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

Company	Research	Consulting
Rib-x		▲
Pfizer	▲	▲
3M		▲
Boehringer Ingelheim		▲
Biomerieux		▲
Sanofi-Aventis		▲
Vestagen	▲	

No speaking bureau; no stocks, no royalties

Acinetobacter: An MDR Nosocomial Pathogen

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Acinetobacter* (ακινετοσ, akinetos)

- Gram negative aerobes, non-motile
- Non-fermenting, non-fastidious
- Catalase positive, oxidase negative
- Important MDR hospital pathogen
- 87% resistance genes on large "resistance island", AbaR1- almost all from other GNRs

Prof. Beijerinck identifies Acinetobacter in soil - 1911

Bristov and Prevot *Ann Inst Pasteur* 1954; 86:722-8 (d.Herentiate nonmotile among Achromobacter)
Peleq et al *Clin Microbiol Rev* 2008; 21:538-82
Fournier et al *PLoS Genet* 2006; 2:E7

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

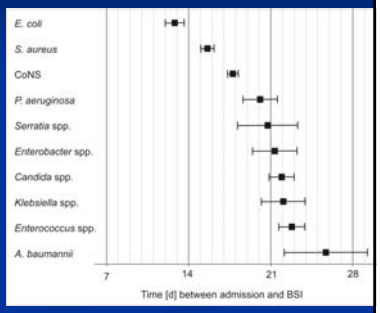
Cho et al *J Clin Microbiol* 1999; 37:2962-7

- 50% increased infection rates from July-October
- For each 10ºF increase a 17% increase in monthly infection rate

Monoz-Price & Weinstein *NEJM* 2008; 12:1271-81
Perencevich et al *ICHE* 2008; 29:1124-31

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

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



Wisplinghoff H, et al. Clin Infect Dis. 2004;39:309-17

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

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

Risk Factor	OR (CI_{95})
CVC	17.7 (4.3 – 71.6)
Charlson score >3	17.5 (4.3 – 73.1)
Prior MRSA**	12.7 (1.9-83.1)
Prior β-lactam*	9 (2.4-33.5)
Surgery	6 (1.6-221.1)

* last 30 d / ** last 6 mo

JAC 2008; 62:1130-7

Acinetobacter and Insulin Resistance

Acinetobacter: insulin – cleaving protease in periplasm

Biomed Biochem 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 2005; 26:405-8

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 (1.1901.89)
  - Septic shock RR 1.65 (1.23-1.85)
  - Diabetes Mellitus RR 1.68 (1.22-1.76)

Metan et al *Europ J Int Med* 2009; 20:540-4

Acinetobacter: Spread by Contaminated Gloves

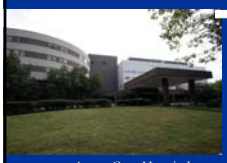
- Carbapenam resistance 36% VAP/BSI

  Infect Contr Hosp Epidemiol 2008; 29:996 TOII
- Carbapenam-resistant strains found on 60% gloves following patient care

  J Hosp Infect 2009; online 21 June
- Transmission in an ICU

  Am J Med 1991; 91:479-83

Acinetobacter Acquired in Acute Care Hospital Leads to High Prevalence in a LTC Facility



Acute Care Hospital

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

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

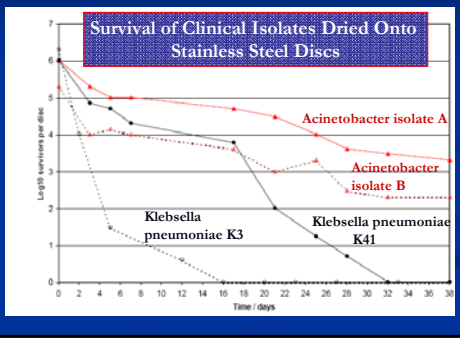
LTCF

LTCF exposure RR=19[6.6-54] *JAMA* 2008; 299:2513

- Patient carriage can be prolonged *J Clin Microbiol* 2007; 45:1551

Furino et al *AJIC* 2008; 36:468

Acinetobacter: 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

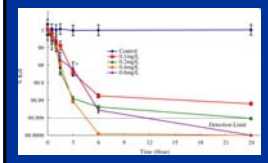
+/- environmental surveys

Staff education/posters re: contact isolation

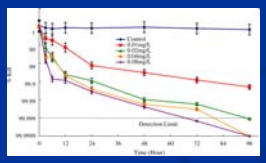
Valencia et al ICHE 2009; 30:257-63

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



0.04–0.08 mg/L of silver ions achieved more than 99.999% reduction of *A. baumannii* within 96 h.

Water Res 2008; 42:73-80

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

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

P<0.01

* Only 1/19 original clone

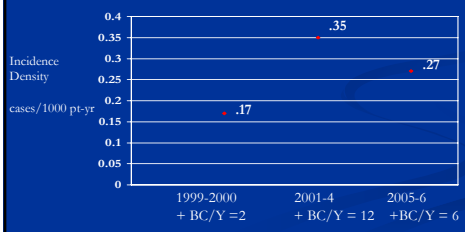
Flushing synchronized in all sinks

Am J Infect Control 2009; Epub Nov 7th

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

Multivariate Analysis: RR=0.5 (.4 -.64)

After control gender, age, immunosuppresion, 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)

Borer et al. *J Hosp. Infect* 2007; 67:149-55

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

- Gardine (combination of brilliant green dye and chlorhexidine)
- Synergistic antimicrobial eficacy

  Oral Oncol 2007; 43:159-64
- Gloves swabbed with 1.5 x 10^8 cfu/mL

  dried -> segments streaked onto agar
- All Acinetobacter killed within 10 minutes

Reitzel et al *Am J Infect Control* 2009; 37:294-300

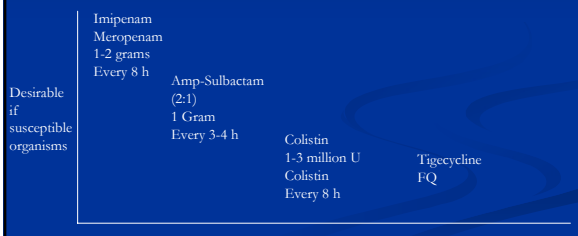
MDR Acinetobacter: Prevention

- 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 gardine 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



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

Curr Opin Infect Dis 2009; 22:535-43

Colistin – Dosage Interval

Rapid, concentration – dependent bactericidal drug

JAC 2008; 62:1311-8

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

ICAAC 2007; Duchani et al

More emergence of resistance to *Ps. 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

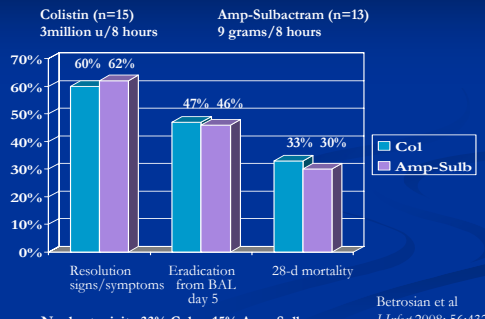
C max after 1st dose . 60 mg/l,

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*

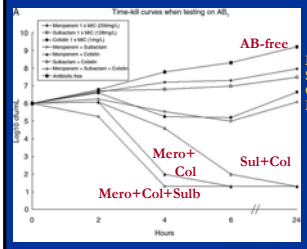


Nephrotoxicity 33% Col vs 15% Amp-Sulb

Betrosian et al *J Infect* 2008; 56:432-6

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

Fatal case in 78 male s/p. external ventricular drain
Intravenous Meropenam + Sulbactam
Later colistin added
MIC: Mero (250); Sulb (128); Col (1)



Meropenem
Sul
Col
Mero+Sulb

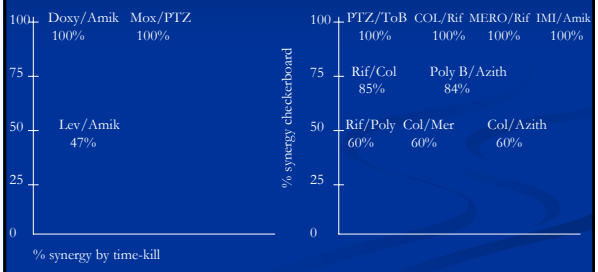
Lee et al *Microb Drug Resist* 2008; 14:233-7

Colistin, Meropenam, Rifampin CombinationRx for MDR *A. baumanii*

- 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

JAC 2008; 61:417-20

Retrospective:

Colistin base 400 mg every 8 hours

Rifampin 600 mg daily

7/10 with VAP improved

Internat J Antimicrob Agents 2008; 32:281-4

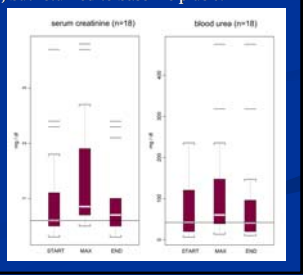
Toxicity After Several Weeks of Colistin (n=19)

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

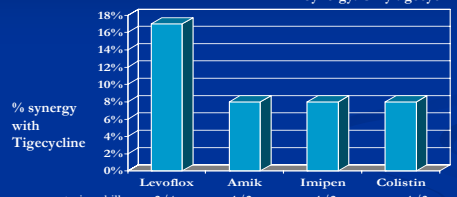
No apnea. No neuromusc. blockade.



BMC Infect Dis. 2005; 5:1 (10 January)

In Vitro Interaction of Tigecycline with Other Antibiotics for MDR *A. baumannii* (n=22)

Synergy: Only tigecycline non-susceptible



	Levoflox	Amik	Imipen	Colistin
+ time kill:	2/4	1/2	1/2	1/2

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

No synergetic activity was bactericidal

Ann Clin Microbiol Antimicrob 2009; 8:18 (21 May)

Acinetobacter VAP

No pts	Drugs	Effect
14	Colistin 2 million units every 8 Rif 600 mg/d plus Sulbactam if suscept	Micro clearance 9/14 *Clin Micro Infect* 2005; 11:682-3
26	Aerosolized colistin 1 million u every 8 h IV Rifampin 10 mg/kg over 12 hours	All favorable outcome *J Infect* 2006; 53: 274-8

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

Drugs 2008; 68:165-89

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

	Intrathecal †† (n=8)	Intraventricular (n=24)	
Mean age	35	40	• external ventricular drainage in 30/32
Mean dose (mg)*	8 ± 3.3	13.5 ± 7.3	
Mean duration (d)	14.6 ± 5.7	18.9 ± 7.9	• unclear if IV colistin adds advantage
Chemical meningitis or ventriculitis	2/8	1/24	• authors cite safety of intrathecal Rx

IDSA recommends 10 mg every 24 hr

†† Manufacturer does not recommend intrathecal.

Int J Infect Dis 2009; doi 10.101.6/J izid 2009.06.032

Rx Acinetobacter - Pending Antibiogram

VAP
- Colistin aerosolized
- Colistin aerosolized plus IV Colistin

BSI
- Colistin IV
- Colistin IV plus IV Rifampin

Meningitis
- IT Colistin
- IT Colistin plus Rifampin

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

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

Condition	Initial Rx	Final Rx
* Septic shock[1] Pancreatitis abd abscess	Colistin Meropenam	Colistin Meropenam Tigecycline
* BSI[2] Pneumonia s/p trauma	Ticar-Clav Rifampin	Pip-Tazo Sulfamethox Tigecycline

[1] *Eur J Clin Microbiol Infect Dis* 2006; 25:257-60
[2] *Ann Fr Anesth Reanim* 2007; 26:1056-8

Acinetobacter: Nosocomial Meningitis

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

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

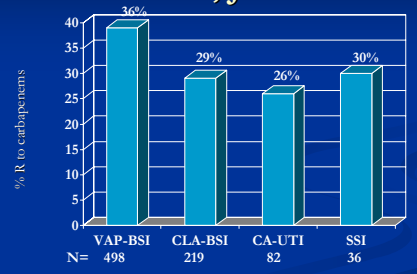
Drugs 2008; 68:165-89

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

Marchaim et al. *J Clin Microbiol* 2007;45:1551.

Acinetobacter: Carbapenam Resistance Offers Successful Strategy NHSN Data, Jan '06-Oct '07



463 U.S. Hospitals in the National Healthcare Safety Network
Hidron AI, et al. *Infect Cont Hosp Epidemiol* 2008;29:996-1011.

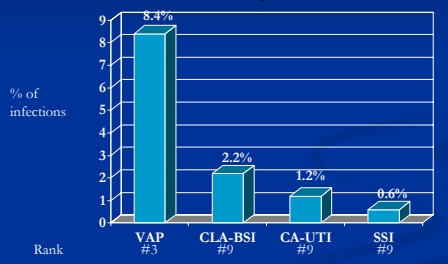
Polymyxin B (1 mg = 10,000 units)

Differs by 1 AA from Polymixin E-Colistin

Dose – $CL_{CR} \geq 80$	1.5-2.5 mg/kg/d – 2 doses
30-80	2.5 mg/kg load =>
	1-1.5 mg/kg/d
<30	2.5 mg/kg load =>
	1-1.5 mg/kg every 2-3 days
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
Hidron AI, et al. *Infect Cont Hosp Epidemiol* 2008;29:996-1011.

Long Term Care: A Risk for *Acinetobacter* Colonization

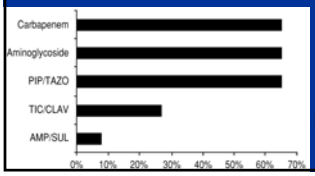
- Active surveillance cultures for MDR Acinetobacter on 1111 consecutive patients admitted to adult ICU.
- Sites: axilla, wounds, respiratory
- Frequency: admission and weekly
- Admission prevalence: 0.82%
- Possible Transmission rate: 0.43%
- **LTCF exposure: RR 19 [6.6-54]**

Maragakis et al. *JAMA* 2008;299:2513.

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

Ann Pharmother 2006; 40:1939-45

Med age 41
ICU days prior to inf – median 18
Clin cure – 22/29 (76%) evaluable
Micro cure – 17 (81%)
Nephrotox – 7 (21%) – 5/7 baseline later
Neurotox – 2 (6%) – AMS or parertherias
Mortality – 9 (27%)



Antibiotics received prior to Development of multidrug-resistant Acinetobacter baumannii infections (n=37).
AMP/SUL – ampicillin/sulbactram
PIP/TAZO – piperacillin/tazobactram;
TIC/CLAV – ticarcillin/clavulante

Colistin

Acts at the lipid a portion of LPS, displacing Ca# and Mg# from PO_4 group

Lancet Inf Dis 200-6; 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