RESISTANT PATHOGENS

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Courtesy of American College of Surgeons Division of Education
Clinical Congress 2015

Disclosures

- Contracted Research: AstraZeneca, Bayer, Merck.
- Advisory Boards/Consultant: Allergan (Actavis, Forest Laboratories), AstraZeneca, Bayer, Merck (Cubist), Pfizer.

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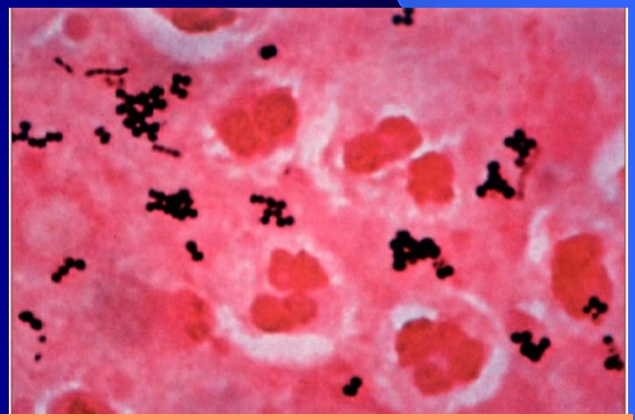
Topics

- **Resistant Gram positive pathogens:**
  - **Methicillin-resistant Staphylococcus aureus (MRSA).**
  - **Vancomycin-resistant *Enterococcus* (VRE).**
- **Resistant Gram negative pathogens:**
  - ***Enterobacteriaceae:***
    - **Extended spectrum-β-lactamase (ESBL)-producing *E. coli.***
    - **Carbapenemase-producing *Klebsiella sp.***
  - **Non-lactose fermenters:**
    - ***Pseudomonas aeruginosa.***
    - ***Acinetobacter* spp.**

MRSA



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MRSA

- Types of infections:
  - Bloodstream infection.
    - CLABSI.
  - Endocarditis.
  - Pneumonia.
  - Osteomyelitis.
  - Skin/soft tissue infections.

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MRSA Skin/Soft Tissue Infections

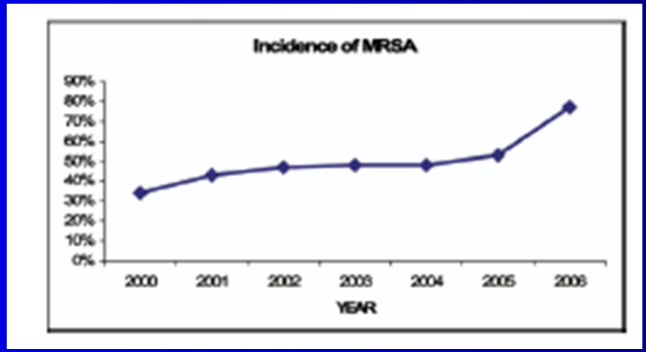
- **Increased incidence of SSTI: and in the numbers of those infections due to MRSA:**

Table 1. Estimated total number of US hospital admissions for SSTIs and infectious pneumonia, 2000–2004*

Principal diagnosis	2000	2001	2002	2003	2004	Change from 2000 to 2004
SSTI	674,939	701,672	757,858	810,768	869,777	194,838 (+28.9%)
Infectious pneumonia	1,202,387	1,177,972	1,229,204	1,272,686	1,172,304	–30,083 (–2.5%)

*SSTI, skin and soft tissue infection. Source: Healthcare Cost and Utilization Project National Inpatient Sample, 2000–2004.

- **Increased incidence in the number of patients undergoing operative management of SSTI**



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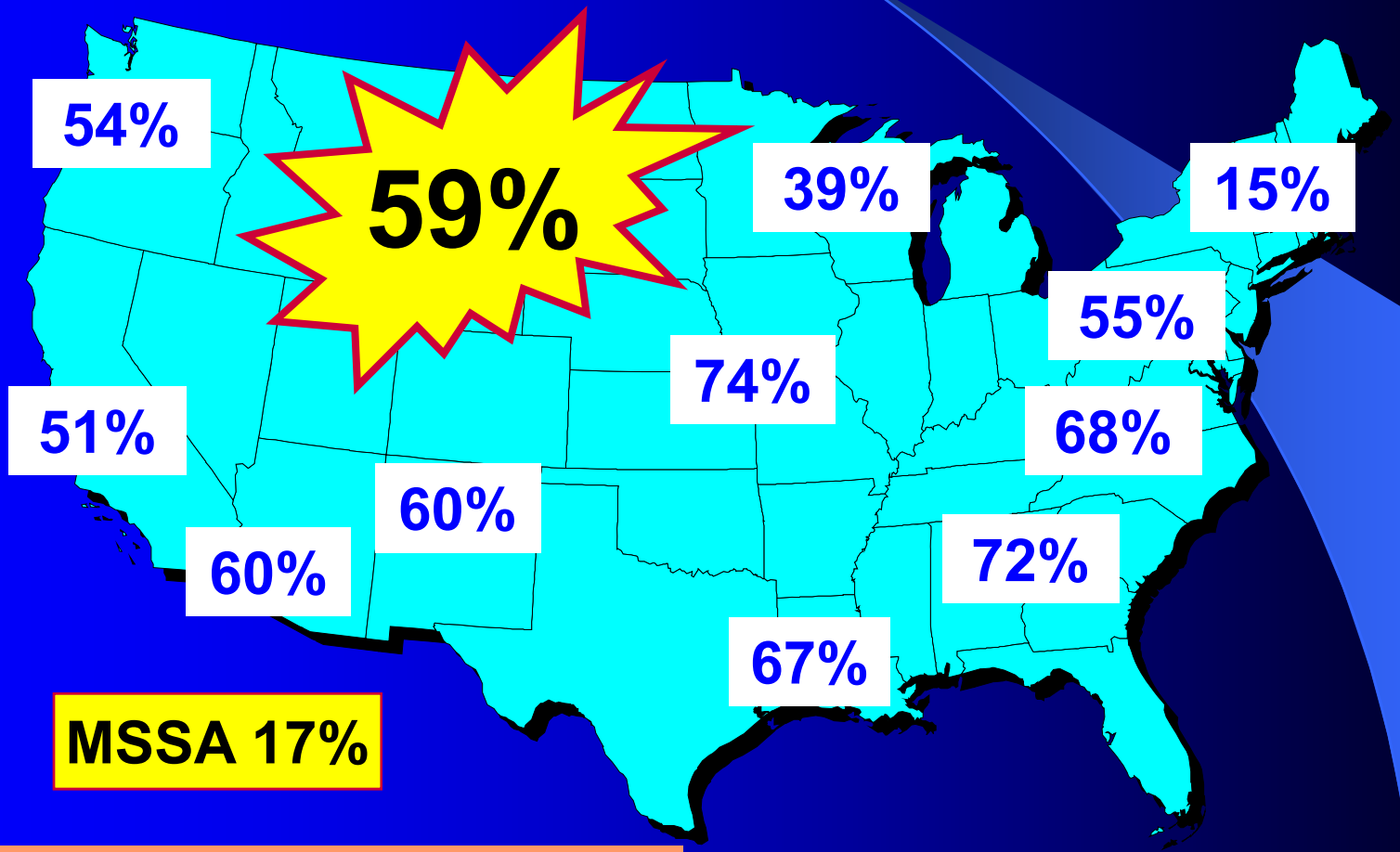
Edelsberg J et al: *Emerging Infect Dis* 2009;15:1516
Awad S et al. *Am J Surg* 2007;194:606

MRSA

- Prevalence of MRSA in ER patients with SSTI:



Courtesy of American College of Surgeons Division of Education
Clinical Congress 2015

Moran GJ, et al. *N Engl J Med*. 2006;355:666

Microbiology of SSI:
2011 NHSN Data

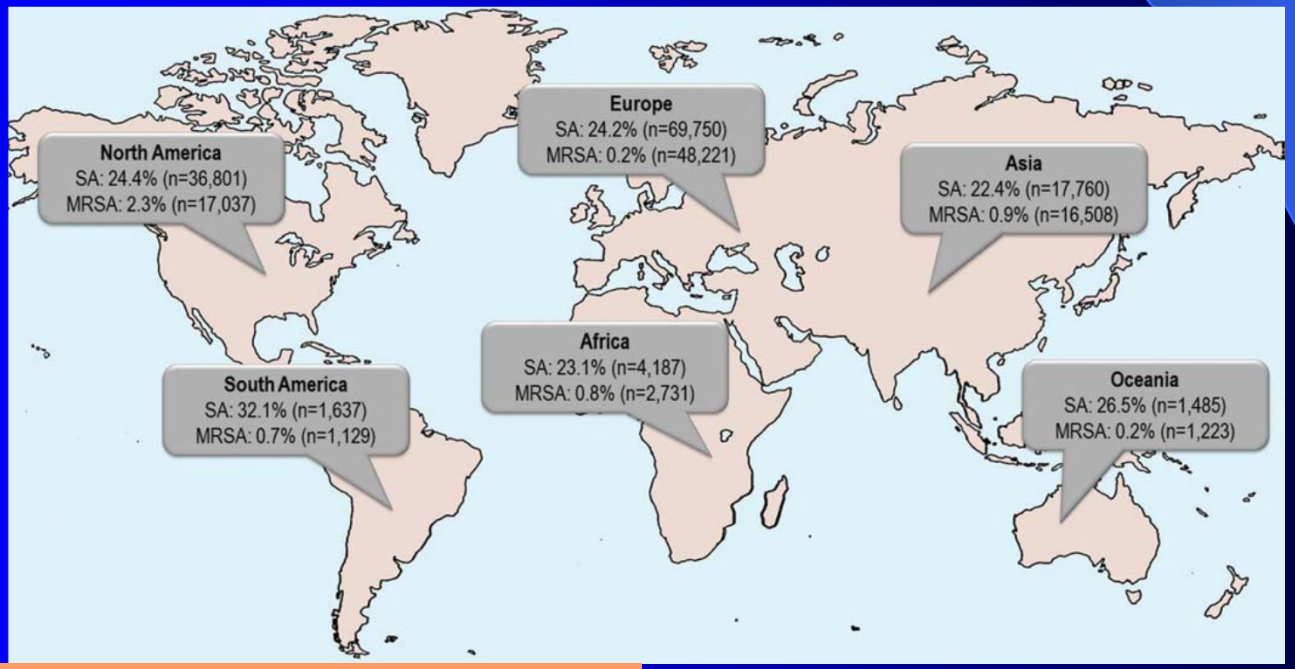
	All Procedures		Orthopedic		Abdominal		Cardiac		Ob/Gyn		Neurological	
PATHOGEN	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Staphylococcus Aureus												
Methicillin Susceptible	1,656	14.2	1,112	24.9	131	3.1	272	20.3	35	4.1	61	19.6
Methicillin Resistant	1,199	10.3	779	17.4	141	3.3	193	14.4	34	4.0	21	6.7
Not Tested	97	0.8	67	1.5	6	0.1	17	1.3	4	0.5	2	0.6
Escherichia coli.	1,184	10.2	203	4.5	773	18.1	55	4.1	123	14.4	8	2.6
Coagulase-negative staphylococci	1,084	9.3	601	13.5	128	3.0	194	14.5	45	5.3	78	25.0
Enterococcus faecalis	691	5.9	174	3.9	383	9.0	38	2.8	76	8.9	4	1.3
Pseudomonas aeruginosa	561	4.8	169	3.8	210	4.9	104	7.8	29	3.4	14	4.5
Klebsiella (pneumoniae/oxytoca)	491	4.2	92	2.1	285	6.7	54	4.0	29	3.4	11	3.5
Enterobacter spp.	483	4.1	168	3.8	185	4.3	76	5.7	20	2.3	13	4.2
Enterococcus spp.	410	3.5	73	1.6	256	6.0	18	1.3	35	4.1	2	0.6
Enterococcus faecium	290	2.5	39	0.9	201	4.7	15	1.1	7	0.8	2	0.6
Candida albicans	218	1.9	12	0.3	157	3.7	19	1.4	14	1.6	5	1.6
Other *Candida* spp. or NOS	124	1.1	17	0.4	82	1.9	13	1.0	2	0.2	2	0.6
Acinetobacter baumanii	40	0.3	21	0.5	6	0.1	6	0.4	2	0.2	2	0.6
Other	3,122	26.8	941	21.1	1,320	31.0	267	19.9	397	46.6	87	27.9
TOTAL	**11,650**	**100.0**	**4,468**	**100.0**	**4,264**	**100.0**	**1,341**	**100.0**	**852**	**100.0**	**312**	**100.0**

Courtesy of American College of Surgeons Division of Education Clinical Congress 2015

Data provided by Philip Ricks, CDC

MRSA Carriage

- Found in 2-3% of the normal U.S. population.
  - Much less common than MSSA carriage.
  - Rates are lower in Europe and other areas.
  - Higher prevalence in ICU patients (9%), during outbreaks, and in some high prevalence populations.



Courtesy of American College of Surgeons Division of Education Clinical Congress 2015

McKinnell JA, et al. *Infect Control Hosp Epidemiol* 2013;34:161
Verhoeven PO et al. *Expert Rev Anti Infect Ther* 2014;12:75

Community-Associated MRSA (CA-MRSA)

- Less resistant than healthcare-associated strains of MRSA (HA-MRSA).
  - Typically susceptible to clindamycin, trimethoprim-sulfamethoxazole, tetracyclines, and variably to fluoroquinolones.
- Produce Panton-Valentine leukocidin and other toxins.
  - Necrosis due to these toxins may be important in pathogenesis.

Courtesy of American College of Surgeons Division of Education
Clinical Congress 2015

Pichereau S, Rose WE. *Exp Opin Pharmacother* 2010;11:3009

Community-Associated MRSA

- CA-MRSA is increasingly prevalent in hospitalized patients.
  - Suppression of virulence factors in HA-MRSA strains may make it less pathogenic.
  - Larger resistance plasmid makes HA-MRSA less robust.
- Mathematical models suggest CA-MRSA strains will increasingly replace HA-MRSA strains by in hospitalized patients.

Mediavilla JR et al. *Curr Opin Microbiol* 2012;15:588
Otter JA, French GL. *J Hosp Infect* 2011;79:189
D'Agata MC et al. *Clin Infect Dis* 2009;48:274
Skov RL, Jensen KS. *J Hosp Infect* 2009;73:364

Antibiotic Therapy for CA-MRSA: Summary of Recommendations

- **Outpatient treatment (oral):**
  - **Clindamycin[#*]**
  - **Trimethoprim/sulfamethoxazole[#*]**
  - **A tetracycline (doxycycline or minocycline)[#*]**
  - **Linezolid[#*]**
  - **Fluoroquinolones[#]**
  - **Erythromycin[#]**

[#]Surgical Infection Society SIS

[*]Infectious Diseases Society of America

Courtesy of American College of Surgeons Division of Education Clinical Congress 2015

May A et al. *Surg Infect* 2009;10:267
Liu C et al. *Clin Infect Dis* 2011:52:285

Antibiotic Therapy for CA-MRSA: Summary of Recommendations

- Inpatient treatment:
  - Vancomycin (or teicoplanin, where available)[#*]
  - Linezolid[#*]
  - Daptomycin[#*] - Not effective for pulmonary infections
  - Televancin[*]
  - Clindamycin[*]
  - Quinupristin/dalfopristin[#] - Rarely used
  - Tigecycline[#] - FDA black box warning on potentially decreased efficacy

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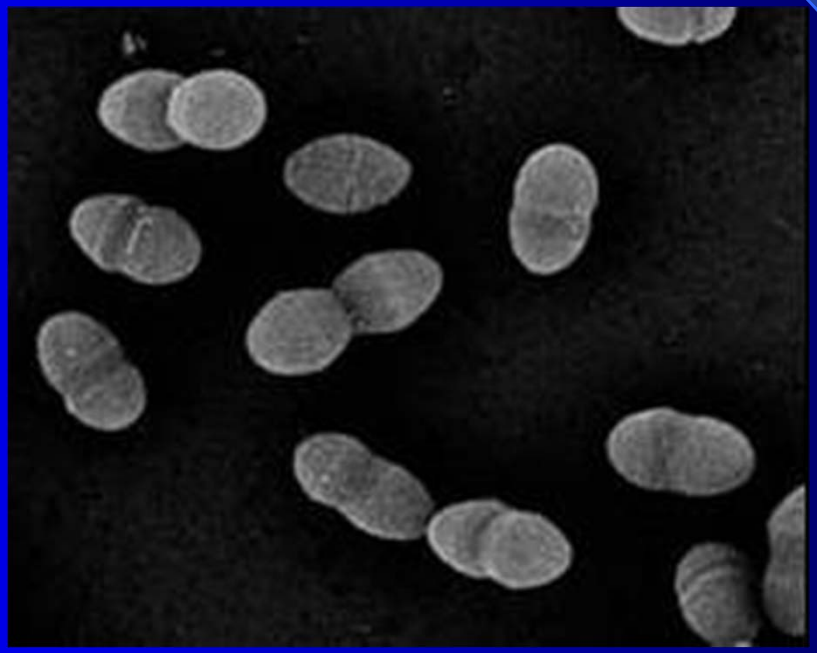
Clinical Congress 2015

May A et al. *Surg Infect* 2009;10:267
Liu C et al. *Clin Infect Dis* 2011:52:285

Antibiotic Therapy for MRSA: Recently Released Agents

- Ceftaroline
  - Cephalosporin with anti-MRSA activity.
- Glycopeptides:
  - Oritavancin
  - Dalbavancin
    - Both have very prolonged half-lives
- Tedizolid
  - An oxazolidinone with less drug:drug interactions than linezolid.

VRE



Courtesy of American College of Surgeons Division of Education
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VRE

- NHSN data - 35.5% of enterococci causing invasive infections in the U.S. are resistant to vancomycin.
  - Incidence of VRE is substantially lower in Europe.
- *E. faecium* accounts for the majority of VRE in US hospitals.

Table 2 Surveillance of vancomycin-resistant enterococci around the world

Species	Percent of *Enterococcus* isolates resistant to vancomycin by region (no of isolates)					
	Europe[8] 2013	US[11] 2009–2010	Worldwide[115] 2007–2012	Canada[50] 2007–2011	Asia-Pacific[118] 2007–2008	Latin America[118] 2007–2008
E. faecium	8.8 (729)	79.4 (2,572)	–	22.4 (60)	14.1 (270)	48.1 (54)
E. faecalis	1.0 (126)	8.5 (444)	10.3 (27)	0.1 (1)	0.01 (440)	3.1 (195)
All enterococci	4.0 (855)	35.5 (3,016)	–	6.0 (61)	11.9 (710)	12.9 (249)

Courtesy of American College of Surgeons Division of Education
Clinical Congress 2015

Driscoll T, Crank CW. *Infect Drug Resist* 2015:8:217

VRE Infections

- Types of infections due to VRE are typical of infections due to susceptible enterococci:
  - Intra-abdominal.
    - Less than 10% of IAI are due to enterococci.
  - Urinary tract.
  - Bacteremia.
  - Endocarditis (3% of patients with VRE bacteremia).
  - Skin/soft tissue.
  - CNS - uncommon.
  - Respiratory - very rare.

Courtesy of American College of Surgeons Division of Education Clinical Congress 2015

Driscoll T, Crank CW. *Infect Drug Resist* 2015:8:217
Vergis EN et al. *Ann Intern Med* 2001;135:484

VRE Colonization

- VRE infections develop in patients colonized with VRE.
- VRE colonization is primarily depends on acquisition in healthcare institutions
  - Contingent on:
    - 1) Reservoir of VRE.
    - 2) A “susceptible host”.

Courtesy of American College of Surgeons Division of Education Clinical Congress 2015

Zirakzadeh A, Patel R. *Mayo Clin Proc* 2006;81:529

The "Susceptible Host" for VRE Colonization

- Risk factors for colonization:
  - Prolonged length of stay, especially in the ICU.
  - Surgical procedures.
  - Premorbid condition and severity of illness.
  - Liver transplant patients.
- Antibiotic therapy is a major risk factor:
  - Vancomycin, third-generation cephalosporins, ciprofloxacin, aminoglycosides, aztreonam, imipenem, anti-anaerobic agents.
  - Number of antibiotics.
  - Duration of antibiotic exposure.

DeLisle S and Perl TM. *Chest* 2003;123:504S
Zirakzadeh A, Patel R. *Mayo Clin Proc* 2006;81:529
E, Cataldo MA. *Int J Antimicrob Agents* 2008; 31:99
Ziakas PD, et al. Am J Transplant 2014;14:1887

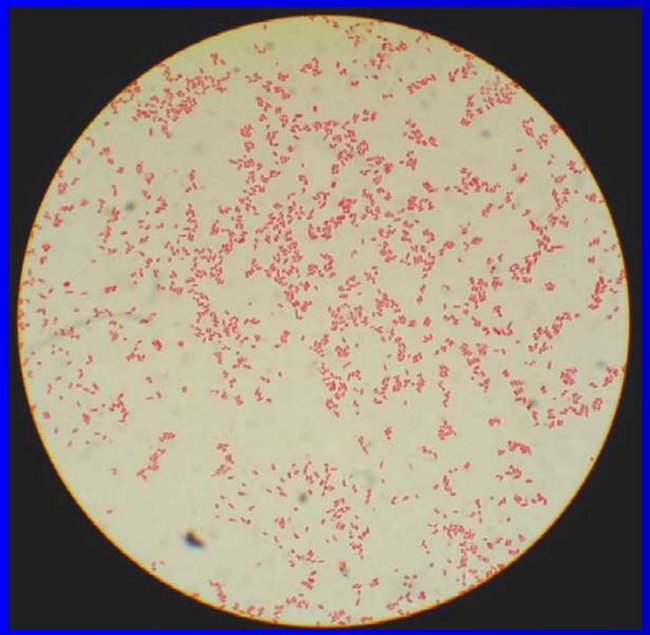
VRE Treatment

- Susceptibilities of vancomycin-resistant *E. faecium*:

	Nichol et al.	Sader et al.
Vancomycin	0	
Teicoplanin	23	42
Linezolid	100	100
Daptomycin	100	100
Quinupristin/ dalfopristin	75.8	21.8
Chloramphenicol	99.4	87
Doxycycline	60.6	

ichol KA et al. *Int J Antimicrob Agents* 2006;27:392
Sader HS et al. *BMC Infect Dis* 2007;7:29

RESISTANT GRAM NEGATIVE BACTERIA



Courtesy of American College of Surgeons Division of Education
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E. coli: Fluoroquinolone Resistance

- Found in both community-acquired and healthcare-associated strains.
- Susceptibilities of *E. coli* isolates from intra-abdominal infections:
  - Africa - 80%.
  - Asia - 47%.
  - Europe - 77%.
  - Latin America - 52%.
  - Middle East - 55%.
  - North America - 72%.
  - South Pacific - 80%.

Courtesy of American College of Surgeons Division of Education Clinical Congress 2015

Hawser SP et al. *J Chemother* 2015;27:67

Extended-Spectrum β-Lactamases

- Over 1300 β-Lactamases have been identified.
- Ambler Classification
  - Class A
    - The most common types cleave cephalosporins, aztreonam, but not carbapenems.
    - However, some have carbapenemase activity.
  - Class B
    - Metallo-β-lactamases cleave nearly all β-lactams.
    - No inhibitors commercially available at present.
  - Class C
    - AmpC-lactamases
    - Can be induced by cephalosporins.
  - Class D
    - Cleave anti-staphylococcal penicillins.
    - Some may have carbapenemase activity.

Courtesy of American College of Surgeons Division of Education
Clinical Congress 2015

Bebrone C et al. *Drugs* 2010;70:651
Nordmann P, et al. *Emerg Infect Dis* 2011;17:1791

Enterobacteriaceae: β-Lactam Resistance

- **ESBL-producing strains of *E. coli* are common in Asia and Latin America.**

Intra-abdominal infections in the Asia-Pacific region, 2010

Bacteria	No. of isolates
Escherichia coli	
ESBL(+)	519
ESBL(−)	754
Klebsiella pneumoniae	
ESBL(+)	114
ESBL(−)	417

40.8%

21.5%

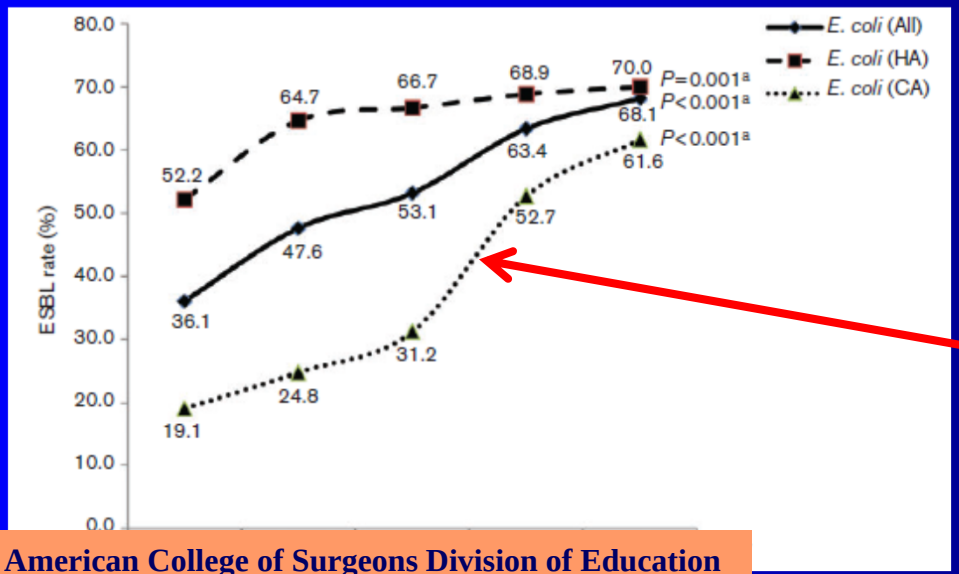
Courtesy of American College of Surgeons Division of Education Clinical Congress 2015

ueh PR. *Int J Antimicrob Agents* 2012;40[Suppl]:S1

Enterobacteriaceae: β-Lactam Resistance

- **ESBL-producing *E. coli* strains are increasingly encountered in isolates from patients with community-acquired intra-abdominal infections.**

Data from China



Community-acquired strains

Courtesy of American College of Surgeons Division of Education Clinical Congress 2015

Yang Q. *J Med Microbiol* 2013;62:1343

Enterobacteriaceae: β-Lactam Resistance

- **ESBL prevalence in *E. coli* intra-abdominal isolates from Latin America (2008-2009):**

Country	All	*n* ESBL*	% ESBL
Argentina	176	11	6.3
Brazil	74	10	13.5
Chile	190	56	29.5
Colombia	120	10	8.3
Dominican Republic	38	6	15.8
Ecuador	84	30	35.7
Guatemala	123	37	30.1
Mexico	232	96	41.4
Panama	65	3	4.6
Puerto Rico	47	0	0
Venezuela	217	64	29.5
Latin America	1366	323	23.6

Courtesy of American College of Surgeons Division of Education Clinical Congress 2015

Hawser SP et al. *J Chemother* 2012;24:6

Enterobacteriaceae: Carbapenem Susceptibilities

- **Resistance patterns of Gram negative pathogens isolated from patients with intra-abdominal infections in the Asia-Pacific region, 2010.**

	Ceftriaxone	Ceftazidime	Cefepime	Piperacillin/ Tazobactam	Ertapenem	Imipenem	Cipro-floxacin
	CRO	CAZ	FEP	PTZ	EPM	IPM	CIP
Escherichia coli							
ESBL(+)	0.6	35.7	6.4	89.4	99.0	99.8	21.6
ESBL(−)	84.8	86.5	98.0	92.4	98.8	99.2	67.1
Klebsiella pneumoniae							
ESBL(+)	1.8	29.8	17.5	65.8	95.6	98.3	34.2
ESBL(−)	95.9	96.2	99.5	96.9	98.6	98.8	92.6
Pseudomonas aeruginosa	0.7	63.9	65.3	69.0	-	62.1	71.5
Enterobacter cloacae	42.2	56.2	81.8	66.9	77.7	86.0	81.8
Acinetobacter baumannii	0.0	16.0	18.3	20.6	-	20.6	16.8

Courtesy of American College of Surgeons Division of Education Clinical Congress 2015

ueh PR. *Int J Antimicrob Agents* 2012; 40[Suppl]:S1

Carbapenem Resistance

- Although susceptibility of *Enterobacteriacae* to carbapenems remains high in Asia, resistance of other Gram negative bacilli to carbapenems is increasing.

Resistance in Gram negative bacteria

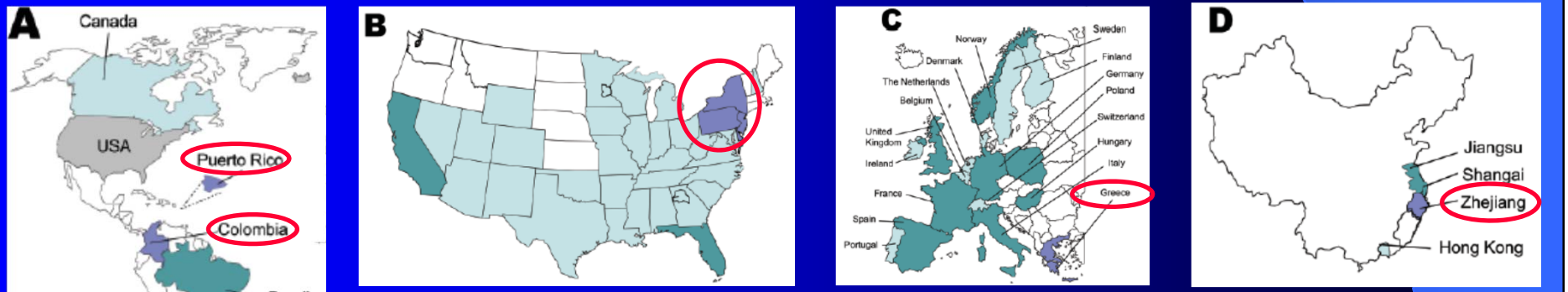
Country	*Pseudomonas aeruginosa*	Enterobacteriaceae	*Acinetobacter baumannii*	All isolates
New Zealand	10.3	12.5	–	11.7
Philippines	31.1	2.9	25.0	18.9
Singapore	23.3	4.2	90.5	22.1
Thailand	28.7	0.4	76.3	22.2
Vietnam	46.7	5.6	89.5	35.0
Overall	29.8	2.8	73.0	23.0

Courtesy of American College of Surgeons Division of Education
Clinical Congress 2015

atisin P, et al: *Int J Antimicrob Agents* 2012; 39:311

Carbapenem Resistance in *Klebsiella* spp.

- *Klebsiella pneumoniae* carbapenemase-producing strains are becoming established in some geographic areas.
- Resistant to most β-lactam antibiotics.



Courtesy of American College of Surgeons Division of Education Clinical Congress 2015

Nordmann P et al. *Emerg Infect Dis* 2011;17:1791

Resistance in Non-Lactose Fermenting Gram Negative Bacteria

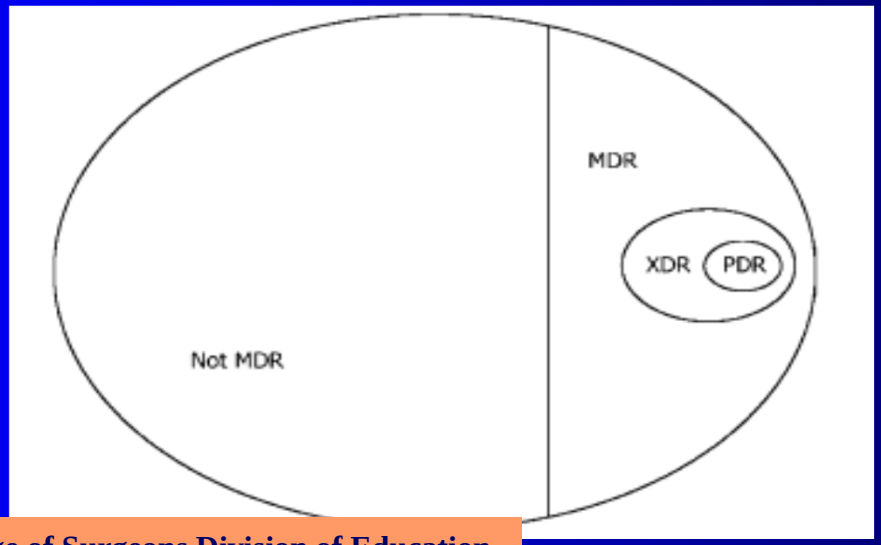
- *P. aeruginosa* and *Acinetobacter* spp.
- Multiple resistance mechanisms:
  - β-lactamases.
  - Efflux pumps.
  - Target site modifications.
  - Outer membrane modifications.

Courtesy of American College of Surgeons Division of Education Clinical Congress 2015

scki AP et al. *Expert Rev Anti Infect Ther* 2010;8:71

Resistance in Non-Lactose Fermenting Gram Negative Bacteria

- Antimicrobial selection may result in highly resistant organisms:
  - Multidrug-resistant (MDR) bacteria.
  - Extensively drug-resistant (XDR) bacteria.
  - Pandrug-resistant (PDR) bacteria.



Courtesy of American College of Surgeons Division of Education Clinical Congress 2015

giorakos AP et al. *Clin Microbiol Infect* 2012;18:268

Treatment of Resistant Gram Negative Bacteria

- Carbapenems are frequently the first line agents.
- Carbapenem-sparing agents:
  - Tigecycline has activity against many resistant microorganisms.
    - Not active against *Pseudomonas*.
    - FDA black box warning; should be used in combination with another agent.
  - Other β-lactam antibiotics:
    - Piperacillin/tazobactam.
    - Cephamycins (cefoxitin, cefotetan).
  - Fluoroquinolones, aminoglycosides, fosfomycin, colistin.

Newly-Approved Antibiotics

- **Ceftolozane/tazobactam:**
  - **Newly-approved agent with enhanced anti-pseudomonal activity.**
    - **Has *in vitro* activity against many MDR and XDR strains of *P. aeruginosa*.**
  - **Has increased activity against a number of ESBL-producing *Enterobacteriaceae*.**
  - **Not active against carbapenemase-producing strains.**
  - **Poor activity against *Acinetobacter* spp.**

Courtesy of American College of Surgeons Division of Education Clinical Congress 2015

Zhanel GG, et al. *Drugs* 2014;74:31

Newly-Approved Antibiotics

- **Ceftazidime/avibactam:**
  - **Enhanced activity against many ESBL-producing *Enterobacteriaceae*.**
    - **Has *in vitro* activity against KPC-producing organisms (Ambler class A), but not against metallo-β-lactamase producing strains (Ambler class B).**
  - **Enhanced anti-pseudomonal activity.**
  - **Poor activity against *Acinetobacter* spp.**

Courtesy of American College of Surgeons Division of Education Clinical Congress 2015

Zhanel GG, et al. *Drugs* 2013;73:159

Antimicrobial Stewardship Programs

- Selecting appropriate patients for antimicrobial therapy.
- Appropriate selection of antimicrobials.
- Appropriate dosing of antimicrobials.
- Appropriate route of administration.
- Appropriate duration of antimicrobial therapy.

Courtesy of American College of Surgeons Division of Education
Clinical Congress 2015

Society for Healthcare Epidemiology of America, et al. *Infect Control Hosp Epidemiol* 2012;33:322
Cotta MO, et al. *Expert Rev Anti Infect Ther* 2014;12:581

The Optimal Antimicrobial Agent for Surgical Infections

Source Control

Courtesy of American College of Surgeons Division of Education
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Summary

- Community-associated MRSA is established in North America.
- ESBL-producing *E. coli* are increasingly common in many parts of the world.
- There are significant threats related to even more resistant Gram negative bacteria.
- Antimicrobial stewardship programs are important for preserving our current antibiotic resources.

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