Optimising the use of old drugs (colistin, fosfomycin, rifampin) to suppress emergence of resistance and minimise toxicity in severe infections

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Transparency Declaration

- I have no conflicts to declare relating to this presentation
Outline of the presentation

- Brief summary of recent evidence relating to the treatment of MDR pathogens
  - Colistin
  - Fosfomycin
  - Rifampin
- Important in vitro data
- Clinical efficacy
- Resistance reports
- Unanswered questions
Colistin: the Phoenix arises

An antibiotic of the polymyxin family, abandoned in the 1970s due to toxicity issues
Marketed in Europe for systemic use as Colistimethate sodium, the inactive prodrug of colistin (Polymyxin E)
Polymyxin B is available in US and South America
• Scarce early PK studies hampered by the use of microbiological method
• Combinations? Synergy?
• Suboptimal dosing is associated with increased mortality
• Pharmacokinetics in special populations?
• Optimal dosing regimen?
  • Once daily, twice daily or three times daily?
Caution: Do we have a common glossary for colistin?

Different commercially available products of CMS worldwide, employing different dosage definitions

Equivalence of colistin base and colistimethate sodium, expressed either as mg or as IU

<table>
<thead>
<tr>
<th>Colistin Base Activity/CBA (mg)</th>
<th>Colistimethate sodium/CMS (mg)</th>
<th>Colistimethate sodium/CMS (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1mg</td>
<td>2.7mg</td>
<td>30000 IU</td>
</tr>
<tr>
<td>-</td>
<td>1mg</td>
<td>12500 IU</td>
</tr>
<tr>
<td>30mg</td>
<td>~80mg</td>
<td>1 MIU</td>
</tr>
</tbody>
</table>

Administered in 18 patients as 3 MU q8h
- T 1/2: 14.4 h
- Cmax of colistin after the first dose: 0.6mg/L
- in steady state: 2.3mg/L
- Subtherapeutic concentrations
- Therapeutic levels achieved after Tx day 2

Plasma colistin A and colistin B concentrations were determined by a novel liquid chromatography-tandem mass spectrometry method

Therapeutic failures=mortality
Emergence of resistance
A dosage regimen reevaluation was proposed:

A loading with 9MIU followed by 3MIU q8h

Pharmacokinetics of Colistin in Critically ill Patients

Plachouras D et al. AAC 2009;53:3430
- A Multicentre study of 105 critically ill patients (and on Renal Replacement Treatment)
- Blood sampling on day 3 or 4
- Colistin $t_{1/2}$ : 13 h
- Steady state concentration: 2.36 mg/L
- An algorithm was proposed for colistin dosing targeting a steady state concentration ~ 2 mg/L
## Suggested Colistin Dosing for Various Patients Categories

Targeting peak blood level of 2μg/ml in

<table>
<thead>
<tr>
<th>Loading dose (MIU)</th>
<th>Maintenance dose (MIU)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All patients</strong></td>
<td>Body weight$^a$ divided by 7.5 (maximum permitted dose 10 mil iu) The next dose should be given 24h post loading dose</td>
</tr>
<tr>
<td>Normal renal function</td>
<td>$(\text{Cl}_{\text{cr}}$ divided by 10) + 2 given in 2-3 doses</td>
</tr>
<tr>
<td>Continuous veno-venous haemodiafiltration (CVVHDF)</td>
<td>5-6$^b$MIU every 12h</td>
</tr>
</tbody>
</table>

$^a$ Ideal or real body weight in Kg (choose the least)

$^b$ Caution with daily doses exceeding 10MU

Adapted from Garonzik SM, et al. AAC 2011;55:3284
Maintenance dose for Haemodilution (HD*)

CMS and colistin are removed by the filter

<table>
<thead>
<tr>
<th>Non-HD days</th>
<th>1 MU q12h</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD days</td>
<td>+50% of daily recommended dose if given towards the end of HD session OR +30% of daily recommended dose if given after the end of the dialysis session</td>
</tr>
</tbody>
</table>

* HD session is preferable at the tail of colistin dosing interval

Garonzik et al, AAC 2011
Jitmuang et al. JAC, 2015
Pharmacokinetics of Colistin Methanesulfonate and Formed Colistin in End-Stage Renal Disease Patients Receiving Continuous Ambulatory Peritoneal Dialysis


- 8 Patients
- CMS and colistin only minimally reduced during CAPD

| Continuous ambulatory peritoneal dialysis (CAPD) | 5 - 6 MU q24h |
Patients with Augmented creatinine clearance have decreased probability of achieving the PK/PD target $\text{Css, avg} \geq 2\text{mg/L}$

Almost only 30% of patients with CrCl > 80 achieved $\text{Css, avg} \geq 2\text{mg/L}$ (1, 2)

<table>
<thead>
<tr>
<th>Creatinine Clearance ($\text{ml/min/1.73m}^2$)</th>
<th>Target attainment - $\text{Css, avg} \geq 2\text{mg/L}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 – 99</td>
<td>3/7</td>
</tr>
<tr>
<td>100 – 119</td>
<td>6/16</td>
</tr>
<tr>
<td>120 – 139</td>
<td>1/10</td>
</tr>
<tr>
<td>&gt;140</td>
<td>1/6</td>
</tr>
</tbody>
</table>

Garonzik et al, AAC 2011 & ECCMID 2013
Karaiskos et al, ICAAC 2013

Combination with other antibiotic may be warranted

Courtesy of Dr I. Karaiskos

Garonzik et al, AAC 2011 & ECCMID 2013
Karaiskos et al, ICAAC 2013
Colistin monotherapy or in combination?
High-Dose, Extended-Interval Colistin administration in Critically Ill Patients: Is This the Right Dosing Strategy? A Preliminary Study

• Prospective study 28 septic episodes in ICU patients
• Cr_cl > 50 mL/min loading CMS dose of 9 MU, maintenance dose of 4.5 MU every 12 hours.
  ▫ Cr_cl <50 mL/min, loading dose of 9 MU, maintenance doses of 4.5 MU/24 hours for Cr_cl 20–50 mL/min, or 4.5 MU/48 hours for Cr_cl of <20 mL/min
• 50% of episodes received colistin monotherapy
• Bloodstream infection (64.3%) and ventilator-associated pneumonia (35.7%), K. pneumoniae (46.4%),
• Clinical cure was observed in 23 cases (82.1%)
  ▫ 40% microbiological eradication in VAP episodes

*Dalfrino L et al, CID 2012:54*
Colistin for the treatment of ventilator-associated pneumonia caused by multidrug-resistant Gram-negative bacteria: A systematic review and meta-analysis

Wan-Jie Gu a, Fei Wang b, Lu Tang b, Jan Bakker a, Jing-Chen Liu a,*

- 14 studies, 1167 patients with VAP
- 6 studies (2003 – 2013): colistin vs carbapenems (IMP)
- XDR or MDR A.baumannii and P.aeruginosa
- No statistical difference in:
  - Clinical resolution
  - Microbiological eradication
  - Mortality
  - Nephrotoxicity
- 5 studies monotherapy vs 9 studies combination treatments: no difference in clinical outcome

Prospective observational study from 28 Spanish hospitals and 101 patients
67.3% received monotherapy (M) 32.7% combined therapy (CT)
Pneumonia was the most common infection (50.5%)
Colistin (67.6%) and carbapenems (14.7%) the most common monotherapies
Colistin + tigecycline (27.3%) and carbapenems + tigecycline (12.1%) the most commonly used combinations
30-day mortality: 23.5% vs 24.2% for M and CT respectively
(p = 0.94)

JAC 2014;69:3119
Colistin-based treatment for extensively drug-resistant *Acinetobacter baumannii* pneumonia

Thana Khawcharoenporn\(^a\), Nattapol Pruetpongsun\(^a\), Pimsiri Tiamsak\(^b\), Sasinuch Rutchanawech\(^a\), Linda M. Mundy\(^c\), Anucha Apisarnthanarak\(^a\)

- Retrospective study
- HAP/VAP, by XDR AB, 236 patients
- Colistin-based two drug combination treatment was prescribed to 166 subjects (70%); regimens included (i) colistin and high-dose sulbactam \((n = 93)\); (ii) colistin and tigecycline \((n = 43)\); and (iii) colistin and high-dose prolonged infusion of a carbapenem \((n = 30)\)
- All groups received also inhaled colistin (>90%)
- The 28-day survival rate were not statistically different between these three regimens (65%, 53% and 60%)
• 125 ICU patients with bloodstream infections (BSIs) caused by KPC-producing Kp isolates

• The overall 30-day mortality rate was 41.6%
  ▫ significantly higher among patients treated with monotherapy (54.3% vs. 34.1% in those who received combined drug therapy, \( P = 0.02 \)).

• Definite treatment with a triple combination of tigecycline, colistin, and meropenem was associated with lower mortality (OR, 0.11; 95% CI, 0.02 to 0.69; \( P = 0.01 \)
Data compilation favors combination treatment for CPE-infected patients

- Review of 20 clinical studies compiling data from 889 patients with Carbapenem Producing Enterobacteriaceae infections
- Treatment with a single *in vitro* active agent resulted in mortality rates not significantly different from that observed in patients treated with no active therapy
- Combination therapy with two or more *in vitro* active agents provided a clear survival benefit (mortality rate, 27.4% vs. 38.7%; p <0.001)
- The lowest mortality rate (18.8%) was observed in patients treated with carbapenem-containing combinations
Outcomes of 889 patients infected with carbapenemase-producing *Klebsiella pneumoniae*, according to treatment regimen

Regimen A: inappropriate therapy (no drug was active in vitro).
Regimen B: monotherapy (one drug was active in vitro).
Regimen C: combination therapy (two or more drugs active in vitro)
Regimen C1: combination of two or more in vitro-active drugs not including a carbapenem
Regimen C2: combination of two or more in vitro-active drugs, one of which was a carbapenem

Regimen B vs. regimen A: p, not significant.
Regimens C, C1 and C2 vs. regimen B: p 0.001, p 0.034, and p <0.0001, respectively.
Carbapenemase-Producing *Klebsiella pneumoniae* Bloodstream Infections: Lowering Mortality by Antibiotic Combination Schemes and the Role of Carbapenems


**FIG 1** Kaplan-Meier survival estimates of patients with carbapenemase-producing *K. pneumoniae* bloodstream infections according to treatment regimen: combination therapy (continuous line) versus monotherapy (dotted line). *P* = 0.003 (log rank test).

**TABLE 4** Outcomes of 79 patients with CP-Kp bloodstream infections treated with carbapenem combinations stratified by carbapenem MIC

<table>
<thead>
<tr>
<th>Carbenpenem MIC (μg/ml)</th>
<th>In vitro active agent(s)</th>
<th>No. of patients who survived/died</th>
<th>Mortality, %</th>
<th>In vitro inactive agent(s)</th>
<th>No. of patients who survived/died</th>
<th>Mortality, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤8</td>
<td>25/6</td>
<td>19.3</td>
<td></td>
<td>5/7</td>
<td>58.3</td>
<td></td>
</tr>
<tr>
<td>&gt;8</td>
<td>20/11</td>
<td>35.5</td>
<td></td>
<td>4/2</td>
<td>33.3</td>
<td></td>
</tr>
</tbody>
</table>
Adverse Effects of colistin

- **Nephrotoxicity** (by use of RIFLE criteria): 20 – 60 %
- Rare need for RRT: 0 – 28%
- Neurotoxicity: 7 %
  - Paresthesias, apnoea, and respiratory arrest

<table>
<thead>
<tr>
<th>Risk factors for nephrotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of treatment/ Total colistin dose</td>
</tr>
<tr>
<td>Daily colistin dose</td>
</tr>
<tr>
<td>Pre-existing renal impairment</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Other nephrotoxic agent co-administered</td>
</tr>
<tr>
<td>OBESITY (excessive dose)</td>
</tr>
</tbody>
</table>

Justo JA, Bosso JA. Pharmacotherapy. 2015;35:28-33
Fosfomycin

- Active *in vitro* against ESBL and Carbapenemase producing *Enterobacteriaceae* (*Klebsiella pneumoniae*) as well as against MRSA and VRE
- Moderate activity against *P. aeruginosa* (EUCAST removed the breakpoints from the list)- Not active against *Acinetobacter* sp.
- Rapid bactericidal activity/advantageous pharmacokinetics in difficult compartments
- Easily selects for resistance when used as monotherapy
- Most common adverse events: hypokalemia and sodium overload

Michalopoulos A, et al. CMI 2009
Apisarnthanarak Clin Infect Dis 2010; 51:1352-1354
Breakpoints of resistance are heterogenous

<table>
<thead>
<tr>
<th></th>
<th>CLSI</th>
<th>EUCAST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitive</td>
<td>≤ 64μg/ml</td>
<td>≤ 32μg/ml</td>
</tr>
<tr>
<td>Resistance</td>
<td>&gt;128μg/ml</td>
<td>&gt; 32μg/ml</td>
</tr>
</tbody>
</table>

* With the addition of glucose-6-phosphate

Oteo J, et al. JAC 2009;64:712
In Vitro Interactions of Fosfomycin with other Antimicrobial Agents Against MDR Enterobacteriaceae and *Pseudomonas aeruginosa*: Conclusion out of 4 Studies

- No antagonism in general
- **Against *K. pneumoniae***
  - Synergy with Carbapenems in 30% to 78% of KPC(+)  
  - ~35% synergistic results with colistin and tigecycline  
  - Some others reported antagonism with colistin
- **Against *P. aeruginosa***
  - 47% to 73% synergistic results with carbapenems against *Pseudomonas aeruginosa*
- Tested alone in the controls: 100% resistance development in *Klebsiella* strains

Evren E et al, Diagn Microbiol Infect Dis. 2013 ;76:335  
Fosfomycin and in vitro synergy against Acinetobacter baumannii

- 25 strains of PDR A. baumannii
- Reduction of MIC when fosfomycin was combined with polymyxin B or minocycline
- No antagonism
- Additive or synergistic effect to the combination of fosfomycin+minocycline+polymyxin B

Considered as Inherently resistant to fosfomycin

Microbiologically documented infections by Gram negatives: PDR 15, XDR 30

- 45 pts, Mean age 55.6 years, APACHE II 19.8, SOFA 8.6
- Bacteremia (16 /6), CVCBSIs (8), VAP (14), IAIs(7)
- Sepsis, severe sepsis and septic shock 21.4%, 7.1%, 21.4%
- *K. pneumoniae* KPC(+) 83.7%, *P. aeruginosa* 35.7%
Experience with Fosfomycin IV, 6 gr x 4 per day, for a mean of 12 days + Colistin (28 pts) and/or Tigecycline (17 pts):

- **Clinical Outcome**
  - Successful by day 14 in 55.8%
  - Failure in 27.9%
  - Relapse in 4.7%
  - Superinfection in 4.7%

**Microbiological Outcome**
- Bacterial eradication 54.8%
- Resistance development in 8.9%

**Main adverse event**
- Reversible hypokalemia (6 pts)
Clinical Efficacy of fosfomycin in MDR infections

- French prospective study
- 116 adults and children
- Bacteraemia, osteomyelitis, pneumonia, urinary tract infection
- Fosfomycin 4g / 8 hours
- MDR strains 71.5% mostly MDR/XDR *P. aeruginosa* (n = 28/24) and MRSA
- 44% of patients in ICU and 22.4% in septic shock
- Success: 76.8%
- Combinations of drugs used not mentioned

Open prospective randomized trial

94 patients: 47 randomized to monotherapy with colistin (5 mg/kg/daily) and 47 to colistin + fosfomycin (4gr x2)

Clinical success rates: 55.3% vs 59.6%  p 0.835

28 day mortality: 57.4% vs 46.8%  p 0.409

Microbiological eradication

<table>
<thead>
<tr>
<th></th>
<th>Colistin</th>
<th>Colistin + Fosfomycin</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial 72hours</td>
<td>58.1 %</td>
<td>90.7 %</td>
<td>0.001</td>
</tr>
<tr>
<td>End of treatment</td>
<td>81.2%</td>
<td>100 %</td>
<td>0.01</td>
</tr>
</tbody>
</table>


Acinetobacter baumannii
Inherent resistance to fosfomycin
Some non-antibacterial properties of Fosfomycin

- The antimicrobial activity of fosfomycin in biofilms might have implications in pulmonary exacerbations of cystic fibrosis
- Fosfomycin has been found in vivo to mitigate the toxicity of various co-administered antibiotics, for example nephrotoxicity related to aminoglycosides
- The reduction of nephro- and ototoxicity of aminoglycosides is attributed to the inhibition of their uptake by the epithelial cells of the renal tubes
  - fosfomycin protects the integrity of lysosomal membranes

J Cyst Fibrs 2003;2:19
Immunomodulatory Effects
Fosfomycin has demonstrated:

- To decrease the production of pro-inflammatory cytokines (such as interleukin IL-1, IL-8 and TNF-α)
- To increase the production of other cytokines (IL-6 and IL-10)
- To increase the susceptibility of certain bacteria to phagocytosis

Roussos N, et al. IJAA 2009;34:506
Combinations of Rifampin for Gram-negative infections

An example of demonstrated in vitro synergy with scarcity of clinical data
In vitro and animal model data

- In vitro studies have demonstrated the synergistic activity of rifampicin with other antimicrobials, particularly colistin (but also carbapenems, amikacin and amp/sulbactam), for the treatment of Gram-negative MDR bacteria, even in strains with documented resistance to rifampicin.

- In vivo animal experimental study on neutropenic rats infected with MDR A. baumannii strains, showed that the efficacy of colistin was enhanced after co-administration of rifampicin and the results were statistically significant in terms of reduction in mortality rates.

Literature review

- 19 studies were found from 1992 to 2008
  - 8 observational, 1 randomised-controlled, 8 case reports and 2 case series
  - *A. baumannii* 8 studies, *P. aeruginosa* 6 studies, ESBL-producing enterobacteriaceae 1 study, *K. pneumoniae* 1 study
  - The clinical studies on *A. baumannii* infections (89 patients), of which 75 (84.3%) were referred to ICUs
    - VAP 68.8%, BSI 11.2%, Hip and Joint infections 10.1%
    - 74.1% cure rate
  - In the *P. aeruginosa* studies 138 patients were enrolled
    - 87.7% BSIs, 6.5% Diabetic foot infections +/- osteomyelitis
    - 77.9% cure rate

Drapeau CMJ, IJAA 2010,
Twenty-nine patients: of whom 19 had nosocomial pneumonia and 10 bacteraemia, were treated with intravenous colistin sulphomethate sodium (2 million IU three times a day) in addition to intravenous rifampicin (10 mg/kg every 12 h).

Clinical and microbiological responses were observed in 22 of 29 cases (76%) and the overall infection-related mortality was 21% (6/29).

No Comparator Arm
Results of an early randomised controlled clinical trial with rifampicin-containing combination regimens

- 121 patients with *P. aeruginosa* bacteraemia
- 58 were treated with rifampicin + β-lactam + aminoglycoside whilst the remaining 63 patients received only β-lactam + aminoglycoside
- The cure rate was 75.9% vs. 82.5%, *P* = 0.364.

Korvick JA, AAC 1992
A recent randomised comparative study from Turkey, 43 patients

- Colistin +/- rifampicin in VAP caused by a carbapenem-resistant A. baumannii strain
- Only microbiological clearance statistically better in the combination, although clinical outcomes were in favor of the combination

- Multicenter RCT in 210 patients with infection by XDR A. baumannii in 5 Italian ICU
- IV colistin (2 MU/8h) vs IV colistin plus IV rifampin (600mg/12h)

<table>
<thead>
<tr>
<th></th>
<th>IV colistin</th>
<th>IV colistin + IV Rifampicin</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>30day mortality</td>
<td>42.9%</td>
<td>43.39%</td>
<td>0.55</td>
</tr>
<tr>
<td>Microbiological eradication</td>
<td>44.8%</td>
<td>60.6%</td>
<td>0.34</td>
</tr>
<tr>
<td>Length of hospital stay (days)</td>
<td>44</td>
<td>41</td>
<td>0.96</td>
</tr>
<tr>
<td>Liver toxicity</td>
<td>11.9%</td>
<td>20.8%</td>
<td>0.13</td>
</tr>
</tbody>
</table>
Colistin plus rifampin is the most consistently synergistic combination against KPC-producing K. pneumoniae isolates, including colistin-resistant strains.

Colistin-rifampin combinations may have a role in the treatment of multidrug-resistant K. pneumoniae and may possibly slow the selection of heteroresistant subpopulations during colistin therapy (?)
E. Tagliaferri, et al, CMI 2014

Easy synergism for colistin-resistant KPC-producing Klebsiella pneumoniae: the E-test with supplemented agar

<table>
<thead>
<tr>
<th>Strain</th>
<th>Method</th>
<th>Alone</th>
<th>+RIF 2 mg/L</th>
<th>+RIF 4 mg/L</th>
<th>+RIF 8 mg/L</th>
<th>+RIF 16 mg/L</th>
<th>+RIF 32 mg/L</th>
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<tbody>
<tr>
<td>8252/10</td>
<td>E-test</td>
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<td>2</td>
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<td>0.5</td>
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<tr>
<td>8546/10</td>
<td>Checkerboard</td>
<td>32</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>9761/10</td>
<td>E-test</td>
<td>12</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>2</td>
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<tr>
<td>4680/11</td>
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<td>0.75</td>
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<tr>
<td>12 613/10</td>
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<td>6</td>
<td>1</td>
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<td>2018/12</td>
<td>E-test</td>
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<tr>
<td>2550/12</td>
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<td>16</td>
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<td>2762/12</td>
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<td>3031/12</td>
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<td>3342/12</td>
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<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0.5</td>
</tr>
</tbody>
</table>

FIG. 1. Minimum inhibitory concentrations of colistin on Mueller-Hinton agar alone (left) and supplemented with rifampin 32 mg/L (right) against Klebsiella pneumoniae carbapenemase (KPC)-producing K. pneumoniae (KPC-Kp).
Two VIM- and two NDM-producing *K. pneumoniae* strains, all susceptible to colistin, were exposed to antibiotics at clinically relevant static concentrations during 24-h time-kill experiments.

The combination of rifampin-meropenem-colistin was the most effective regimen, demonstrating synergistic and bactericidal effects against all four strains with metallo-beta-lactamase mechanism of resistance.
Conclusions
Combined therapeutic regimens with rifampin

- The real clinical benefit of using rifampicin-containing therapies for the treatment of Gram-negative MDR bacteria and particularly Klebsiella pneumoniae merits further assessment.
Nebulized antibiotics

Nebulized/inhalation route

Ventilator-Associated pneumonia (VAP)
Ventilator-Associated tracheobronchitis (VAT)
Pharmacokinetics of nebulised colistin

- Patients with VAT
- No iv administered antibiotics
- Nebulization
  - Vibrating mesh nebulizer
  - CMS 1MU x 3
  - Standard nebulization protocol
- Mini BAL 1, 4 and 8 hours after inhalation
- CMS 1MU x 3: Inadequate dosage

Athanassa et al, Intensive Care Med 2012
• 12 patients with VAP
• Nebulised colistin:
  2MU every 8 hours
• ELF colistin levels:
  9.53 – 1137mg/L (□)
• Plasma colistin levels:
  0.15 – 0.73 mg/L (▲)
• 9% of CMS dose reaches ELF and only 1.4% converts to colistin

 ELF: Epithelial Lining Fluid – Υγρό που επαλείφει τις κυψελίδες

• Retrospective matched case-control study (1:1) 208 patients
• Colistin was given as
  • 1 MU x 3 via jet or ultrasonic nebulizer
  • IV: 100 000 IU / kg daily in 2-3 doses
• AB>PA>KP
• The combined IV and aerosolized colistin cohort:
  ▫ had a higher clinical cure rate (69.2% vs 54.8%, \( P < 0.03 \))
  ▫ required fewer days of mechanical ventilation (8 days vs 12 days, \( P < 0.001 \))
  ▫ had a more frequent eradication of the causative organism
  ▫ NO difference in nephrotoxicity

Days on mechanical ventilation

_Tumbarello M, CHEST 2013; 144(6):1768–1775_
1/1/2006 to 31/12/2010

VAP, *Pseudomonas* sp, Acinetobacter sp, 165 patients

- Pathogens *β*-lactam susceptible (122pts, 14 days iv antibiotics)
- Pathogens *β*-lactam resistant (44pts, nebulized colistin 7-19 days±3 days iv aminoglycoside)
- Empiric coverage at the discretion of treating physicians

Hypothesis: *monotherapy* with nebulized colistin is non-inferior to standard iv treatment with a *β*-lactam with aminoglycoside or a quinolone (non-inferiority margin 16%)

- Nebulized colistin dose: 5 million international units every 8 h

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Lu et al, Anesthesiology 2012
Summary of the study by Lu et al

• Nebulized colistin was effective to treat VAP caused by multidrug-resistant *P. aeruginosa* and *A. baumannii*; the clinical cure rate (66%) was non-inferior to that obtained in VAP caused by susceptible *P. aeruginosa* and *A. baumannii* (67%)

• The risk of developing colistin resistance after nebulization was low

• Nebulized colistin did not increase the risk of kidney failure, although repeated nebulization induced systemic accumulation

Lu Q et al, Anesthesiology 2012
Palmer L et al, AJCCRM 2014
Can inhaled antibiotics reduce resistance?

- Double blind randomized placebo controlled single center trial
- 42 patients: Nebulised amikacin and vancomycin (Aerotech nebuliser®) or placebo
  - IV antibiotics similar to both groups
- Conclusion: Inhaled antibiotics eradicated resistant organisms in tracheal secretions and reduced the development of new resistance to systemic agents.
- CPIS was significantly improved in AA compared to placebo
- No resistance to the inhaled drug emerged; resistance emerged in the placebo group

<table>
<thead>
<tr>
<th>Table 4. Microbiologic response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td># of randomization organisms*</td>
</tr>
<tr>
<td>eradicatd</td>
</tr>
<tr>
<td># of patients with eradication of resistant organisms</td>
</tr>
</tbody>
</table>

*Resistant and Non-resistant organisms
†Fischer’s exact
# Inhaled colistin for infections due to MDR Gram-negative pathogens

<table>
<thead>
<tr>
<th>Author year</th>
<th>Patients</th>
<th>Infection</th>
<th>Pathogen</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michalopoulos 2005</td>
<td>8</td>
<td>VAP</td>
<td>(AB, PA)</td>
<td>Clinical cure 87.5%</td>
</tr>
<tr>
<td>Kwa, 2005</td>
<td>21</td>
<td>VAP</td>
<td>(AB, PA)</td>
<td>Clinical cure 85.7%</td>
</tr>
<tr>
<td>Berlana, 2005</td>
<td>80</td>
<td>VAP</td>
<td>(AB, PA)</td>
<td>Microbiological cure 92%</td>
</tr>
<tr>
<td>Mataouakkil 2006</td>
<td>26</td>
<td>VAP, bacteremia (3)</td>
<td>(AB)</td>
<td>Clinical cure 100%</td>
</tr>
<tr>
<td>Pereira 2007</td>
<td>19</td>
<td>VAP/VAT, only inhaled</td>
<td>(PA, KP)</td>
<td>Cure 53%, Improvement 42%, mortality 47%</td>
</tr>
<tr>
<td>Michalopoulos 2008</td>
<td>60</td>
<td>VAP</td>
<td>(AB, PA, KP)</td>
<td>Clinical and Microbiologic cure 83.3%</td>
</tr>
<tr>
<td>Falagas 2009</td>
<td>5</td>
<td>VAP, HAP</td>
<td>(AB, PA, KP)</td>
<td>Clinical cure 80%</td>
</tr>
<tr>
<td>Lin 2010</td>
<td>15</td>
<td>VAP</td>
<td>(AB)</td>
<td>Clinical cure 57.8% mortality 42%</td>
</tr>
<tr>
<td>Athanassa 2011</td>
<td>12</td>
<td>VAT, only inhaled</td>
<td>(AB, PA, KP)</td>
<td>Clinical cure 75%</td>
</tr>
<tr>
<td>Korbila 2010</td>
<td>121</td>
<td>VAP</td>
<td>(AB, PA, KP)</td>
<td>Clinical cure 60 vs 79.5% favors combination</td>
</tr>
<tr>
<td>Rattanapumawan 2010 randomised</td>
<td>100</td>
<td>VAP</td>
<td>(AB, PA)</td>
<td>Clinical cure 51% vs 52% (indifferent)</td>
</tr>
<tr>
<td>Arnold, 2012</td>
<td>93</td>
<td>VAP</td>
<td>(AB, PA)</td>
<td>Survival favors combination</td>
</tr>
<tr>
<td>Lu, 2012 Comparative/prospective</td>
<td>145</td>
<td>VAP, Only inhaled</td>
<td>(AB, PA)</td>
<td>Non-inferior 66% vs 67%</td>
</tr>
<tr>
<td>Kofteridis 2012 matched case control</td>
<td>43+43</td>
<td>VAP</td>
<td>(AB, PA, KP)</td>
<td>Indifference in survival, eradication, clinical cure</td>
</tr>
</tbody>
</table>

The Role of Aerosolized Colistin in the Treatment of Ventilator-Associated Pneumonia: A Systematic Review and Metaanalysis*

Antonis Valachis, MD, PhD1; George Samonis, MD, PhD2; Diamantis P. Kofteridis, MD, PhD2

- Meta-analysis/ Systemic review
- 16 studies (8 comparative)

Crit Care Med. 2015;43:527-33

Addition of nebulised to i.v colistin

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical improvement</td>
<td>1.57</td>
<td>0.006</td>
</tr>
<tr>
<td>Microbiological eradication</td>
<td>1.61</td>
<td>0.01</td>
</tr>
<tr>
<td>Infection-related mortality</td>
<td>0.58</td>
<td>0.04</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.74</td>
<td>0.06</td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>1.18</td>
<td>0.45</td>
</tr>
</tbody>
</table>
The amikacin-fosfomycin inhalation system (AFIS), a combination of antibiotics administered with an in-line nebulizer delivery system, is being developed for adjunctive treatment of ventilator-associated pneumonia (VAP).

The reduced incidence of development of resistance to amikacin-fosfomycin (5:2) compared with that for amikacin or fosfomycin alone, and the lack of negative interactions with commonly used intravenous antibiotics, further supports the development of AFIS for the treatment of VAP.
Is the addition of Nebulised antibiotics beneficial in adults with VAP/VAT?
The NebAt project, developed by ESGCIP in collaboration with the Cochrane

Possible confounders:

- TYPE OF NEBULIZER (vibrating mesh vs ultrasonic or jet or common nebulisers)
- timing of antibiotic onset, type of antibiotics co-administered,
- dosage of iv colistin, dosage of nebulised colistin
- Data in process.............
Conclusions 1

- Revived antibiotics still need further evaluation for clinical efficacy, dosage and PKs in critically ill patients
- Colistin: emerging PK/PD data are helpful to optimize its clinical profile and reduce adverse events
- Fosfomycin: synergism has been demonstrated in vitro awaiting in vivo validation; early clinical experience in MDR/XDR infections is encouraging; requires companion drug to avoid resistance
- Rifampin: in vitro synergy against KPC producers gives it a new challenging opportunity
Conclusions 2

- Colistin could stand alone with the new dose regimens; however all data collected from non RCTs with *Klebsiella pneumoniae* point towards the necessity of combination treatments to maximise clinical efficacy.
- For *A. baumannii* and *Pseudomonas aeruginosa* infections, the necessity of colistin given in combinations was less clearly demonstrated.
- Nebulised route seems a new heaven for the revived antibiotics: increased clinical efficacy, avoidance of selection of resistance are reported; but more clinical data is required.
- Results of a systematic literature review with implementation of guidelines on the use of nebulized antibiotics in critically ill patients are pending.
Thank you for your attention

Grado on my arrival 7.5.15
9.00pm