Treatment options for MDR, XDR and PDR GNRs

Robert A. Bonomo, MD
Chief, Medical Service
Director VISN 10 GRECC
Louis Stokes Cleveland VAMC
Vice Chairman, Department of Medicine
University Hospitals Case Medical Center
Professor, Case Western Reserve University School of Medicine
Appreciation

- ECCMID organizing committee; Drs. Jordi Vila and Johann Pitout
- Support from VA and NIH
- Steris Foundation
- Currently (or have received) research grants from Pfizer, Merck, Rib-X, Check-Points, Abbott, Achaogen, AstraZeneca
Objective

- Personal approach: summarize select studies and treatment regimens being used against M-, X- and PDR GNRs; V Part story...
  - Colistin, Tigecycline, and Ab (I and II)
  - Combo rx for *P. aeruginosa* /Carbapenems (III)
  - Rx for Carbapenem Resistant *Kp*/Fosfomycin (IV, V)

- Apologies: becoming more of a believer in combo chemo
E-mail morning of 30th March.....

Robert

“....my grandfather (now in China) has been diagnosed with pneumonia caused by XDR A. baumannii. However, the drug to treat this infection--colistin antibiotic (Coly-mycin M 150 mg) is not available in China currently. His life is in danger if he can't be treated as soon as possible. Do you know any way [to get the drug]”?
Who are “M-, X-, and PDR GNRs”?

- *Acinetobacter baumannii*
- *Pseudomonas aeruginosa*
- *Klebsiella pneumoniae*
- *Burkholderia*
- *Stenotrophomonas*
- *E. coli*
- *Enterobacter spp.*
- *Citrobacter*

Criteria depend upon where one draws the line for R or S US or EU?

β-Lactams and Carbapenems
MDR is defined as resistance to one or more tested antimicrobials from 3 or more different classes.

Current Epidemiology of Multidrug-Resistant Gram-Negative Bacilli in the United States

Prevalence (%) of MDR among isolates reported to NNIS system and NHSN

<table>
<thead>
<tr>
<th>Year</th>
<th>Ab</th>
<th>Pa</th>
<th>Ec &amp; Kp</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>64</td>
<td>18</td>
<td>7</td>
</tr>
<tr>
<td>2002</td>
<td>66</td>
<td>20</td>
<td>9</td>
</tr>
<tr>
<td>2004</td>
<td>68</td>
<td>21</td>
<td>15</td>
</tr>
<tr>
<td>2006</td>
<td>63</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td>2008</td>
<td>74</td>
<td>17</td>
<td>13</td>
</tr>
</tbody>
</table>

M/SICU

VAP, CAUTI, CLABSI

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What are our current options for MDR GNRs?

“The basis for a new research agenda in Infectious Diseases”

“The old guard”

Colistin (Colistin methanesulfonate or Polymyxin E)?
Tigecycline?
Fosfomycin?
Carbapenem?????
Part I: A clinician’s contemporary look at colistin

Colistin: The Revival of Polymyxins for the Management of Multidrug-Resistant Gram-Negative Bacterial Infections

Matthew E. Falagas\textsuperscript{1,2,3} and Sofia K. Kasiakou\textsuperscript{1}

Polymyxins Revisited

David Landman, Claudiu Georgescu, Don Antonio Martin, and John Quale\textsuperscript{*}

Division of Infectious Diseases, SUNY-Downstate Medical Center, Brooklyn, New York
Basic PK/PD principles as they relate to MDR GNRs

T> MIC
- β-Lactams
- Monobactams
- Tigecycline

AUC or Cmax/MIC
- Aminoglycosides
- Quinolones
- Metronidazole

- Colistin displays concentration-dependent killing against susceptible strains of *P. a, A. b* and *K. p*
- fAUC/MIC best correlate with its efficacy.
- Optimal bactericidal effects against *P. a* were observed when AUC/MIC= 30
What Is the Efficacy and Safety of Colistin for the Treatment of Ventilator-Associated Pneumonia? A Systematic Review and Meta-Regression

Diana F. Florescu,1 Fang Qiu,2 Megan A. McCartan,3 Cezarina Mindrî4 Paul D. Fey,4 and A. C. Kalil1

1Infectious Diseases Division, 2Biostatistics Department, 3Department of Pharmaceutical and Nutrition Care, and 4Pathology Microbiology Department, Nebraska Medical Center, Omaha

- **Extensive review:** 6 controlled studies met inclusion criteria; 14 single-arm studies
- 72% favorable clinical response rate and 34% in-hospital mortality rate with colistin therapy were within the range of clinical response and mortality rates reported in the literature.
- Colistin is indeed a “valuable antibiotic”
Clinical response for colistin for rx of VAP in single arm studies

<table>
<thead>
<tr>
<th>Variables</th>
<th>Studies, No. (Patients No.)</th>
<th>Efficacy of Colistin, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult patients only</td>
<td>13 (409)</td>
<td>71 (.62—.79)</td>
</tr>
<tr>
<td>By route of administration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous</td>
<td>9 (178)</td>
<td>66 (.58—.74)</td>
</tr>
<tr>
<td>Aerosolized</td>
<td>3 (191)</td>
<td>80 (.60—.999)</td>
</tr>
<tr>
<td>Intravenous + aerosolized</td>
<td>3 (169)</td>
<td>78 (.71—.85)</td>
</tr>
<tr>
<td>By definition of VAP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definition provided</td>
<td>12 (399)</td>
<td>71 (.61—.80)</td>
</tr>
<tr>
<td>None provided</td>
<td>3 (30)</td>
<td>80 (.66—.93)</td>
</tr>
<tr>
<td>By study design</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prospective</td>
<td>7 (147)</td>
<td>78 (.67—.89)</td>
</tr>
<tr>
<td>Retrospective</td>
<td>8 (282)</td>
<td>68 (.58—.77)</td>
</tr>
<tr>
<td>By geographic region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>11 (347)</td>
<td>77 (.69—.85)</td>
</tr>
<tr>
<td>Asia</td>
<td>3 (64)</td>
<td>55 (.40—.70)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; VAP, ventilator-associated pneumonia.
Population PK model for CMS and colistin in critically ill patients with a wider range of renal function (105 patients, 851 samples; CCr and BW)

Current dosing is not optimal to achieve bacterial killing...low and potentially suboptimal plasma colistin concentrations
What was learned!!

- Remedy: Administration of a loading dose (300 mg)
- If MIC \( \geq 1 \), use as part of a combination regimen
- Colistin exposure during the first 12 h “may be beneficial, providing enough net killing such that the immune system may be able to eradicate any remaining colistin-resistant cells”
- Paradox? Underdose, yet toxic!
Nephrotoxicity occurs in up to 40-50% of patients.

Oxidative stress plays a role in nephrotoxicity (measured the renal excretion of N acetyl B-D glucosaminidase).

Ascorbic acid is protective!!
Drink your orange juice!
A picture is worth a 1000 words

Control

Mild tubular damage

Tubular damage

Cortical necrosis

Mild focal necrosis

Col + ascorbic acid
• Melatonin is an antioxidant and prevents renal injury of vancomycin and gentamicin.

• Free radical mediated processes.
Colistin and *Acinetobacter* spp.

**Acinetobacter baumannii**: Emergence of a Successful Pathogen

Anton Y. Peleg,¹* Harald Seifert,² and David L. Paterson³,⁴,⁵

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**REVIEW ARTICLE**

**CURRENT CONCEPTS**

Acinetobacter Infection

L. Silvia Munoz-Price, M.D., and Robert A. Weinstein, M.D.

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Are we closing in on an “elusive enemy”? The current status of our battle with *Acinetobacter baumannii*

Federico Perez,¹,² Rafael Ponce-Terashima,² Mark D. Adams³ and Robert A. Bonomo¹,²,⁴,*
“After an exhaustive review of much the available evidence up to 2007....”

TABLE 4. Combinations of antibiotics demonstrating enhanced activity against carbapenem-resistant *A. baumannii*

<table>
<thead>
<tr>
<th>Study type</th>
<th>Antibiotic combination (reference[s])</th>
</tr>
</thead>
<tbody>
<tr>
<td>In vitro</td>
<td>Meropenem + ampicillin-sulbactam (90, 92)</td>
</tr>
<tr>
<td></td>
<td>Imipenem + ampicillin-sulbactam (26)</td>
</tr>
<tr>
<td></td>
<td>Rifampin + ampicillin-sulbactam (197)</td>
</tr>
<tr>
<td></td>
<td>Rifampin + polymyxin B (197, 230)</td>
</tr>
<tr>
<td></td>
<td>Rifampin + colistin (69)</td>
</tr>
<tr>
<td></td>
<td>Imipenem + polymyxin B + rifampin (230)</td>
</tr>
<tr>
<td></td>
<td>Imipenem + polymyxin B (230)</td>
</tr>
<tr>
<td></td>
<td>Cefepime + ampicillin-sulbactam (173)</td>
</tr>
<tr>
<td>Animal models</td>
<td>Meropenem + ampicillin-sulbactam (92)</td>
</tr>
<tr>
<td></td>
<td>Imipenem + ampicillin-sulbactam (226)</td>
</tr>
<tr>
<td></td>
<td>Imipenem + tobramycin (124)</td>
</tr>
<tr>
<td></td>
<td>Imipenem + rifampin (124, 226)</td>
</tr>
<tr>
<td></td>
<td>Rifampin + tobramycin or colistin (124)</td>
</tr>
<tr>
<td></td>
<td>Rifampin + ampicillin-sulbactam (226)</td>
</tr>
<tr>
<td>Clinical experience</td>
<td>Rifampin + colistin (126, 146)</td>
</tr>
<tr>
<td></td>
<td>Colistin + othersa (88, 189)</td>
</tr>
</tbody>
</table>
7 year study

Patients (258) received colistin for at least 72 hours

170 (65.9%) *Acinetobacter baumannii*

83% efficacy rate (colistin alone)
The Outcomes of Using Colistin for Treating Multidrug Resistant Acinetobacter Species Bloodstream Infections

Seung-Kwan Lim¹, Sang-Oh Lee²,³, Seong-Ho Choi⁴, Jae-Phil Choi⁵, Sung-Han Kim²,³, Jin-Yong Jeong³, Sang-Ho Choi²,³, Jun Hee Woo²,³, and Yang Soo Kim²,³

Despite the identification of Acinetobacter baumannii isolates that demonstrate susceptibility to only colistin, this antimicrobial agent was not available in Korea until 2006. The present study examined the outcomes of patients with multidrug resistant (MDR) Acinetobacter species bloodstream infection and who were treated with or without colistin as part of their regimen. The colistin group was given colistin as part of therapy once

Mortality @ 30 days pBSI occurred for 11/31 patients in the colistin group and for 15/39 patients in the non-colistin group (35.5% vs. 38.5%, respectively, \( P = 0.80 \)).

Colistin does NOT influence the 30 day mortality of patients with a MDR Acinetobacter spp. bloodstream infection.
Colistin$^R$


- Col$^R$ due to modifications of LPS; pmr (Adams...Bonomo, AAC US) vs. lpxA,-C, and -D (Li and Nation, Australia); Parks lab in S. Korea found pmr.

- Heteroresistance (subpopulations of genetically identical subclones that are more R than the parent) by Li et al; implications for rx?

- “Colistin dependence”. 77 yo diabetic male with FI and bacteremia; “increasingly luxuriant growth”.

Impaired Virulence and In Vivo Fitness of Colistin-Resistant Acinetobacter baumannii

Rafael López-Rojas,^1^ Juan Domínguez-Herrera,^1,2^ Michael J. McConnell,^1,3^ Fernando Docobo-Pérez^1^ Younes Smani,^1^ María Fernandez-Reyes,^2^ Luis Rivas,^2^ and Jerónimo Pachón^1^

Lower expression of metabolic proteins and OmpA

Progress towards a vaccine
Part II: Is there hope for Tigecycline?
Tigecycline?

1. Rapid resistance can emerge;
2. Cases of breakthrough bacteremia reported;
3. Adequacy of blood levels??
4. Safety??

Bacteremic patients treated with tige failed to clear their bacteremia 10-fold more commonly than patients treated with comparator drugs.

Gordon JAC 2009, Gardiner CID

Giamarellou & Poulakou, Drugs. 2009
14 randomized trials, 7400 patients
Adverse effects were common (n and v);
Lower treatment success -- non significant difference
All cause mortality was higher - non significant difference

Should tige be used in the treatment of serious MDR infections in immuno-compromised hosts ?????
Tigecycline MIC went from < 0.25 to 8 mg/L

Breakthrough bacteraemia due to tigecycline-resistant *Escherichia coli* with New Delhi metallo-β-lactamase (NDM)-1 successfully treated with colistin in a patient with calciphylaxis

Neil R. H. Stone¹, Neil Woodford², David M. Livermore², Julia Howard¹, Rachel Pike², Shazad Mushtaq², Claire Perry² and Susan Hopkins¹

This is the first carbapenemase-producing *E. coli* confirmed to be resistant to tigecycline by the national reference laboratory. An 8-fold reduction in the MIC of tigecycline for the resistant isolate when tested in the presence of the efflux inhibitor phenyl-arginine β-naphthylamide (PAβN; at 40 mg/L) was observed (compared with only a 2-fold reduction for the susceptible isolate), which suggests up-regulated efflux as the resistance mechanism. Future studies will ascertain the specific pump(s) involved.
Many studies (22+) show that MICs for *Acinetobacter* spp are in susceptible range (<2)

Recognizing that resistance emerges on treatment, does one trust monotherapy with tigecycline? Combo is better!!!
Colistin and vanco??

Potent Synergy and Sustained Bactericidal Activity of a Vancomycin-Colistin Combination versus Multidrug-Resistant Strains of *Acinetobacter baumannii*\(^{1}\)

N. C. Gordon, K. Peng, and D. W. Wareham\(^{1,2}\)

*In Vivo Efficacy of Glycopeptide-Colistin Combination Therapies in a Galleria mellonella Model of Acinetobacter baumannii Infection*\(^{1}\)

M. Hornsey\(^{1}\) and D. W. Wareham\(^{1,2}\)
Part III: New treatment regimens for *P. aeruginosa*
Combination therapy for PSDA?

Resistance Emergence Mechanism and Mechanism of Resistance Suppression by Tobramycin for Cefepime for *Pseudomonas aeruginosa*

G. L. Drusano, Robert A. Bonomo, Nadzeya Bahniuk, Juergen B. Bulitta, Brian VanScoy, Holland DeFilio, Steven Fikes, David Brown, Sarah M. Drawz, Robert Kulawy, and Arnold Louie

Ordway Research Institute, Albany, New York, and Louis Stokes Cleveland Department of Veterans Affairs Medical Center, and Department of Medicine, Pathology, Pharmacology, and Molecular Biology and Microbiology, Case Western Reserve University School of Medicine, Cleveland, Ohio

Demonstrated resistance suppression in both the wild-type and the stably derepressed isolates. Quantitating the RNA message by quantitative PCR demonstrated that tobramycin decreased the message relative to that in cefepime-alone experiments. Western blotting with AmpC-specific antibody for *P. aeruginosa* demonstrated decreased expression. We concluded that suppression of β-lactamase expression by tobramycin (a protein synthesis inhibitor) was at least part of the mechanism behind resistance suppression. Monte Carlo simulation demonstrated that a regimen of 2 g of cefepime every 8 h plus 7 mg/kg of body weight of tobramycin daily would provide robust resistance suppression for *Pseudomonas* isolates with cefepime MIC values up to 8 mg/liter and tobramycin MIC values up to 1 mg/liter. For *P. aeruginosa* resistance suppression, combination therapy is critical.
Combinations were additive or synergistic
Synergistic Killing of Multidrug-Resistant Pseudomonas aeruginosa at Multiple Inocula by Colistin Combined with Doripenem in an In Vitro Pharmacokinetic/Pharmacodynamic Model

Phillip J. Bergen,¹ Brian T. Tsuji,² Jurgen B. Bulitta,²,³ Alan Forrest,²,³ Jovan Jacob,¹ Hanna E. Sidjabat,⁴ David L. Paterson,⁴ Roger L. Nation,¹† and Jian Li¹,*†
Part IV: Carbapenem-resistant
*Klebsiella pneumoniae*
Prospective Observational Study of the Impact of VIM-1 Metallo-β-Lactamase on the Outcome of Patients with Klebsiella pneumoniae Bloodstream Infections

George L. Daikos, 1* Panayiotis Petrikkos, 1 Mina Psychogiou, 1 Chris Kosmidis, 1 Evangelos Vryonis, 2 Athanasios Skoutelis, 2 Kleoniki Georgousi, 3 Leonidas S. Tzouvelekis, 4 Panayotis T. Tassios, 4 Christina Bamia, 5 and George Petrikkos 1

- Age
- Rapidly fatal underlying disease
- Carbapenem resistance (MIC > 4 mg/L) were independent predictors of death.
Carbapenemase-producing *Klebsiella pneumoniae*: (when) might we still consider treating with carbapenems?

G. L. Daikos¹ and A. Markogiannakis²

1) First Department of Propaedeutic Medicine, University of Athens and 2) Department of Pharmacy, Laikon General Hospital, Athens, Greece

expressed by several experts. The data analyses presented herein support the notion that carbapenems may be a reasonable treatment option against CPKP, provided that: (i) the carbapenem MIC for the infecting organism is \( \leq 4 \text{ mg/L} \); (ii) a high-dose prolonged-infusion regimen is administered to drive the PK/PD profile to acceptable exposures; and (iii) this class of agent is administered in combination with another active compound. Finally, the data summarized in this review indicate that the EUCAST clinical breakpoints (susceptible, \( \leq 2 \text{ mg/L} \); intermediate, 4 mg/L) can direct physicians in making treatment decisions. In the absence of control trials, the continued
The problem: A patient, hospitalized for Ao dissection complicated by “intra-abdominal catastrophe” and ATN, developed bacteremia with $bla_{KPC-2}$.

The solution: High-dose, continuous-infusion meropenem $>$ MIC eradicated the infection.
Dori (4 mg/L) and erta (64 mg/L) together are better than either alone
Comparative Effectiveness of Aminoglycosides, Polymyxin B, and Tigecycline for Clearance of Carbapenem-Resistant Klebsiella pneumoniae from Urine

Michael J. Satlin,¹* Christine J. Kubin,² Jill S. Blumenthal,³ Andrew B. Cohen,³ E. Yoko Furuya,⁴ Stephen J. Wilson,¹ Stephen G. Jenkins,¹ and David P. Calfee¹

FIG. 2. Microbiologic clearance rates by the antimicrobial treatment cohort. AG, aminoglycoside; PB, polymyxin B; TG, tigecycline; *, *P = 0.02; **, *P < 0.001. *P values calculated using the χ² test to compare the clearance rate of the cohort to that of the AG cohort.
Combination regimen was independently associated with survival ($P=0.02$).

The 28-day mortality was 13.3% in the combination therapy group compared with 57.8% in the monotherapy group ($P=0.01$).
<table>
<thead>
<tr>
<th>Definitive treatment</th>
<th>n (%)</th>
<th>Mortality n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination therapy</td>
<td>15 (44)</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td>Colistin-polymyxin B combined with:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbapenem</td>
<td>5 (33)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>4 (12)</td>
<td>0</td>
</tr>
<tr>
<td>Fluoroquinolone</td>
<td>1 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Tigecycline combined with:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbapenem</td>
<td>3 (20)</td>
<td>0</td>
</tr>
<tr>
<td>Aminoglycoside</td>
<td>1 (12)</td>
<td>0</td>
</tr>
<tr>
<td>Carbapenem-fluoroquinolone</td>
<td>1 (7)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Aztreonam-fluoroquinolone</td>
<td>1 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Cefepime-gentamicin</td>
<td>1 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>19 (46)</td>
<td>11 (57.8)</td>
</tr>
<tr>
<td>Colistin-polymyxin B</td>
<td>7 (36.8)</td>
<td>4 (57.1)</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>5 (26.3)</td>
<td>4 (80)</td>
</tr>
<tr>
<td>Carbapenem</td>
<td>4 (21)</td>
<td>2 (50)</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>15 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Ampicillin-sulbactam</td>
<td>1 (5.2)</td>
<td>0</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>1 (5.2)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Total</td>
<td>34 (83)</td>
<td>13 (38.2)</td>
</tr>
</tbody>
</table>
Part V: Fosfomycin, a last resort

In Vitro Activity of Fosfomycin against bla<sub>KPC</sub>-Containing Klebsiella pneumoniae Isolates, Including Those Nonsusceptible to Tigecycline and or Colistin▼

Andrea Endimiani,¹,²*, Gopi Patel,³ Kristine M. Hujer,¹,² Mahesh Swaminathan,³ Federico Perez,¹,² Louis B. Rice,² Michael R. Jacobs,⁴ and Robert A. Bonomo¹,²,5,6,*
More studies with Fosfomycin

- Micro: 17 studies, 5057 isolates; 11 / 17 studies - at least 90% were S to fosfo; 94% efficacy rate
- Synergy w/gent, amik, taz, fep, cipro, levo, and aztreonam; *Kp, Ec, Pa* – carbs, col netil and tige
- Mutants selected? Maybe not a real clinical phenomenon?
- UTI indication and success (meta-analysis of 27 trials)
- Combination therapy?

“New kids on the block”

- ACHN-490 (Plazomicin)
- BAL30072 a siderophore sulfactam
- GSK2251052 -boron containing aminoacyl -tRNA synthetase inhibitor
- NXL104 (Avibactam)
Letters to the Editor

In Vitro Activity of NXL104 in Combination with β-Lactams against Klebsiella pneumoniae Isolates Producing KPC Carbapenemases

Evaluation of Ceftazidime and NXL104 in Two Murine Models of Infection Due to KPC-Producing Klebsiella pneumoniae

Andrea Endimiani, Kristine M. Hujer, Andrea M. Hujer, Mark E. Pulse, William J. Weiss, and Robert A. Bonomo

Graph showing survival percentage (%) against Ceftazidime dose (mg/Kg) in murine models.
ACHN-490, a Neoglycoside with Potent In Vitro Activity against Multidrug-Resistant Klebsiella pneumoniae Isolates

Andrea Endimiani,1,2* Kristine M. Hujer,1,2 Andrea M. Hujer,1 Eliana S. Armstrong,3 Yuvraj Choudhary,1 James B. Aggen,3 and Robert A. Bonomo1,2,4,5*

![Chemical structure of ACHN-490]

Activity of ACHN-490 Tested Alone and in Combination with Other Agents against Pseudomonas aeruginosa

Glenn A. Pankuch,1 Gengrong Lin,1 Aya Kubo,2 Eliana S. Armstrong,2 Peter C. Appelbaum,1 and Klaudia Kosowska-Shick1*

*Corresponding author.
In vivo and in vitro activity of the siderophore monosulfactam BAL30072 against Acinetobacter baumannii

Thomas A. Russo¹⁻⁵*, Malcolm G. P. Page⁶, Janet M. Beanan¹⁻², Ruth Olson¹⁻², Andrea M. Hujer⁷, Kristine M. Hujer⁷, Michael Jacobs⁸, Saralee Bajaksouzian⁸, Andrea Endimiani⁷ and Robert A. Bonomo⁷⁻¹¹

MICs, time kill, and animal models--promising

In vitro activity of the siderophore monosulfactam BAL30072 against meropenem-non-susceptible Acinetobacter baumannii

Paul G. Higgins¹, Danuta Stefanik¹, Malcolm G. P. Page², Meredith Hackel³ and Harald Seifert¹*
E-mail evening of 30th March.....

- .....is intermediate to cefoperazone/sulbactam & tigecycline

- My grandfather has been treated with cefoperazone/sulbactam plus tacicoplanin initially but lately with cefoperazone/sulbactam, azithromycin & tigecycline to get his fever down & lung inflammation controlled....
Summary

• Extraordinary challenge against cunning pathogens

• Patterns are clear
  – Colisitin is here to stay and it works; get the dosing right; better with a partner against some infections ($Kp$, $Pa$)? Mitigate toxicity with antioxidants
  – Not sure about tige (alone)
  – Fosfo will be capitalized further
Summary

• For *Acinetobacter*, Colistin with a partner? Complex issue/strain type; Maybe a vaccine???

• Await more studies with new drugs (Avibactam, BAL30072, and plazomicin)

• Can I be optimistic? Yes, I think...