MDR Acinetobacter baumanii

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Outline

- Introduction
- Epidemiology
- Clinical presentations
- Diagnosis
- Treatment
- Prevention
Acinetobacter calcoaceticus-baumannii complex

- First described in 1911 as *Micrococcus calco-aceticus*
- Named Acinetobacter in the 1950s
- Strictly aerobic
- Gram negative bacilli or coccobaccilli
- Lactose non-fermenter
- Oxidase negative
- Non-motile

MDR Acinetobacter

- Emerging as a problematic, nosocomial and community-acquired pathogen.
- ICU and hospital outbreaks
- Incidence of severe infections caused by *Acinetobacter* species has been increasing.
- Infection with MDR A. baumannii is associated with:
  - Increased morbidity
  - Excess mortality
  - Longer hospital stay

Clinical Infectious Diseases. 2006;42:657-668
The Alphabet:

MDR ... XDR ... PDR

MDR: non-susceptible to $\geq 1$ agent in $\geq 3$ antimicrobial categories

XDR: non-susceptible to $\geq 1$ agent in all but $\leq 2$ categories

PDR: non-susceptible to all antimicrobial agents listed

Magiorakos AP. Clin Microbiol Infect 2012; 18: 268–281

**Urgent Threats**
- *Clostridium difficile*
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant *Neisseria gonorrhoeae*

**Serious Threats**
- Multidrug-resistant *Acinetobacter*
- Drug-resistant *Campylobacter*
- Fluconazole-resistant *Candida* (a fungus)
- Extended spectrum β-lactamase producing Enterobacteriaceae (ESBLs)
- Vancomycin-resistant *Enterococcus* (VRE)
- Multidrug-resistant *Pseudomonas aeruginosa*
- Drug-resistant Non-typhoidal *Salmonella*
- Drug-resistant *Salmonella* Typhi
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Drug-resistant *Streptococcus pneumoniae*
- Drug-resistant tuberculosis

**Concerning Threats**
- Vancomycin-resistant *Staphylococcus aureus* (VRSA)
- Erythromycin-resistant Group A *Streptococcus*
- Clindamycin-resistant Group B *Streptococcus*
Trust Surveillance Study
Carbapenem susceptibilities for 994 A. baumannii from the USA (2007–2009)

Adapted from Davies TA. J Antimicrob Chemother 2011; 66: 2298–2307
MDR Rates: US Data

Adapted from “The Antibiotic Resistance Threats in the United States, 2013”


Antimicrobial Resistance in 250 Acinetobacter isolates in Kuwait

MDR Rate: 88%
Rates of MDR Acinetobacter at KHCC: 2006-2008

MDR: Multi-Drug Resistant, ESBL: Extended Spectrum B-Lactamase
Screening ICU Patients at KHCC

- From Feb, 2006 to July, 2008
- Screened 2720 patients on admission
- Nasal and rectal swab cultures

- Cultures were screened for the presence of Acinetobacter, Pseudomonas, ESBL E. coli and Klebsiella spp, VRE and MRSA
2720 Screened ICU Patients on Admission

Rate: 8.6%

- Total number of Screened ICU Patients
- Patients with Resistant Bacteria on Admission

- Resistant Gram Negative Bacteria
- Resistant Gram Positive Bacteria

Graphs showing the distribution of resistant bacteria among screened ICU patients.
Risk Factors for MDR Acinetobacter Colonization and Infection

- ICU stay (prolong)
- Recent surgery
- Invasive procedures (e.g. CVC)
- Mechanical ventilation & Tracheostomy
- Enteral feedings
- Antimicrobial therapy
- Residents of long term care facilities

Potential Mechanisms of Antimicrobial Resistance in Acinetobacter

- Porin loss
- Efflux pump
- β-Lactamase enzyme
  - Carbapenemase
  - Cephalosporinase
- Target modifications
  - PBP
  - DNA gyrase
- Aminoglycoside-modifying enzymes

Clinical Presentations

Common
- Ventilator-associated pneumonia (VAP)
- Blood stream infection (BSI)
  - Central line associated BSI (CLABSI)

Less common
- Skin and soft tissue infections
- Surgical site infections
- UTI (CA-UTI)
- Device-related infections (shunt, prosthesis, etc)
Diagnosis

• Gram stain: GN bacilli or coccobacilli
• Easily isolated in standard cultures
• Nonreactive in many biochemical tests commonly used to differentiate GN bacilli.
• Microlabs should follow standard antimicrobial susceptibility testing for A. *baumannii*
Therapy for Acinetobacter

• Always follow the results of susceptibility testing
• In cases of moderately resistant isolates:
  – B-Lactam/B-Lactamase inhibitor combinations
  – Carbapenems (Meropenem and Imipenem)
• MDR isolates: use Colistin.
• Colistin is currently the agent with most reliable activity
### Antibiotics for MDR Acinetobacter infections

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage³</th>
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</thead>
<tbody>
<tr>
<td>Sulbactam (amp/suib in the United States)</td>
<td>6 g per day</td>
</tr>
<tr>
<td>Imipenem-cilastatin</td>
<td>500 mg every 6 h up to 1 g every 6–8 h</td>
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<tr>
<td>Meropenem</td>
<td>500 mg to 1 g every 8 h</td>
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<tr>
<td>Doripenem</td>
<td>500 mg every 8 h</td>
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<tr>
<td>Amikacin</td>
<td></td>
</tr>
<tr>
<td>Regimen 1</td>
<td>15 mg/kg daily</td>
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<tr>
<td>Regimen 2</td>
<td>30 mg</td>
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<tr>
<td>Tobramycin</td>
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<tr>
<td>Regimen 1</td>
<td>4–7 mg/kg daily</td>
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<tr>
<td>Regimen 2</td>
<td>300 mg (1 ampule) twice daily</td>
</tr>
<tr>
<td>Regimen 3</td>
<td>5– 20 mg</td>
</tr>
<tr>
<td>Colistin (colistimethate)</td>
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<tr>
<td>Regimen 1</td>
<td>5 mg/kg/day, 2–4 divided doses</td>
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<tr>
<td>Regimen 2</td>
<td>1–3 million IU every 8 h</td>
</tr>
<tr>
<td>Polymyxin B [25]</td>
<td>50,000 units daily (5 mg)</td>
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<tr>
<td>Polymyxin E (colistimethate [25])</td>
<td>10 mg daily</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>100 mg once then 50 mg every 12 h</td>
</tr>
<tr>
<td>Minocycline</td>
<td>100 mg every 12 h</td>
</tr>
</tbody>
</table>

Wisdom does not always come with age!

- Gram negative pathogens only
  - Not active against Serratia, Proteus and Providentia sp
- Loading dose (9 million unit) is required
- First maintenance dose should be given after 24 hours
- Maintenance dose (normal renal function):
  - 3 million units every 8 hours
  - 4.5 million units every 12 hours
- Side effects: nephrotoxicity, neurotoxicity

Garonzik SM. ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 2011, p. 3284–3294
Dalfino L. Clinical Infectious Diseases 2012;54(12):1720–6
Peck KR. Journal of Medical Microbiology (2012), 61, 353–360
Vicari J. Clinical Infectious Diseases 2013;56(3):398–404
Other Routes of Colistin Administration

• Aerosolized colistin
  – With or without IV colistin
  – Patients with pneumonia only
  – Dose:
    • 1 million U every 8H
    • 2 Million U every 12H

• Intra-thecal and intra-ventricular
  – Patients with CNS infections
  – Dose range: 62,500U-125,000U-500,000U

Kwa AL. Clinical Infectious Diseases 2005; 41:754–7
Kofteridico DM. Clinical Infectious Diseases 2010; 51(11):1238–1244

Antibiotic Combinations

- Colistin plus Rifampin
- Colistin plus Imipenem
- Colistin plus Meropenem
- Colistin plus Sulbactam
- Carbapenem plus Sulbactam

Most of the studies are:
- Small series/cohorts
- Retrospective studies
- No randomization
- No comparator
- In vitro
- Heterogeneous patients

Primary outcome: compare 30-day all-cause mortality of Rx with colistin plus a carbapenem (imipenem or meropenem) versus colistin alone for subjects with BSI and/or pneumonia due XDR Gram-negative bacilli.
Colistin plus Rifampin was associated with:
- Reduced time to microbiological clearance
- Higher microbiological eradication rate
- No difference in mortality or length of stay

Caveat:
Studies used lower colistin dose than what is currently recommended
Extended-Infusions of B-Lactam Antibiotics

- Continuous infusions or extended infusions has been used with good results
- The IDEA: infuse concentration-dependent antibiotics (e.g. B-lactams) to maintain drug levels above MIC
- Promising approach for MDR bacteria with low-intermediate level resistance
- Existing studies on extended infusions on some Abx (e.g. Pip/tazo, Doripenem, Meropenem, Imipenem)

Falagas M et al. Clinical Infectious Diseases 2013;56(2):272–82
Cooper TW. The Annals of Pharmacotherapy. 2011 February, Volume 45:229-240
### Colistin-Resistant Acinetobacter

<table>
<thead>
<tr>
<th>Drug</th>
<th>MIC</th>
<th>Interps</th>
<th>Origin</th>
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<td>Amikacin</td>
<td>&gt;32</td>
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<tr>
<td>Amox/K Clav</td>
<td>&gt;16/8</td>
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<td>Ampicillin</td>
<td>&gt;16</td>
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<td>&gt;16</td>
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<td>&gt;16</td>
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<td>Gentamicin</td>
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Colistin-Resistant A. baumannii

Emergence of Colistin-Resistance in Extremely Drug-Resistant Acinetobacter baumannii Containing a Novel pmrCAB Operon During Colistin Therapy of Wound Infections

- 28 XDR A. baumannii isolates were recovered during colistin therapy.
  - 14 were susceptible to colistin
  - 14 were resistant to colistin.
- Colistin resistance was associated with point mutations in the pmrA1 and/or pmrB genes.
- Colistin-resistant isolates displayed lower growth rates and lowered fitness.
- Colistin resistance emerged from a single progenitor colistin-susceptible isolate.

Lesho E. The Journal of Infectious Diseases 2013;208:1142–51
Management of Colistin-Resistant *A. baumannii*?

- Confirm the presence of infection not colonization
- Confirm colistin-resistance (MIC method)
- Test all antibiotics with known activity against Acinetobacter spp
- Optimize non-pharmaceutical management:
  - Remove infected devices or materials
  - Drain abscesses, collections
- Extended infusion/high doses of antibiotics
- Use combinations!

How to Control MDR Acinetobacter?

Infection Control Components

Prevent Infections ➔ Prevent spread of resistance ➔ Track resistance patterns

Develop novel antibiotics and therapeutics ➔ Stewardship programs ➔ Improve antibiotic prescribing

Antimicrobial Control Components

Adapted from cdc.gov

Novel Antibiotics in the Pipeline

ANTIBIOTIC STEWARDSHIP
IN YOUR FACILITY WILL

DECREASE

- Antibiotic resistance
- C. Difficile infections
- Costs

INCREASE

- Good patient outcomes

PROMOTE ANTIBIOTIC BEST PRACTICES—
A FIRST STEP IN ANTIBIOTIC STEWARDSHIP

- Ensure all orders have dose, duration, and indications
- Get cultures before starting antibiotics
- Take an “Antibiotic Timeout” reassessing antibiotics after 48-72 hours