

The real hospital threat: Untreatable Gram- negative bacteria

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The War Against Infectious Diseases Has Been Won!

U.S Surgeon General, 1969.

“ One can think of the middle of the 20th
Century as one of the most important social
events in history:

The virtual elimination of infectious
diseases as a significant factor in social
life.”

Sir MacFarland Burnett, Natural History of
Infectious Disease, 1962.

**The current antibiotic crisis
differs from those in the past
because several different
organisms are involved and
because there are no immediate
solutions on the horizon.**

**The prevalence of antimicrobial-
resistant human pathogens is
rapidly increasing, but the
discovery and development of
new antimicrobial drugs have
slowed dramatically particularly
for Gram-negative bacteria.**

Outline

- What drives antibiotic-resistant bacteria
- Overview of important Gram-negative antibiotic resistant bacteria
 - *Acinetobacter baumannii*
 - Carbapenem-resistant *Klebsiella*
 - *Pseudomonas aeruginosa*
- Unanswered antibiotic stewardship and infection control questions
- Unanswered treatment questions

Case

- 45 year old male transferred from a chronic rehab facility with fever and respiratory distress. Bronchoalveolar lavage reveals pan-resistant *Acinetobacter baumannii*

Case

- 60 year old male with multiple prior hospital admissions for COPD exacerbations and CAD procedures. Has had multiple out-patient antibiotic courses. Admitted with *Klebsiella pneumoniae* bacteremia that is carbapenem-resistant

Rates of Resistance Among Nosocomial Infections Reported in Intensive Care Unit Patients

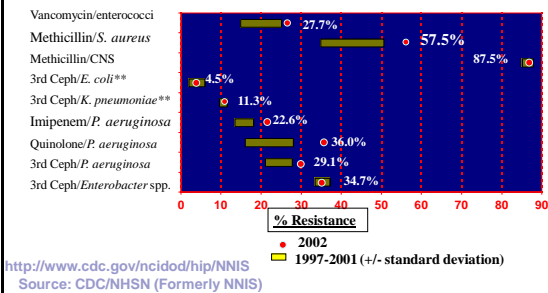


TABLE 4. Distribution and Rank Order of Selected Pathogens Associate to the National Healthcare Safety Network, January 2006–October 2007.

Pathogen	Overall*		CLABSI	
	No. (%) of pathogenic isolates	Rank	No. (%) of pathogenic isolates	Rank
CoNS	5,178 (15.3)	1	3,900 (34.1)	1
<i>Staphylococcus aureus</i>	4,913 (14.5)	2	1,127 (9.9)	4
<i>Enterococcus</i> species		3		2
<i>E. faecalis</i>	1,177 (3.5)		627 (5.5)	
<i>E. faecium</i>	1,888 (5.6)		942 (8.2)	
NOS	1,028 (3.0)		265 (2.3)	
<i>Candida</i> species		4		3
<i>C. albicans</i>	2,295 (6.8)		673 (5.9)	
Other <i>Candida</i> spp.				
Other NOS	1,333 (3.9)		669 (5.9)	
<i>Escherichia coli</i>	3,264 (9.6)	5		
<i>Pseudomonas aeruginosa</i>	2,664 (7.9)	6	31.9%	
<i>Klebsiella pneumoniae</i>	1,956 (5.8)	7		
<i>Enterobacter</i> species	1,624 (4.8)	8	443 (3.9)	6
<i>Acinetobacter baumannii</i>	902 (2.7)	9	252 (2.2)	9
<i>Klebsiella oxytoca</i>	359 (1.1)	10	99 (0.9)	10
Other	5,267 (15.6)		1,201 (10.5)	
Total	33,848 (100)		11,428 (100)	

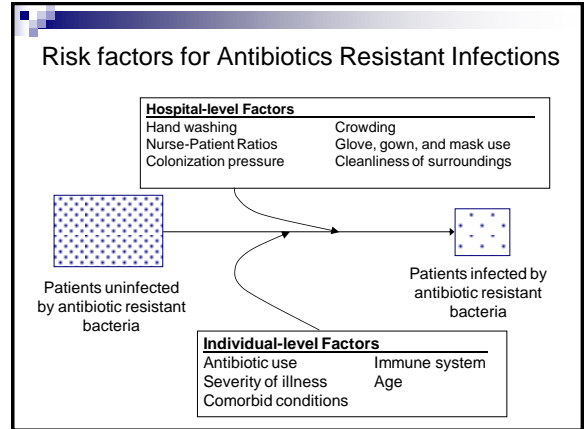
NOTE. Of the 28,502 cases of HAI reported, 4,671 (16.4%) were polymicrobial, associated bloodstream infection; CoNS, coagulase-negative staphylococci; NOS, no organism.

NHSN: Antibiotic-resistance

Bacteria	CLABSI (% imipenem resistant)	VAP (% imipenem resistant)	CAUTI (% imipenem resistant)	Pooled (% imipenem resistant)
<i>Pseudomonas</i>	23.0%	25.1%	26.4%	25.3%
<i>Klebsiella</i>	10.8%	10.1	3.6	
<i>Acinetobacter</i>	29.2	25.6	36.8	

What drives antibiotic-resistant bacteria emergence?

- Antibiotics
- Patient-to-patient transmission

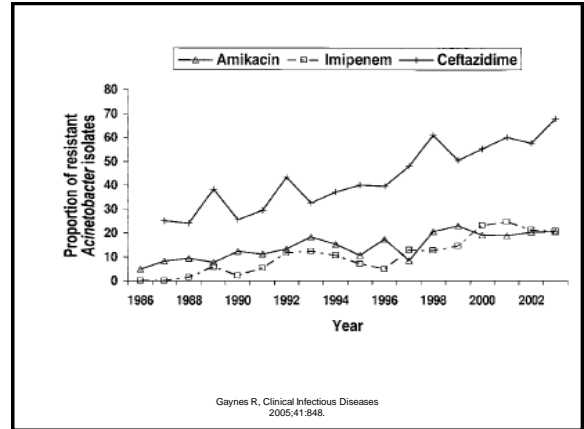
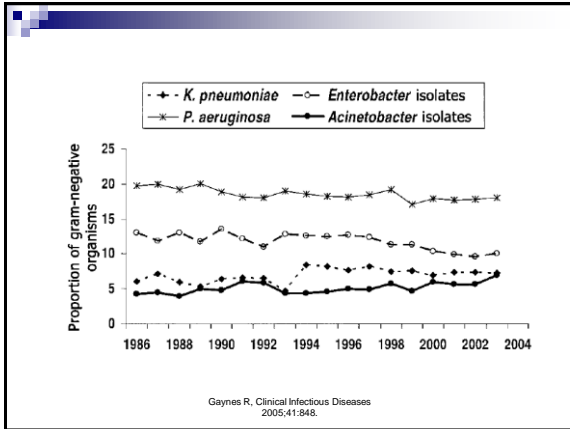


- ## Gram negative bacteria resistant to antimicrobial agents
1. *Acinetobacter baumannii*
 2. *Klebsiella* species
 3. *Pseudomonas aeruginosa*
 4. *E. coli*
 5. *Enterobacter* species
 6. *Serratia*
 7. *Stenotrophomonas maltophilia*

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- ## Increasing Incidence in US
- CDC National Nosocomial Infections Surveillance report the following increases in *Acinetobacter*
 - Proportion of *Acinetobacter* ICU pneumonia increased from 4% in 1986 to 7% in 2003
 - Proportion of *Acinetobacter* UTIs and SSIs also increased
 - Increase noted at multiple US hospitals and not confined to 1 geographic region
- Gaynes R. Clinical Infectious Diseases 2005;41:848.



Increasing Incidence Worldwide

- Middle East
- Australia
- South Africa
- Spain
- South America

Attributable Mortality

Reference	Clinical Setting	Cases	Controls	Attributable Mortality
Grupper et al. 2007	Nosocomial BSI ICU, med-surg wards Israel	52 cases of AB-BSI	52 Matched Controls w/o AB	36.5%
Playford et al. 2007	Infection/Colonization General ICU Australia	66 cases of Infection or Colonization	131 Matched controls w/o AB	20%
Sunenshine et al. 2007	MDR-AB infections 3 rd Care Hospitals Baltimore, MD	96 cases of MDR-AB Infections	91 Susceptible-AB	8.4%
			89 Un-infected	14.8%
Kwon et al. 2007	CR-AB BSI 3 rd Care Hospitals Korea	40 cases of CR-AB Infection	40 Imipenem-susceptible	25-30%
Robenshtok et al. 2006	Nosocomial BSI Israel	112 cases of AB-BSI	90 controls w/ <i>Klebsiella</i> BSI	22.7%
Blot et al. 2001	Nosocomial BSI ICU Belgium	45 cases of BSI	90 Matched Controls w/ AB	7.8%

Transmission

- Patient-to-Patient
 - Hands of Healthcare Workers
 - Droplet
- Environmental Sources

Transmissibility compared to other organisms

Organism	HCW Room Entries	Hand + Before (%)	Gown and/or Glove + After %	Hands + After Removal
<i>A. baumannii</i>	199	1.7%	38.7%	4.5%
<i>P. aeruginosa</i>	133	0%	8.2%	0.8%
VRE#	94	0%	9%	0%
MRSA#	81	2%	19%	2.6%

Snyder G, et al, Infect Control Hosp Epidemiol July 2008; 29:584 and Morgan D, et al, Infect Control Hosp Epidemiol, June 2010;31:716

After Contact with Patients Infected/Colonized with ...

... MDR *Acinetobacter baumannii*

40% of Gloves/Gowns were Contaminated
4% of Hands were Contaminated after removal of gloves

... MRSA

18.5% of Gloves/Gowns
1% of Hands Contaminated

... VRE

8.5% of Gloves/Gowns
No Hands Contaminated

Outline

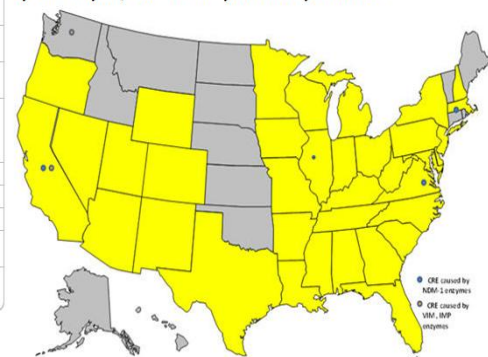
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KPC/CRE: Epidemiology

- First reports in 2004 in New York
- In 2007 CDC data, 8% of all *Klebsiella* isolates were reported to be carbapenem resistant, compared to just under 1% in 2000.

Srinivasan A. Infect Contrl Hospit Epi.
2008;29:1099.

2010 Location of Carbapenem-Resistant *Enterobacteriaceae* (CRE) caused by KPC enzyme; CRE caused by other enzymes noted



KPC: Resistance

- Most commonly seen in *Klebsiella pneumoniae*
 - Carbapenem-resistant *Enterobacteriaceae*
- KPC confers resistance to penicillins, cephalosporins and carbapenems
- Present on a plasmid

KPC: Microbiological detection

- Difficult to identify for laboratories which has important clinical implications
 - Ertapenem better method than imipenem or other carbapenems
- New MIC breakpoints

Anderson KFJ Clin Micro, 2007;27:23.

KPC: Risk factors

- Usual risk factors
 - Antibiotic use
 - Comorbid conditions
 - Contact with hospitals
- One study identified severity of illness, prior fluoroquinolone and cephalosporin use as risk factors
- Another study identified carbapenems, cephalosporins, mechanical ventilation and length of stay prior to infection

Gasink LB, Infect Contr Hospit Ep 2009
Patel G, Infect Contr Hospit Epi 2008.

KPC: Outcomes

- Likely leads to increased LOS in hospital and increased mortality
- One study showed an increased mortality (AOR, 3.60; 95% CI, 1.87-6.91)
- Another study also showed increased mortality (48% vs 20%; $P < .001$)

1. Gasink LB, Infect Contr Hospit Ep 2009
2. Patel G, Infect Contr Hospit Epi 2008.

KPC: Infection control

- Difficult to determine if infection control measures should be the same for KPC as for ESBL-producing *Klebsiella*

Current Epidemiology of US cases of NDM

- All patients have had relatively recent and well documented exposure to healthcare facilities in other countries.
- No evidence of transmission in US hospitals.
 - Active surveillance has been done to look.

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The Cohort



- Tertiary Center Medical and Surgical Intensive Care Units
- Peri-anal surveillance cultures
 - Admission
 - Weekly
 - Discharge

Cohort

- Data on cohort linked to hospital's Oracle Central Data Repository (CDR)
- CDR has patient demographics, pharmacy medications, other microbiology results
- We have used the CDR for over 50 publications

Cohort

- Active surveillance cultures on all patients admitted to MICU and SICU from 9/1/01 to the present
- Cultures obtained on admission, weekly and upon discharge
- Over 40,000 peri-rectal swabs have been obtained and frozen
- These 40,000 swabs are from over 12,000 unique patients

Cohort

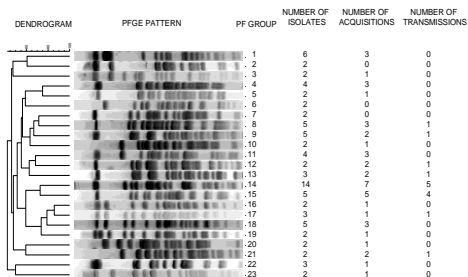
- Swabs obtained can be frozen and re-analyzed
- Freezing method validated for multiple gram-positive and gram-negative bacteria

Green HP. Infection Control and Hospital Epidemiology, 2007

UMMC imipenem-resistant *P. aeruginosa*

- Among 149 patient acquisitions, there were 46 (31%) patients who had similar PFGE types
- Only 16 (11%) also had overlapping hospital length of stay

Johnston JK. J Infect Dis. 2009



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Infection control questions about untreatable Gram-negative bacteria

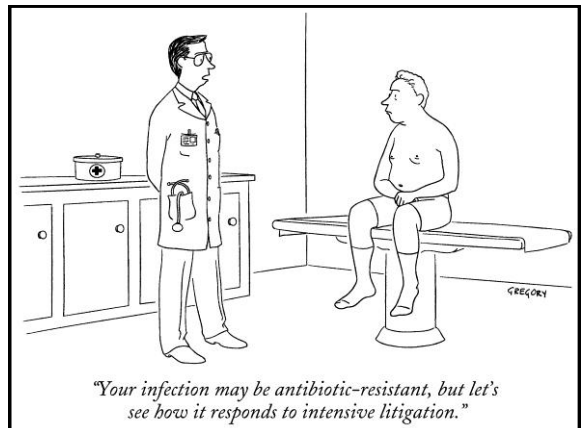
- Should I be placing these patients on contact isolation precautions?
- Should I be performing active surveillance culturing?
- Should I be focusing my efforts on antimicrobial stewardship or infection control?
- Should we be cohorting these patients?
- Should I be culturing hospital personnel?

Unanswered treatment questions

- Controversy re susceptibility testing for colistin/Polymixin B
- Emergence of polymixin resistance in countries
- For pan-resistant *Pseudomonas* or *Acinetobacter* what should I use

Unanswered treatment questions

- Combination therapy versus monotherapy
 - Polymixin as monotherapy vs combination therapy
 - Combination therapy versus monotherapy for *Pseudomonas aeruginosa*



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- "Article on most recent NHS resistance rates". Hidron AI. Infect Control Hosp Epidemiol 2008;29:996.

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