

Antimicrobial Resistance, Human Pathogens

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Improving People's Lives
through innovations in personalized health care



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Disclosures

- No financial disclosures or conflicts of interest relative to this presentation.



Time Magazine-Feb 25, 1966

- “Nearly all experts agree that (by the year 2000) bacterial and viral diseases will have been wiped out. Probably arteriosclerotic heart disease will also have been eliminated.”



Critical impact of antimicrobial resistance

“If we do not act to address the problem of AR, we may lose quick and reliable treatment of infections that have been a manageable problem in the United States since the 1940s. Drug choices for the treatment of common infections will become increasingly limited and expensive - and, in some cases, nonexistent.”

-A Public Health Action Plan to Combat Antimicrobial Resistance

CDC

Underline added



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1940

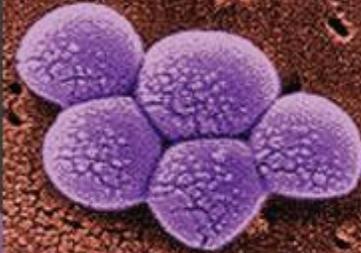
1940

Penicillinase, an enzyme capable of destroying penicillin, identified in bacteria

1945

More than 20% of *S. aureus* hospital isolates are penicillin-resistant as penicillinase begins to spread worldwide

S. AUREUS (MRSA)



1958

Vancomycin introduced, although rarely used until the mid-1980s

1964

Cephalothin, first antibiotic in the cephalosporin class, introduced

1942

First therapeutic use of penicillin

1947

Streptomycin approved by FDA

1952

Tetracycline approved by FDA

1959

Methicillin introduced

1966

Cephalothin resistance observed

1943

Penicillin mass-produced

1947

Streptomycin resistance observed

1956

Tetracycline resistance observed

1961

Methicillin-resistant *S. aureus* (MRSA) observed

1967

Gentamicin approved by FDA

1970

Gentamicin resistance observed

Science 2008;321:356-361



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1976

Transferable penicillinase first observed in a gonococcus

1981

Cefotaxime approved by FDA

1983

Cefotaxime resistance observed

1983

First penicillin-resistant *Enterococcus* reported

1987

Vancomycin-resistant *Enterococcus* (VRE) observed

ENTEROCOCCUS FAECIUM (VRE)



1987

First outbreak of *Klebsiella pneumoniae* resistant to third-generation cephalosporins

1996

S. aureus with intermediate resistance to vancomycin (VISA) reported

1999

Community-acquired MRSA reported

2000

Linezolid, first antibiotic in the oxazolidinone class, approved by FDA

2001

Linezolid-resistant *S. aureus* and VRE observed

2002

S. aureus with complete resistance to vancomycin (VRSA) observed



KLEBSIELLA PNEUMONIAE

2002

Science 2008;321:356-361

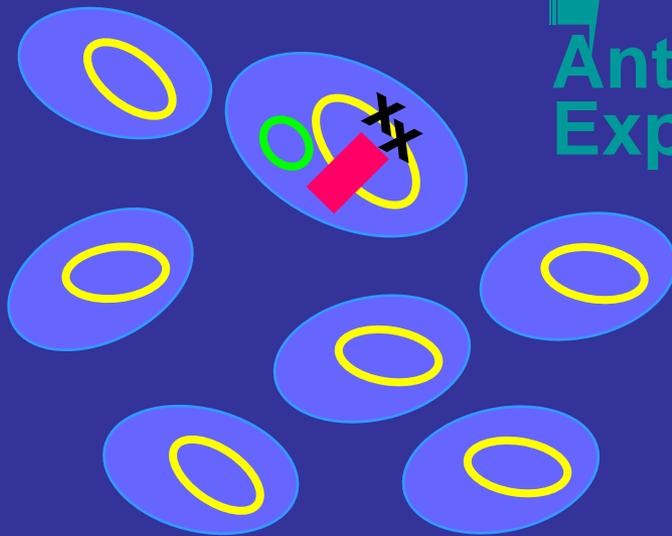


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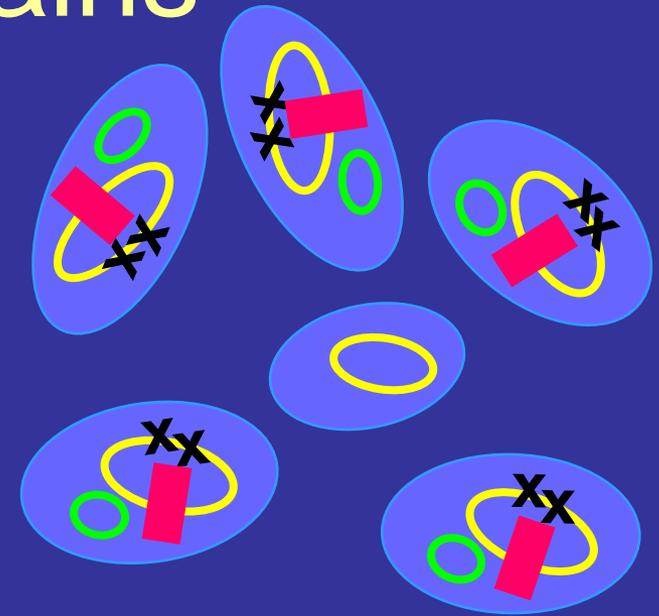


Selection for antimicrobial-resistant Strains

Resistant Strains
Rare



Antimicrobial
Exposure



Resistant Strains
Dominant

ESKAPE pathogens

- *Enterococcus faecium* (VRE)
- *Staphylococcus aureus* (MRSA)
- *Klebsiella pneumonia* (ESBL-producing)
- *Acinetobacter baumannii*
- *Pseudomonas aeruginosa*
- *Enterobacter* species

Rice LB. *J Infect Dis* 2008;197:1079-81



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Emerging antimicrobial resistance of importance in human medicine

- Methicillin-Resistant *Staphylococcus aureus* (MRSA)
- **Multi-drug resistant gram-negative bacilli**
 - “SPACE” organisms (Serratia, Pseudomonas, Acinetobacter, Citrobacter, Enterobacter)
 - Ciprofloxacin resistance
 - AmpC/inducible beta-lactamases
 - Extended spectrum beta-lactamases (ESBLs)
 - Carbapenem-resistance
 - **Now with colistin resistance**



Emerging antimicrobial resistance of importance in human medicine

- Epidemic strains of *C. difficile*
- Vancomycin-resistant *Enterococcus ssp.* (VRE)
- Vancomycin-intermediate *Staphylococcus aureus* (VISA)
- Vancomycin-resistant *Staphylococcus aureus* (VRSA)



Definitions of antimicrobial resistance

MDRO=multidrug resistant organisms

- Resistant to more than one class of antimicrobial agent (IOM, 1998)
 - Although this definition suggests resistance to only one class, most of the pathogens discussed are resistant to multiple classes
 - May use more explicit definitions
- Epidemiologically important
 - Known to be transmitted in the healthcare environment
 - Modifiable risk factors
 - Effective infection control interventions



Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance

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Abbreviations

- MDR=multidrug-resistant
- XDR=extensively drug-resistant
- PDR=pandrug-resistant



TABLE 6. Definitions for multidrug-resistant (MDR), extensively drug-resistant (XDR) and pandrug-resistant (PDR) bacteria

Bacterium	MDR	XDR	PDR
<i>Staphylococcus aureus</i>	The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table 1 ^a	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 1.	Non-susceptibility to all agents in all antimicrobial categories for each bacterium in Tables 1–5
<i>Enterococcus</i> spp.	The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table 2	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 2.	
<i>Enterobacteriaceae</i>	The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table 3	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 3.	
<i>Pseudomonas aeruginosa</i>	The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table 4	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 4.	
<i>Acinetobacter</i> spp.	The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table 5	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 5.	

^aAll isolates are defined as MDR because resistance to oxacillin or ceftazidime predicts non-susceptibility to all categories of β -lactam antimicrobials listed in this document, with the exception of the anti-MRSA cephalosporins (i.e. all categories of penicillins, cephalosporins, β -lactamase inhibitors and carbapenems currently approved up until 25 January 2011).
http://www.ecdc.europa.eu/en/activities/diseaseprogrammes/ARHAI/Pages/public_consultation_clinical_microbiology_infection_article.aspx



Methicillin-resistant *S. aureus* (MRSA)

- A group of anti-penicillinase antibiotics were developed in the 1960s to treat penicillin-resistant staph (methicillin, nafcillin, oxacillin)
- MRSA contains *mecA* gene which encodes for a modified penicillin-binding protein with reduced binding of methicillin, oxacillin, or nafcillin
- Also resistant to cephalosporins
- *mecA* gene is housed within the staphylococcal chromosomal cassette (SCC) which also houses multiple resistance genes



MRSA

■ Hospital-acquired

- Large SCCmec A (types I,II,III)
- Multi-drug resistance
- Multiple risk factors for contact with the healthcare system
- Infections at many sites (blood, lung, skin, etc)
- USA 100, 200, 500, 600, 800 PFGE types (2003)

■ Community-acquired

- Small SCCmecA (Type IV)
- Typically resistant only to beta-lactam drugs
- No risk factors for contact with healthcare system
- Younger patients
- Skin and soft tissue infections
- Toxin-producing strains
- USA 300, 400 PFGE types



VRE, VISA, VRSA

- Vancomycin resistant enterococcus
 - *vanA*, *vanB*, *vanC* genes
- Vancomycin intermediate *S. aureus*
 - Lower MICs
 - Thickened cell wall
- Vancomycin resistant *S. aureus*
 - Very high MICs
 - *vanA* gene



Pseudomonas aeruginosa

- Gram-negative, non-fermenting bacillus
- Common environmental pathogen, especially in water
- Reservoirs for infection can develop, even in intensive care units
- One of the most serious causes of ventilator-associated pneumonia (VAP)



Imipenem-resistant *Pseudomonas aeruginosa*

- University of Pennsylvania
- 1991 to 2000, significant increase in imipenem resistance ($p < 0.001$)
- Only independent risk factor for acquisition was prior fluoroquinolone use
- Resistant infections resulted in longer hospital stay (15.5 vs 9 days, $p = 0.02$) and increased costs (\$81,330 vs \$48,381)
- Increased mortality rate (31.1 vs 16.7%)

Lautenbach E et al. Infect Cont Hosp Epidem 2006;27:893-900



Extended spectrum β -lactamases

- *K. pneumoniae*, *E. coli*
- Also reported with *Salmonella*, *Proteus*, *Enterobacter*, *Citrobacter*, *Serratia*, and *Pseudomonas*
- Plasmid-mediated enzymes able to hydrolyze most penicillins and cephalosporins
- Mutated from native β -lactamases, particularly TEM-1, TEM-2, and SHV-1; heterogenous group of enzymes also derived from other β -lactamases-now CTX-M

Clin Infect Dis 2006;42:S153



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ESBLs

- Phenotype: resistance to 3rd generation cephalosporins and monobactams
- Their proliferation is a global concern and results in serious limitations in treatment options
- Usually carbapenems are the best and only treatment option



Table 3. Risk factors associated with infection or colonization with extended-spectrum β -lactamase–producing pathogens.

Prolonged hospital stay
Prolonged intensive care unit or neonatal intensive care unit stay
Residency in long-term care facility
Exposure to third-generation cephalosporins
Exposure to trimethoprim-sulfamethoxazole
Exposure to ciprofloxacin
Total antibiotic use
Delayed appropriate therapy
Indwelling catheter
Gastrostomy or tracheostomy
Severity of illness
Decubitus ulcer
Total dependence on health care workers
Endotracheal or nasogastric tube

NOTE. Data are from [30–37].

Carbapenemases

- Carbapenemases are enzymes which can inactivate a wide range of antibiotics including the carbapenem class, thus rendering the bacteria highly resistant to most treatment modalities
- Two current classes noted:
 - KPC: class A
 - NDM-1: class B



Outbreak of *Klebsiella pneumoniae* Producing a New Carbapenem-Hydrolyzing Class A β -Lactamase, KPC-3, in a New York Medical Center

Neil Woodford,^{1*} Philip M. Tierno, Jr.,² Katherine Young,³ Luke Tysall,¹ Marie-France I. Palepou,¹ Elaina Ward,¹ Ronald E. Painter,³ Deborah F. Suber,³ Daniel Shungu,³ Lynn L. Silver,³ Kenneth Inglis,² John Kornblum,⁴ and David M. Livermore¹

Antibiotic Resistance Monitoring and Reference Laboratory, Specialist and Reference Microbiology Division—Colindale, Health Protection Agency, London, United Kingdom¹; Departments of Microbiology & Pathology, Tisch Hospital, NYU Medical Center,² and New York City Department of Health, Public Health Laboratory,⁴ New York, New York; and Human and Animal Infectious Disease Research, Merck Research Laboratories, Rahway, New Jersey³

From April 2000 to April 2001, 24 patients in intensive care units at Tisch Hospital, New York, N.Y., were infected or colonized by carbapenem-resistant *Klebsiella pneumoniae*. Pulsed-field gel electrophoresis identified a predominant outbreak strain, but other resistant strains were also recovered. Three representatives of the outbreak strain from separate patients were studied in detail. All were resistant or had reduced susceptibility to imipenem, meropenem, ceftazidime, piperacillin-tazobactam, and gentamicin but remained fully susceptible to tetracycline. PCR amplified a *bla*_{KPC} allele encoding a novel variant, KPC-3, with a His(272)→Tyr substi-

KPC

- 96 isolates from 10 Brooklyn hospitals
- All resistant to carbapenems and most other antibiotics
- About 50% susceptible to aminoglycosides and 90% to polymixin B; all susceptible to tigecycline.
- Therapeutic options: colistin, tigecycline

JAC 2005;56:128



NDM-1 strain

- New Delhi metallo-beta-lactamase-1
- *Klebsiella pneumoniae* and *Escherichia coli*.
- NDM-1 has been reported in >37 states within the United States, including Ohio



Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study

Karthikeyan K Kumarasamy, Mark A Toleman, Timothy R Walsh, Jay Bagaria, Fafhana Butt, Ravikumar Balakrishnan, Uma Chaudhary, Michel Doumith, Christian G Giske, Seema Irfan, Padma Krishnan, Anil V Kumar, Sunil Maharjan, Shazad Mushtaq, Tabassum Noorie, David L Paterson, Andrew Pearson, Claire Perry, Rachel Pike, Bhargavi Rao, Ujjwayini Ray, Jayanta B Sarma, Madhu Sharma, Elizabeth Sheridan, Mandayam A Thirunarayan, Jane Turton, Supriya Upadhyay, Marina Warner, William Welfare, David M Livermore, Neil Woodford

Lancet Infect Dis 2010;10:597-602



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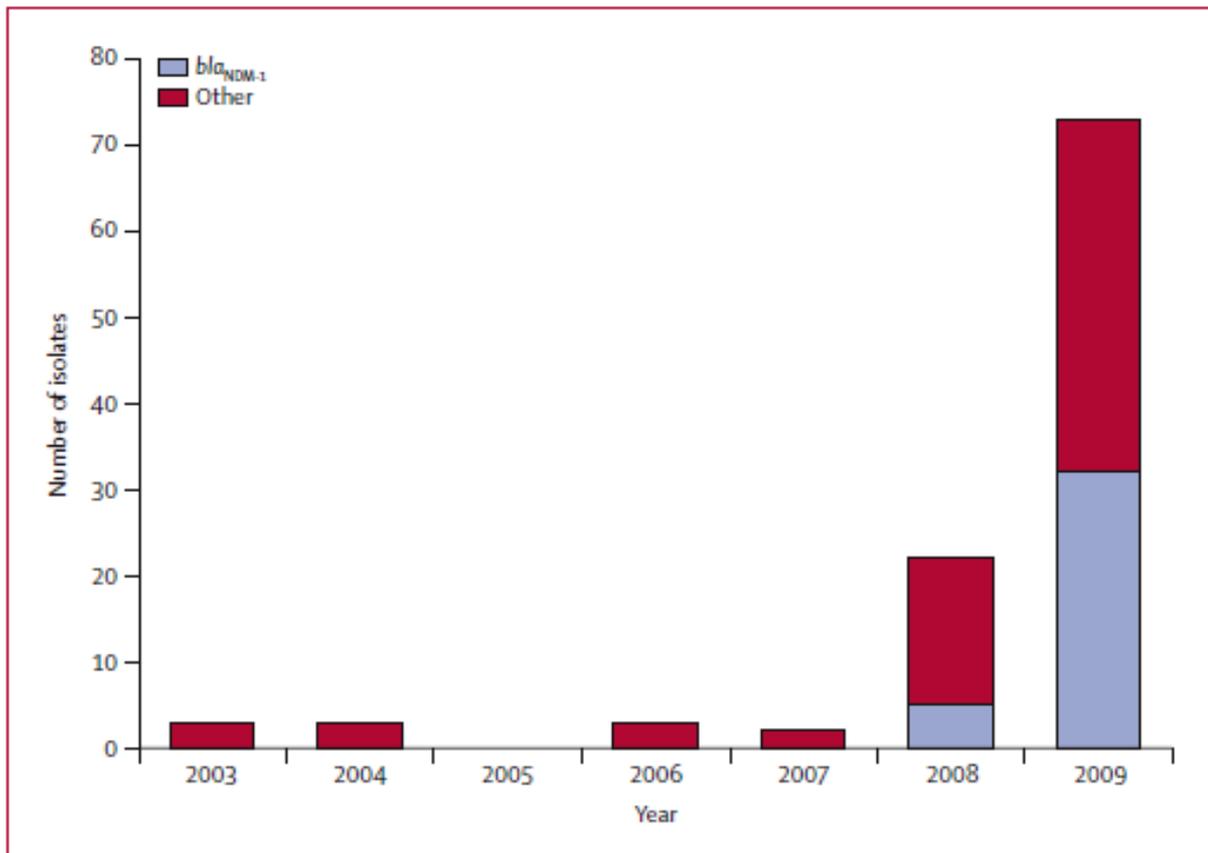


Figure 1: Numbers of carbapenemase-producing Enterobacteriaceae referred from UK laboratories to the UK Health Protection Agency's national reference laboratory from 2003 to 2009

The predominant gene is *bla_{NDM-1}*, which was first identified in 2008. The other group includes diverse producers of KPC, OXA-48, IMP, and VIM enzymes.

Lancet Infect Dis 2010;10:597-602



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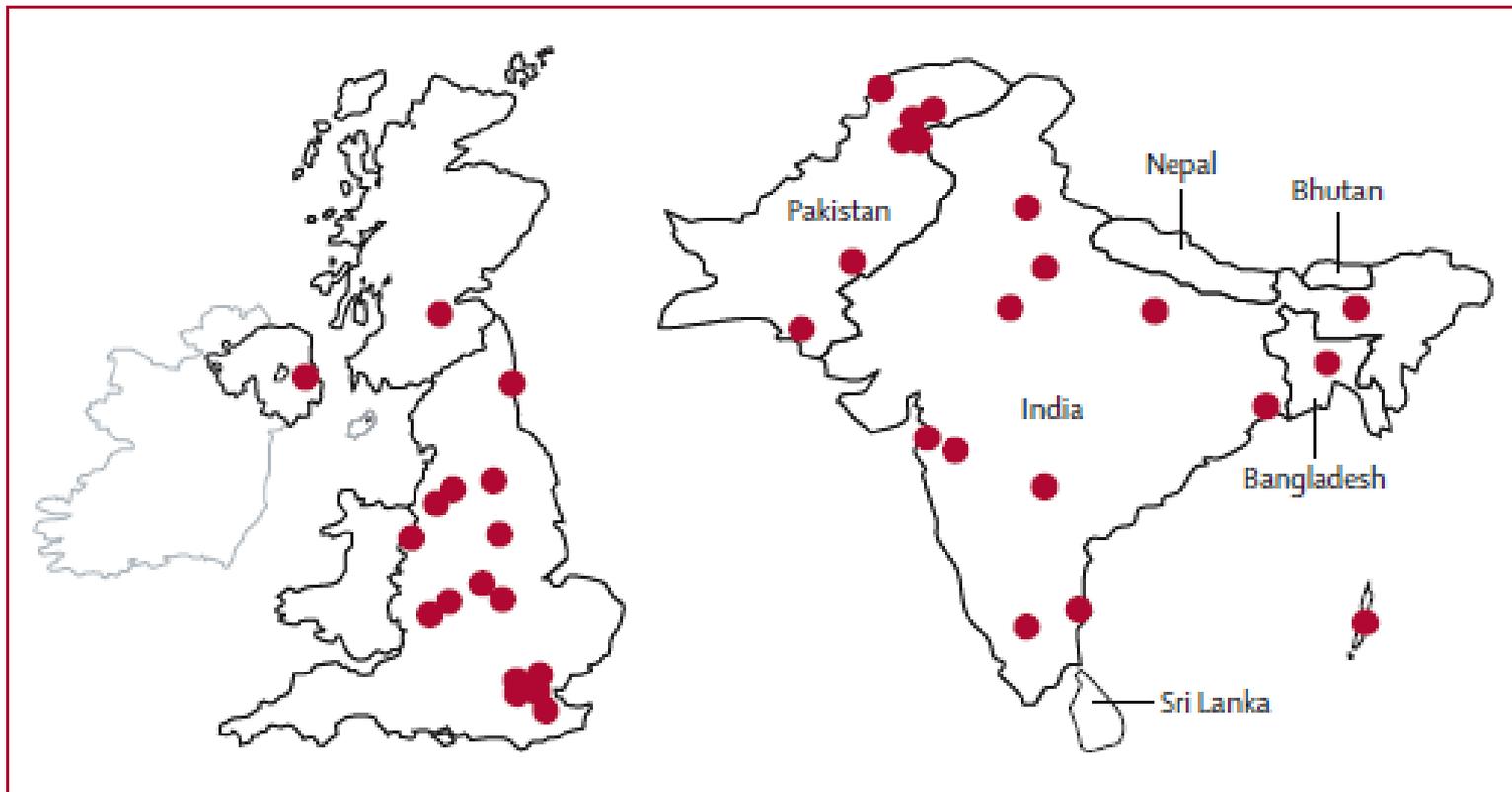


Figure 5: Distribution of NDM-1-producing Enterobacteriaceae strains in Bangladesh, Indian, Pakistan, and the UK

Lancet Infect Dis 2010;10:597-602



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Acinetobacter baumannii

- *Acinetobacter baumannii* (*Ab*) is a ubiquitous encapsulated, aerobic, nonfermentive gram-negative coccobacillus
- It is capable of causing both community and healthcare-associated infections involving pulmonary system, urinary tract, bloodstream, and surgical wounds
- These organisms have a high propensity to accumulate mechanisms of drug-resistance; large HAI outbreaks with pan resistant strains have been reported

Acinetobacter baumannii (Ab)

- Major risk factors include invasive procedures such as using mechanical ventilation, central venous or urinary catheters, and exposure to broad spectrum antimicrobials
- The organisms exist in the environment in both wet and dry conditions and can survive for months on clothing, bedrails, ventilators, and other surfaces

Clin Infect Dis 2006;42:692-699

J Clin Microbiol 1996;34:2881-2887

Principles and Practices of Infectious Diseases 2000:2339-2344



MDR *Ab* outbreaks across geographic distances

- Citywide clonal outbreak of MDR-*Ab*; involved 15 hospitals in Brooklyn (based on ribotyping)
- Interhospital transfer of MDR-*Ab* among 4 hospitals in Johannesburg, South Africa (based on PFGE)

Arch Intern Med 2002;162:1515-1520

Am J Infect Control 2004;32:278-281



Colistin

- Mixture of cyclic polypeptides (polymixin A and B); polycationic with both hydrophilic and lipophilic moieties
- Disrupts cell membrane
- Active against gram negative bacteria esp *Pseudomonas* and *Acinetobacter*
- Previous concerns for neurotoxicity and nephrotoxicity
- Resistance currently has been generally rare



Colistin resistance

- 265 isolates of *Acinetobacter* from 2 Korean hospitals
- Categorized into 3 subgroups:
 - Subgroup I (142 isolates [53.6%])
 - Subgroup II (54 [20.4%])
 - Subgroup III (18 [6.8%])
- Forty-eight isolates (18.1%) and 74 isolates (27.9%) were resistant to polymyxin B and colistin, respectively.

J Antimicrob Chemother. 2007 Aug 29



Questions?

