td>
<td>2</td>
<td>99.1</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Sader et al. AAC 2017; on-line
MDR Acinetobacter US data

40,000 isolates from 200 US centers

Back to the Future: Using Aminoglycosides Again and How to Dose Them Optimally

George L. Drusano, Paul G. Ambrose, Sujata M. Bhavnani, Joseph S. Bertino, Ann N. Nafziger, and Arnold Louie

Ordway Research Institute, Albany, New York
Contemporary use of aminoglycosides

- Empirical combination with beta-lactams in patients with high illness severity (shock) especially when suspicion of MDR organisms
- Targeted therapy against MDR gram negatives if there are no alternatives (monotherapy or combination)
- In combination therapy for gram positive (enterococcal and streptococcal) endocarditis - lower doses (3mg/kg/d) are used for synergy only
Aminoglycosides

- Broad spectrum, fast bactericidal effect (inhibition of ribosomal protein synthesis), synergy with beta-lactams and low costs
- PD: concentration-dependent killing - $C_{\text{max}}/\text{MIC}$ 8-10

Increased MIC
Aminoglycosides

- Clinical breakpoints for Pseudomonas/Acinetobacter

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC Breakpoints</th>
<th>Cmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>≤8 = S, 16 = I, &gt;16 = R</td>
<td>Cmax 64 (if MIC not known)</td>
</tr>
<tr>
<td>Genta-tobramycin</td>
<td>≤4 = S, &gt;4 = R</td>
<td>Cmax 32</td>
</tr>
</tbody>
</table>

- PK
  - Vd ~ EC volume
  - mainly renal clearance
AG: extended interval dosing

- Concentration-dependent killing -> high peak required
- Post-antibiotic effect = persistent antimicrobial effect after the concentration has decreased below the peak
- Time for deactivation of adaptive resistance = reversible resistance developing because bacteria decrease active uptake of the aminoglycoside within 1-2 after exposure, disappearing after the antibiotic is no longer present
- Saturable uptake in tubular cells -> reduced nephrotoxicity
Amikacin in sepsis/septic shock

In ICU patients **high loading dose** because of increased Vd

Genta-tobra 7mg/kg    Amikacin 20-30mg/kg

\[ n=99 \text{ sepsis or septic shock} \]

Amikacin in sepsis/septic shock

- 181 episodes in 146 patients receiving amikacin loading dose 25mg/kg

Amikacin in sepsis/septic shock

- 63 ICU pts
- Loading dose
  18-24mg/kg IBW
- Cpeak/MIC ≥8 in 63%
- Daily TDM to achieve Cpeak/MIC ≥8

Duszynska et al. Crit Care 2013; 17: R165
Aminoglycosides

- Clearance mainly renal - reduced kidney function requires dosage adaptation

- Monitoring of both peak and trough level!!

Aminoglycosides and RRT

High trough level

-> increase dosing interval (duration PAE?)

-> increase clearance $\rightarrow$ RRT

Drug characteristics associated with important RRT removal are

- low MW (450-600kD)
- hydrophyl (low Vd)
- low protein binding
- mainly renal elimination

The amount removed depends on duration and dose of RRT
Amikacin during CRRT

Amikacin loading dose of 25mg/kg in 13 patients with sepsis + CVVHDF (Qd20-40ml/min - Qf 25-50ml/min)
Median time to Cmin <5 = 34h (range 15-75h)

-> important PK variability
-> importance of TDM

-> higher dose CRRT could have resulted in lower time to reach Cmin

RRT to maximize PD/minimize toxicity

- 2 patients with MDR pseudomonas (intermediate sensitivity = MIC 16µg/ml)
- high doses Amikacin (2500mg/6000mg) in monotherapy -> adequate peak levels (>100µg/ml)
- high volume CVVHDF (Qeffl 5L) -> safe trough levels (<5-10µg/ml) after 24h, daily administration of a bactericidal dose and clinical cure

Aminoglycosides in IHD

Eschenauer et al. Semin Dialysis 2016; 29: 204-13
AG nephrotoxicity

- Incidence 4-40% depending on definition and presence of risk factors

- Mechanism
  - Binding to brush border and uptake by megalin receptor (saturable phenomenon)-ODD
  - Endosome -> lysosome -> apoptosis/necrosis
  - Inhibition of membrane transporters
    -> inhibition of reabsorption -> TGF -> GFR
  - mesangial contraction -> GFR

- AKI occurs 7-10d after start of therapy
- Usually recovery upon discontinuation
# AG nephrotoxicity: risk factors

## Table 1: Risk factors for nephrotoxicity with aminoglycosides in patients with sepsis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Metabolic disturbances</th>
<th>Aminoglycoside treatment</th>
<th>Other nephrotoxic drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age [38, 55]</td>
<td>Hypercalcaemia [93]</td>
<td>Duration of therapy &gt;5d</td>
<td>Furosemideᵃ [14, 55, 169, 170]</td>
</tr>
<tr>
<td>Diabetes [90, 172]</td>
<td>Magnesium depletion [93]</td>
<td>High daily AUC &gt;120</td>
<td>NSAIDs [22, 93]</td>
</tr>
<tr>
<td>Cirrhosis [55, 173]</td>
<td>Potassium depletion [93]</td>
<td>High trough concentrations &gt; 0.5-2 for genta-tobra &gt; 2.5-5 for amika</td>
<td></td>
</tr>
<tr>
<td>Ascites [54, 174]</td>
<td>Sodium depletion [93]</td>
<td></td>
<td>Ciclosporin (cyclosporine) [22, 93]</td>
</tr>
<tr>
<td>Low albumin concentration [54, 175]</td>
<td></td>
<td></td>
<td>Iodide contrast media [22, 90, 93]</td>
</tr>
<tr>
<td>Reduced renal function [22, 37, 38, 44, 73, 93, 173]</td>
<td></td>
<td></td>
<td>Other antibacterials</td>
</tr>
<tr>
<td>Reduced renal mass [22]</td>
<td></td>
<td></td>
<td>Vancomycin [22, 23, 54, 168]</td>
</tr>
<tr>
<td>Leukaemia [54]</td>
<td></td>
<td></td>
<td>Cephalosporins [22, 54]</td>
</tr>
<tr>
<td>Illness severity</td>
<td></td>
<td></td>
<td>Piperacillin [168]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Clindamycin [168]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Amphotericin B [22, 54, 93]</td>
</tr>
</tbody>
</table>

- **Bold text** indicates risk factors described by at least two authors with multivariate analysis
- **Normal text** indicates risk factors described by only one author with multivariate analysis
- **Italicised text** indicates risk factors cited by review articles without references

**Microorganism**: high MIC

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AG nephrotoxicity: protection

- **extended interval dosing**
  not confirmed in all meta-analyses
  safe trough difficult in reduced kidney function

- **Short duration (<7d)**
  stop or switch if possible after microbiological information is available / short empiric combination therapy has very low or no risk

- **TDM**
  benefit not shown in ICU patients
  more for efficacy than for toxicity
Aminoglycosides: conclusions

- Concentration-dependent killing and thus require high peak levels especially in MDR pathogens with high MIC
- Loading doses should be high to compensate for the high Vd in fluid resuscitated patients
- Individual dosing based on MIC and TDM is required because of a narrow therapeutic index and extremely variable kinetics
- Kidney dysfunction increases trough levels
- Administration before IRRT and using high-dose CRRT allows adequate peak levels + earlier achievement of safe trough levels
- Treatment should be limited to a few days (when used in combination) and should be stopped when the pathogen is resistant
Parenteral polymyxins (polymyxin B and polymyxin E [colistin]) have become one of the most important antibiotics for therapy of extensively drug-resistant Gram-negative bacterial infections over the past decade, including infections caused by carbapenem-resistant nonfermenters and carbapenem-resistant Enterobacteriaceae.
Polymyxins / Colistin

- Activity against MDR gram-negative pathogens such as Acinetobacter, Pseudomonas, CPE-producing Klebsiella
- Main mechanism of antibacterial activity = disruption of outer bacterial membrane resulting in osmotic destruction → increased bactericidal activity of other antibiotics
- 50% protein binding
- Concentration dependent killing: PD target is AUC/MIC >20
- Susceptibility breakpoints

<table>
<thead>
<tr>
<th></th>
<th>EUCAST</th>
<th>CLSI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacteriaceae</td>
<td>( S \leq 2 )</td>
<td>( S \leq 2 )</td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>( S \leq 4 )</td>
<td>( S \leq 2 )</td>
</tr>
</tbody>
</table>

- ... for MIC 2 \( \rightarrow AUC_{24h} 40 \) or \( C_{SS} \) above 2
Polymyxins

- Polymyxin B, administered as active drug
- Polymyxin E = Colistin, administered as prodrug, colistine methane sulfonate (CMS)
- Important for pharmacokinetics and dosing!

- Different units -> confusion
  - US: mg CBA (colistin-base activity)
  - Europe: IU (international units)
  - 240 mg CMS = 100mg CBA = 3 Million IU
Pharmacokinetics Colistin

CMS

Colistin

Cleared by the kidney

Only 20-30% with nl RF

Renal handling = filtration + reabsorption

Non-renal clearance

\[ C_{ss} = \frac{\text{dose}_{CMS} \times fr_{(CMS\rightarrow CS)}}{Cl_{CS} \times \tau} \]
Pharmacokinetics polymyxin B

Polymyxin B

Renal handling = filtration + reabsorption

Non-renal clearance
Colistin E in renal dysfunction

Renal handling = filtration + reabsorption

Non-renal clearance

Clearance by the kidney

\[ Css = \frac{\text{dose}_{CMS} \times fr_{(CMS->CS)}}{Cl_{CS} \times \tau} \]

More colistin is formed!!
## Polymyxin E: dose recommendations

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>European Medicines Agency–Approved</th>
<th>US Food and Drug Administration–Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Daily Dose&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Daily Dose&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>≥80</td>
<td>9 MIU&lt;sup&gt;c&lt;/sup&gt; (approximately 300 mg CBA)</td>
<td>2.5–5 mg CBA/kg</td>
</tr>
<tr>
<td>50 to &lt;80</td>
<td>9 MIU&lt;sup&gt;c&lt;/sup&gt; (approximately 300 mg CBA)</td>
<td>2.5–3.8 mg CBA/kg</td>
</tr>
<tr>
<td>30 to &lt;50</td>
<td>5.5–7.5 MIU (approximately 183–250 mg CBA)</td>
<td>2.5 mg CBA/kg</td>
</tr>
<tr>
<td>10 to &lt;30</td>
<td>4.5–5.5 MIU (approximately 150–183 mg CBA)</td>
<td>1 mg CBA/kg&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>&lt;10</td>
<td>3.5 MIU (approximately 117 mg CBA)</td>
<td>Not stated</td>
</tr>
</tbody>
</table>

<sup>a</sup> Daily Maintenance Dose

Colistin dosing

Nation et al. Clin Infect Dis 2017; on-line
PMB in renal dysfunction

Tamlikitkul et al. Antimicrob Agents Chemother 2017; on-line
Importance of loading dose

**CMS**

**Colistin**

Slow formation
Long half-life

Polymyxins: importance of dose

- Retrospective study in 151 pts with blood stream infection with MDR pathogens treated with polymyxin B

<table>
<thead>
<tr>
<th>Dosing range (mg/kg/day)</th>
<th>30-day mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.3</td>
<td>33/71 (46.5)</td>
</tr>
<tr>
<td>1.3–2.4</td>
<td>16/61 (26.2)</td>
</tr>
<tr>
<td>≥2.5</td>
<td>5/19 (26.3)</td>
</tr>
</tbody>
</table>

Colistin in CRRT

CMS

\[ \text{CMS} \]

\[ \text{colistin} \]

\[ \text{CRRT = filtration + no reabsorption} \]

Non-renal clearance

Clearance by the kidney

More colistin is formed!!

CRRT removes colistin

“normal doses” required
## Colistin dosing

<table>
<thead>
<tr>
<th>Cl Cr</th>
<th>loading</th>
<th>Maintenance (after 12h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50ml/min</td>
<td>&gt;50kg 9MIU &lt;50kg 6MIU</td>
<td>2MIU q6h</td>
</tr>
<tr>
<td>30-50</td>
<td>id</td>
<td>2MIU q8h</td>
</tr>
<tr>
<td>10-30</td>
<td>id</td>
<td>2MIU q12h</td>
</tr>
<tr>
<td>&lt;10</td>
<td>id</td>
<td>2MIU q24h</td>
</tr>
<tr>
<td>IHD</td>
<td>id</td>
<td>After IHD: 3MIU No IHD day: 2MIU</td>
</tr>
<tr>
<td>CRRT</td>
<td>id</td>
<td>2MIU q6h (3MIU if treatment failure)</td>
</tr>
</tbody>
</table>

Colistin in IHD for AKI

Population Pharmacokinetics of Colistin Methanesulfonate and Colistin in Critically Ill Patients with Acute Renal Failure Requiring Intermittent Hemodialysis

M. Jacobs, a,b N. Grégoire, a,b B. Mégarbane, c P. Gobin, a,d D. Balayn, a,d S. Marchand, a,b,d O. Mimoz, a,b,d W. Couet a,b,d
Inserm U1070, Poitiers, France a; Université de Poitiers, UFR Médecine-Pharmacie, Poitiers, France b; Hôpital Lariboisière, Paris, France c; CHU Poitiers, Poitiers, France d

- HD days -> 3 MIU before HD + 1.5MIU 12h later
- nonHD days -> 2 x 1.5 MIU
- Css 3-4mg/L
Polymyxins: nephrotoxicity

- Most studies on CMS

- Filtration and reabsorption -> large exposure of tubular cells (megalin receptor)

- Incidence up to 55%
- Time of onset within first 5-7 days

Tamlikitkul et al. Antimicrob Agents Chemother 2017; on-line

Polymyxins: nephrotoxicity

- Risk factors not uniformly reported
  - Narrow therapeutic spectrum (antibacterial levels overlap with toxic levels)
  - Dose-related toxicity (different units, actual vs ideal BW)
  - Concomitant nephrotoxins
  - Age
  - Hyperbilirubinemia
  - Hypoalbuminemia (increased free fraction)

- Usually not severe (less than previously reported!) and reversible on discontinuation

Polymyxins: nephrotoxicity

- Retrospective control group - Standard dose 6MIU/d
- High dose 9MIU loading and 2x4.5MIU/d
- Matched for age, severity and nature of infection

Cure rate of both groups

- High-dose colistin
- Standard-dose colistin

Cure rate: 63% and 41.30%

\[ p = 0.04 \]
Polymyxins: nephrotoxicity

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.01 (0.95-1.08)</td>
<td>0.75</td>
</tr>
<tr>
<td>Charlson score</td>
<td>1.04 (0.71-1.52)</td>
<td>0.84</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.89 (0.33-2.42)</td>
<td>0.83</td>
</tr>
<tr>
<td>1CMS cumulative dose at day 7</td>
<td>0.99 (0.94-1.04)</td>
<td>0.73</td>
</tr>
<tr>
<td>$C_{min}$</td>
<td>4.7 (2.38-9.29)</td>
<td>$&lt;$ 0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.98 (0.93-1.03)</td>
<td>0.51</td>
</tr>
<tr>
<td>Charlson score</td>
<td>1.3 (1.01-1.57)</td>
<td>0.036</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.59 (0.25-1.38)</td>
<td>0.22</td>
</tr>
<tr>
<td>CMS cumulative dose</td>
<td>0.99 (0.98-1)</td>
<td>0.38</td>
</tr>
<tr>
<td>CMS duration treatment</td>
<td>1.03 (0.98-1.08)</td>
<td>0.24</td>
</tr>
<tr>
<td>$C_{min}$</td>
<td>2.1 (1.33-3.42)</td>
<td>0.002</td>
</tr>
<tr>
<td>NSAID use</td>
<td>5.09 (0.9-28.54)</td>
<td>0.64</td>
</tr>
<tr>
<td>Loop diuretic use</td>
<td>1.97 (0.61-6.38)</td>
<td>0.25</td>
</tr>
<tr>
<td>Co-administration of $&gt;$ 2</td>
<td>2.61 (1-6.7)</td>
<td>0.049</td>
</tr>
</tbody>
</table>

CMS (1 à 3x 1million IU)

Nephrotoxicity by RIFLE

Nephrotoxicity at 7d: 25.5%
Nephrotoxicity at 30d: 49%

Sorli et al. BMC Infect Dis 2013; 13: 380
PME vs PMB nephrotoxicity?

- Retrospective studies
- Equipotent doses? Dose PMB often incorrectly reduced
Efficacy and toxicity of aerosolised colistin in ventilator-associated pneumonia: a prospective, randomised trial

Sami Abdellatif, Ahlem Trifi*, Foued Daly, Khouala Mahjoub, Rochdi Nasri and Salah Ben Lakhal

Evaluation at 14 days

- AS colistin
- IV colistin

<table>
<thead>
<tr>
<th>Monotherapy or combination</th>
<th>Cure rate</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS</td>
<td>67.1%</td>
<td>0.59</td>
</tr>
<tr>
<td>IV</td>
<td>72%</td>
<td>0.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Monotherapy or combination</th>
<th>Cure rate</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS</td>
<td>58%</td>
<td>0.17</td>
</tr>
<tr>
<td>IV</td>
<td>63.30%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Combination</th>
<th>Cure rate</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS</td>
<td>84%</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>75.00%</td>
<td></td>
</tr>
</tbody>
</table>

%ARF (p=0.004)

- AS colistin group: 13/73 (17.8%)
- IV colistin group: 30/76 (39.4%)

% RRT (p=0.032)

- AS colistin group: 4/13
- IV colistin group: 12/30
Polymyxins: conclusions

- Importance of loading dose
- Current dosing regimens often inadequate
- Doses of CMS but not polymyxin B should be reduced in kidney dysfunction
- During CRRT high doses will be required
- Because of narrow therapeutic index combination therapy is advised but results from clinical trials are limited
- Role of aerosolized polymyxins?
General conclusions

- The combination of high MIC (MDR pathogens), altered pharmacokinetics and fear for nephrotoxicity often leads to underdosing of antibiotics in critically ill patients.
- Underdosing may be more dangerous than overdosing.
- If nephrotoxicity develops it is important to consider risk/benefit ratio of continuing versus stopping.
- RRT can be used to achieve efficacy and safety of concentration-dependent (toxic) antibiotics.
- The only reliable method for safe and efficacious dosing of antibiotics in the ICU is TDM.
Essentials to Optimize Antibiotic Therapy

- Antimicrobial agent: PK/PD properties
- Adequate dosing
- Tissue penetration
- Infection site
- Appropriate microbial coverage
- Altered antimicrobial PK
- Pathogen + MIC
- Critical illness

ICU Infection Outcome