Disclosure of Relationships to Industry
Richard P. Wenzel, MD, MSc

<table>
<thead>
<tr>
<th>Company</th>
<th>Research</th>
<th>Consulting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rib-X</td>
<td>▲</td>
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</tr>
<tr>
<td>Pfizer</td>
<td>▲</td>
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<tr>
<td>3M</td>
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<tr>
<td>Boehringer Ingelheim</td>
<td>▲</td>
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<td>Biomerieux</td>
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<tr>
<td>Sanofi-Aventis</td>
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<tr>
<td>Vestagen</td>
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<td></td>
</tr>
</tbody>
</table>

No speaking bureau; no stocks, no royalties

Acinetobacter: An MDR Nosocomial Pathogen

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Department of Internal Medicine
Medical College of Virginia
Virginia Commonwealth University
Richmond, Virginia

Acinetobacter* (ακινετοσ, akinetos)

- Gram negative aerobes, non-motile
- Non-fermenting, non-fastidious
- Catalase positive, oxidase negative
- Important MDR hospital pathogen
- 87½ resistance genes on large "resistance island", AbaRI- almost all from other GNRs

Prof. Beijerinck identifies Acinetobacter in soil - 1911

Bristov and Prevot, Ann Inst Pasteur 1954; 86:722-8 (d. Heterotrope monomotile among Achromobacter)
Fournier et al PLoS Genet 2006; 2:17
**Acinetobacter – Increased Colonization and Infection in Warm Months**

- 53% med students and new nurses' skin colonized in summer in Hong Kong vs 32% in winter
- 50% increased infection rates from July to October
- For each 10°F increase a 17% increase in monthly infection rate

*Cho et al J Clin Microbiol 1999; 37:2962-7*

*Monte-Price & Weinstein NJJM 2008; 12:1271-81*

*Perencevich et al ICU 2008; 25:1124-31*

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**Acinetobacter BSI; Late Hospital Stay Infection (week 3-4)**

- SCOPE study
- 1.6% of ICU BSI
- Crude mortality
  - 34% overall
  - 43% in ICU


---

**Identifying Hi-risk Patients for *A.baumanii* Infections**

- 137 patients and controls matched for LOS, ward, time of year

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVC</td>
<td>17.7 (4.3 – 71.6)</td>
</tr>
<tr>
<td>Charlson score &gt;3</td>
<td>17.5 (4.3 – 73.1)</td>
</tr>
<tr>
<td>Prior MRSA**</td>
<td>12.7 (1.9-83.1)</td>
</tr>
<tr>
<td>Prior β-lactam*</td>
<td>9 (2.4-33.5)</td>
</tr>
<tr>
<td>Surgery</td>
<td>6 (1.6-221.1)</td>
</tr>
</tbody>
</table>

* last 30 d / ** last 6 mo

*JAC 2008; 62:1130-7*
**Acinetobacter and Insulin Resistance**

Acinetobacter: insulin – cleaving protease in periplasm

*Biomol Bichem Acta* 1989; 48:661-71

Burn patients 2002-3 (n=473)

9% attack rate with Acinetobacter
- 4/15 (27%) pre-existing D.M.
- 39/458 (8.5%) no prior D.M.

Acquired glucose intolerance (fasting glucose level) 11/16 (69%) infected vs 39/458 (8.5%) uninfected

*J Burn Care Rehab* 2003; 26:405-8

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**Acinetobacter BSI – Predictors of 14-day Mortality**

- Prospective Observational Study (n=100)
- 75% in ICUs/septic shock 37%
- 48% MDR
- 63% mortality – 14 days
- 24% only received initial concordant Rx
  - Univariate RR 1.67 (1.13-2.05)
  - Multivariate predictors
    - Carbapenam resistance RR 1.63 (1.191.89)
    - Septic shock RR 1.65 (1.23-1.85)
    - Diabetes Mellitus RR 1.68 (1.22-1.76)


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**Acinetobacter: Spread by Contaminated Gloves**

- Carbapenam resistance 36%
  - VAP/BSI
  - Inj Int Care Hosp Epidemiol 2008; 29:996-1001
- Carbapenam-resistant strains found on 60% gloves following patient care
  - J Hosp Infect 2009; online 21 June
- Transmission in an ICU
Acinetobacter Acquired in Acute Care Hospital Leads to High Prevalence in a LTC Facility

55% of LTCF patients had been admitted to ACH in year prior to LTC admission

Furino et al AJIC 2008; 36:468

44(30%) Colonized sputum, peri-rectal, wound

Colonized sputum, peri-rectal, wound

Acinetobacter is isolate A

Acinetobacter is isolate B

Klebsella pneumoniae K3

Klebsella pneumoniae K41

Survival of Clinical Isolates Dried Onto Stainless Steel Discs

Acinetobacter isolates have unusually long environmental survival among Gram Negatives

ICU Outbreak of Clonal Colistin-Resistant MDR A. baumannii (n=12) – Spain: Role of Environmental Decontamination

Emphasis on environmental decontamination for control

Median age 55; 75% (9/12) died

1 year for control:

Focus:

Revised cleaning protocol/decontamination

+/− environmental surveys

Staff education/posters re: contact isolation

Valenza et al ICHE 2009; 30:257-63
Acinetobacter – Found in Potable Water, Faucets in Hospitals, Sinks

Is hospital water an unrecognized reservoir? Silver and copper ions will inhibit Acinetobacter (more resistant than Legionella, Ps. aeruginosa and Stenotrophomonas).

0.4 and 0.6 mg/L of copper ions achieved more than 99.999% reduction of A. baumannii within 24 and 6 h, respectively.

0.08–0.08 mg/L of silver ions achieved more than 99.999% reduction of A. baumannii within 96 h.


Acinetobacter in Hospital Water: Daily Flushing for 1 Week Followed by Weekly Thereafter

No. PTS time (mo) 18 10 - before 19 28 - after * P<0.01

* Only 1/19 original clone

1 gal bleach
10 gal water

Flushing synchronized in all sinks

Am J Infect Control 2009; Epub Nov 7th

50% Effectiveness of Isolation Precautions for A. baumannii: An Ecological Study

Multivariate Analysis: RR=0.5 (0.4 - 0.6)

After control gender, age, immunosuppression, McCabe score, antibiotic use (p<0.001)

Private room or cohort
Gown/gloves
HW-alcohol

ICHE 2008; 29:1118-23
Could Daily Bathing with Chlorhexidine Reduce Acinetobacter Acquisition and Infections?

In quasi-experimental study
6 mo reg soap => 6 mo chlorhexidine
► MRSA acquisition decreased 32%
► VRE acquisition decreased 50%
► VRE BSI decreased 73%

Crit Care Med 2009; 37:1858-65

Daily 4% Chlorhexidine Baths Decreased ICU-related MDR A. baumannii Colonization and Bloodstream Infections

Quasi-experimental design
Before 2/01 – 2/02) – after (3/02 – 12/03) comparison

Attack rate of A. baumannii
BSI – decreased
4.6% => 0.6% (OR=7.6, p<.001)

Incidence density of A. baumannii
BSI – decreased
7.8 to 1.25/1000 pt-days (85% reduction)


Gardine-Coated Latex or Nitrile Gloves Significantly Reduced Contamination with MDR Acinetobacter

- Gardine (combination of brilliant green dye and chlorhexidine)
- Synergistic antimicrobial efficacy
  Oral Oncol 2007; 43:159-64
- Gloves swabbed with 1.5 x 10<sup>6</sup> cfu/mL
  dried -> segments streaked onto agar
- All Acinetobacter killed within 10 minutes

MDR Acinetobacter: Prevention

- Daily 4% chlorhexidine baths for ICU patients
- Strict environmental decontamination focus → consider flushing sinks with bleach
- Proper isolation precautions
  - Isolate admits from hi-risk LICF
- Assiduous infection control → consider gauze gloves?

MDR Acinetobacter: Approach to Therapy

- Traditional approach: single agents and physician comfort with drugs
- Higher doses of single agents
- Seeking synergy with ≥ 2 agents
- Considering specific case series on use of drugs

Traditional Approach to MDR Acinetobacter: Physician Comfort with Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipenem</td>
<td>1-2 grams</td>
<td>Every 8 h</td>
</tr>
<tr>
<td>Meropenem</td>
<td>(2:1)</td>
<td>1 Gram</td>
</tr>
<tr>
<td>+ Sulfactam</td>
<td>Every 3-4 h</td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td>1-2 million U</td>
<td>Every 8 h</td>
</tr>
<tr>
<td>Colistin</td>
<td>1-3 million U</td>
<td>Every 8 h</td>
</tr>
<tr>
<td>Tigecycline</td>
<td></td>
<td>FQ</td>
</tr>
<tr>
<td>FQ</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Colistin - Dosages**

Colistin Methanesulfonate (CMS):
- International units (~12,500 iu per mg CMS)
- Dosages used: 1-3 million units every 8 hours for 60 kg patient with normal renal function

Colistin Base Activity:
- Dosages used 2.5-5 mg/kg/day in 2 to 4 divided doses [150-300 mg base] or 400-800 mg CMS per day for a 60 kg patient with normal renal function


**Colistin – Dosage Interval**

Rapid, concentration dependent bactericidal drug

*JAC* 2008; 62:1311-8

AUC/MIC – most predictive index of activity vs *P. aeruginosa* in mouse thigh infection model

*IC-4* 2007; Duchani et al

More emergence of resistance to *P. aeruginosa* in in vitro model with single dose vs 3 doses/day

*JAC* 2008; 61:636-42

More nephrotoxicity in rats with single vs multiple daily doses

*AAC* 2008; 52:1159-61

**Pharmacokinetics of Colistin in Critically Ill Patients (n=18)**

Dose: 3 million units every 8 hours

Cmax after 1st dose: ~60 mg/l,
lower than 4th dose: 2.3 mg/l because of slow formation of colistin from CMS

Question: Loading dose?? — no data

*AAC* 2009; 53:3430-6
High Dose Ampicillin-Sulbactam vs Colistin for MDR *A. baumannii*


<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Resolution signs/symptoms</th>
<th>Eradication from BAL day 5</th>
<th>28-d mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colistin (n=15)</td>
<td>60%</td>
<td>23%</td>
<td></td>
</tr>
<tr>
<td>Amp-Sulbactam (n=13)</td>
<td>62%</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>35% Col vs 15% Amp-Sulbactam</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In Vitro Triple Drug Synergy for CNS/blood Isolate of *A. baumannii*


- Fatal case in 78 year old s/p. external ventricular drain
- Intravenous Meropenam + Sulbactam
- MIC: Mero (250), Sulb (128), Col (1)
- AB-Free: Meropenem, Sulbactam, Colistin
- Mero + Sulb + Col

Colistin, Meropenam, Rifampin Combination Rx for MDR *A. baumannii*

- Colistin – 2 million units twice daily
- Meropenam – 1 Gram 3 times daily
- Rifampin – 600 mg/day
- Synergy demonstrated – checkerboard
- Slow clinical improvement of multifocal infection in 16 yr old, post auto accident pt.
- Col + Rif and Mero + Rif Synergistic
- Col + Mero additive

Minerva Anestesiol. 2007; 73:181-5
MDR Acinetobacter: Looking for High Synergy

Adapted from Gilad and Carmeli Drugs 2008; 68:165-89

Colistin and Rifampin to treat MDR A. baumanii infections

Prospective:
Clinical and microbiological responses in 22/29 ICU patients
Dose: 2 million u colistin every 8 hours
Rifampin 10 mg/kg every 12 hours
No toxicity noted
J-IC 2008; 61:417-20

Retrospective:
Colistin base 400 mg every 8 hours
Rifampin 600 mg daily
7/10 with VAP improved
Internal J Antimicrob Agents 2008; 32:281-4

Toxicity After Several Weeks of Colistin (n=19)

Mean use = 43 d ± 14
Mean dose = 4.4 million U ± 2.1 million
Median creatinine increase 0.25 mg/dL but returned to baseline plus 0.1 mg/dL
No apnea. No neuromus. blockade.

BMC Infect Dis. 2005; 5:1
(10 January)
In Vitro Interaction of Tigecycline with Other Antibiotics for MDR A. baumannii (n=22)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Synergy: Only tigecycline non-susceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levoflox</td>
<td>2/4</td>
</tr>
<tr>
<td>Amik</td>
<td>1/2</td>
</tr>
<tr>
<td>Imipen</td>
<td>1/2</td>
</tr>
<tr>
<td>Colistin</td>
<td>1/2</td>
</tr>
</tbody>
</table>

Antagonism: Tigecycline + pip-tazo (33%) = 8 strains, none confirmed with time-kill

No synergetic activity was bactericidal

Acinetobacter VAP

<table>
<thead>
<tr>
<th>No pts</th>
<th>Drugs</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>Colistin 2 million units every 8 h</td>
<td>Micro clearance</td>
</tr>
<tr>
<td>26</td>
<td>Aerosolized colistin 1 million u every 8 h</td>
<td>All favorable outcome</td>
</tr>
</tbody>
</table>

(Can use aerosolized colistin 500,000 – 2 million U every 8 h)

Intrathecal Colistin Rx for Post-Neurosurgical MDR Acinetobacter baumanii Meningitis (n=32)

<table>
<thead>
<tr>
<th>Intrathecal (n=8)</th>
<th>Intraventricular (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>35</td>
</tr>
<tr>
<td>Mean dose (mg)</td>
<td>8 ± 3.3</td>
</tr>
<tr>
<td>Mean duration (d)</td>
<td>18.6 ± 5.7</td>
</tr>
<tr>
<td>Chemical meningitis or ventriculitis</td>
<td>2/8</td>
</tr>
<tr>
<td></td>
<td>13.8 ± 7.3</td>
</tr>
<tr>
<td></td>
<td>18.9 ± 7.9</td>
</tr>
<tr>
<td></td>
<td>2/8</td>
</tr>
<tr>
<td></td>
<td>1/24</td>
</tr>
</tbody>
</table>

IDSA recommends 10 mg every 24 hr

* Manufacturer does not recommend intrathecal.
Rx Acinetobacter - Pending Antibiogram

VAP
- Colistin aerosolized
- Colistin aerosolized plus IV Colistin

With antiobiogram:
- Focus on synergy
- Test for synergy if possible
- Higher doses are an option
- Safety issues will inform therapy

BSI
- Colistin IV
- Colistin IV plus IV Rifampin

Meningitis
- IT Colistin
- IT Colistin plus Rifampin

IT - intrathecal

MDR Acinetobacter
- Emerging, long-stay ICU pathogen
- Special predilection for diabetics, summer, LTCF
- Reasonable preventive measures defined
- No controlled trials to define optimal therapy
- Knowledge of Colistin Important
Case Reports - Successful Therapy with Tigecycline Plus Other Drugs

<table>
<thead>
<tr>
<th>Condition</th>
<th>Initial Rx</th>
<th>Final Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septic shock</td>
<td>Colistin</td>
<td>Colistin</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Meropenam</td>
<td>Meropenam</td>
</tr>
<tr>
<td>abd abscess</td>
<td></td>
<td>Tigecycline</td>
</tr>
<tr>
<td>BSI*</td>
<td>Ticar-Clav</td>
<td>Pip-Tazo</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Rifampin</td>
<td>Sulfamethox</td>
</tr>
<tr>
<td>s/p trauma</td>
<td></td>
<td>Tigecycline</td>
</tr>
</tbody>
</table>

* Septic shock
* BSI


Acinetobacter: Nosocomial Meningitis

<table>
<thead>
<tr>
<th>Agent</th>
<th>Cure</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulbactam</td>
<td>5/7</td>
<td>J Hosp Inf 2004; 56:328</td>
</tr>
<tr>
<td>1 gm every 6 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colistin</td>
<td>1/1</td>
<td>Eur J Clin Microbiol</td>
</tr>
<tr>
<td>5 mg/kg/d</td>
<td></td>
<td>Infect Dis 2002; 21:212-4</td>
</tr>
<tr>
<td>Colistin</td>
<td>13/14</td>
<td>J Clin Microbiol</td>
</tr>
<tr>
<td>IV/IT/IV</td>
<td></td>
<td>2005; 43:4916-7</td>
</tr>
<tr>
<td>Or IV/IT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IT dose (125,000-500,000 u/d)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Most experience with Colistin alone or with tobram, amik, rifampin

Patient Carriage of MDR A. baumannii

- 52 patients with carriage (recent or remote) were sampled at 6 body sites
- Sensitivity only 55% for recent carriers
  - Pharynx, wounds, ET aspirates highest yield
- 5/30 remote carriers were +, mean duration of 17.5 months, up to 42 months
- Bottom line: Carriage of MDR A. baumannii can be prolonged, and even multisite sampling may be insensitive

Polymyxin B (1 mg = 10,000 units)

Differs by 1 AA from Polymixin E-Colistin

Dose – CL\textsubscript{CR} ≥ 80

- 1.5-2.5 mg/kg/d – 2 doses
- 2.5 mg/kg load => 1-1.5 mg/kg/d

30-80

- 2.5 mg/kg load => 1-1.5 mg/kg every 2-3 days

<30

- Aneuric 2.5 mg/kg/d
- 1 mg/kg every 5-7 d

Ann Pharmacother 2006; 40:1939-45

Acinetobacter: Infrequent but Top 10 Hospital-Acquired Infection

NHSN Data, Jan '06-Oct '07

463 U.S. Hospitals in the National Healthcare Safety Network
Long Term Care: A Risk for *Acinetobacter* Colonization

- Active surveillance cultures for MDR *Acinetobacter* on 1111 consecutive patients admitted to adult ICU.
- Sites: axilla, wounds, respiratory
- Frequency: admission and weekly
- Admission prevalence: 0.82%
- Possible Transmission rate: 0.43%
- LTCF exposure: RR 19 [6.6-54]


Polymixin B for MDR *A. baumannii* in the ICU (n=33)

- Med age 41
- ICU days prior to inf - median 18
- Clin cure = 22/29 (76%) evaluable
- Micro cure = 17 (61%)
- Nephrotox = 7 (24%) = 5/7 baseline later
- Neurotox = 2 (6%) = AMS or parerection
- Mortality = 9 (27%)

*Ann Pharmacother* 2006; 40:199-45

Colistin

Acts at the lipid a portion of LPS, displacing Ca# and Mg# from PO\(_4\) group

*Lancet Inf Dis* 2006; 6:589-601

Hetero resistance reported, especially after colistin
Rx – if expose to colistin => rapid resistance occurs, arguing against monotherapy

*J Infect* 2009; 58:138-44
*AAC* 2007; 51:3413-15