Hartford Hospital
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Antibiotic Stewardship in Times of War

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Disclosures

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Advisory Member: Clinical Laboratory Standards Institute (CLSI)

Improving the Probability of Positive Outcomes

IMPROVING THE ODDS

Civilians

- Varied ages
- Co-morbid conditions

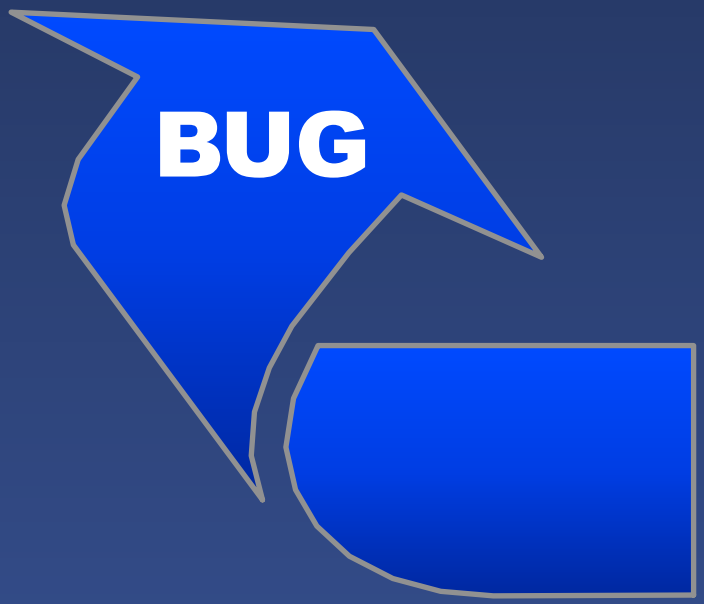
Military personnel

- Generally young
- Healthy
- Enhanced drug clearance → Low Exposures

Nicolau DP Am J Man Care 1998:4(10 Suppl) S525-30

Improving the Probability of Positive Outcomes

IMPROVING THE ODDS



Gram+ Pathogens

- Staphylococcus including Methicillin-Resistant strains (MRSA)

Gram-Negative

- *E. coli*
- *Klebsiella pneumoniae*
- *Pseudomonas aeruginosa*
- Acinetobacter spp.

Nicolau DP Am J Man Care 1998:4(10 Suppl) S525-30

Problematic Gram-Negatives and Mechanisms of Resistance

- ***Pseudomonas aeruginosa***
  - AmpC production, efflux pumps (Mex*AB*-Opr*M*, etc), outer membrane porin changes (i.e., loss of Opr*D*), Metallo-Beta-Lactamase production (e.g., bla_{VIM}, bla_{IMP}), *gyrA*/*parC* mutations, aminoglycoside-modifying enzymes (AME), ESBL/KPC production
- **Enterobacteriaceae (*Klebsiella* species, *E. coli*, *Enterobacter* species)**
  - **ESBL, Klebsiella-producing-carbapenemase (KPC-2, -3, -4, etc.) production, New Delhi Metallo-Beta-Lactamase (NDM-1, -2),** AmpC, outer membrane porin changes, plasmid mediated quinolone resistance gene (*qnrA*)
- ***Acinetobacter* species**
  - AmpC, ESBL (TEM-1, SHV-type, CTX-M-type), and serine (bla_{OXA}) and metallo (bla_{VIM}, bla_{IMP}) carbapenemase production, outer membrane porin changes, AME, *gyrA*/*parC* mutations, efflux pumps
- **Other multidrug resistant, non-fermentative bacteria**
  - ***Stenotrophomonas maltophilia*, *Burkholdheria cepacia* complex**

Bonomo RA, et al. *Clin Infect Dis* 2006;43:S49-56, Nicasio AM, et al. *Pharmacotherapy* 2008;28:235-49

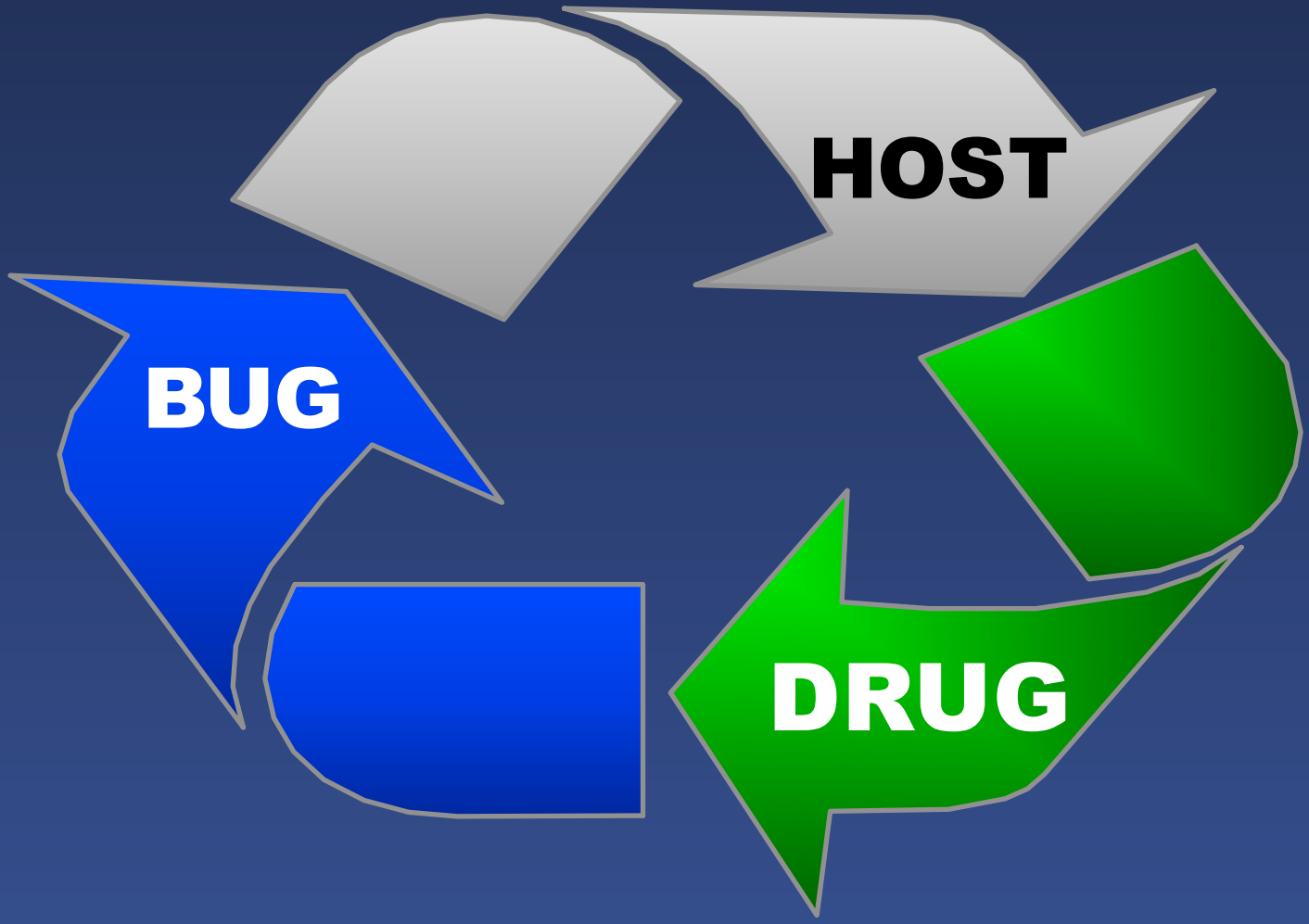
Multidrug Resistant Gram-Negatives in Deployment-Related Trauma Patients

- *2,699 military personnel with deployment-related trauma (2009-2014)*
  - 33% ≥ 1 infection event → 27% of these had MDR Gr- infection
  - 7 day median time to infection, 75% within 13 days pot-trauma
  - SSSI > Pneumonia > BSI > Osteo > UTI > Intra-abdominal
  - Acinetobacter spp. > *E. coli* > Klebsiella spp. > *P. aeruginosa*
  - MDR Gr- infection more frequent in:
    - » Blast injuries, Traumatic amputations, Higher injury severity
  - MDR Gr- patients:
    - » More frequently admitted to ICU
    - » More frequently colonized with MDR Gr- pathogens
    - » Higher antibiotic exposures before MDR infection
- **High rate of MDR Gram-negative pathogens in ↑↑ injury severity population → prolonged hospitalizations**

Campbell WR, et al. Surgical Infections 2017;18(3):357-367

Improving the Probability of Positive Outcomes

IMPROVING THE ODDS



Care Setting:

- **Field based**
- **Hospital**

Nicolau DP Am J Man Care 1998:4(10 Suppl) S525-30

Antimicrobial Stewardship: Part of the Solution?

Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship

Timothy H. Dellit,[1] Robert C. Owens,[2] John E. McGowan, Jr.,[3] Dale N. Gerding,[4] Robert A. Weinstein,[5] John P. Burke,[6] W. Charles Huskins,[7] David L. Paterson,[8] Neil O. Fishman,[9] Christopher F. Carpenter,[10] P. J. Brennan,[9] Marianne Billeter,[11] and Thomas M. Hooton[12]

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The Primary Goal of Antimicrobial Stewardship:

"Optimize clinical outcomes while minimizing unintended consequences of antimicrobial use"

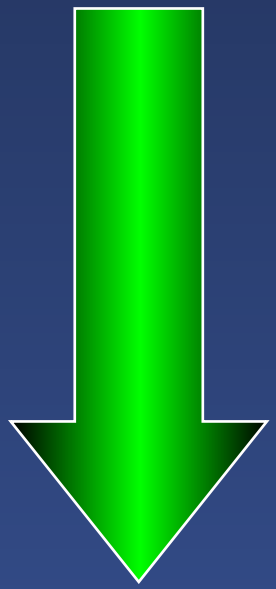
Dellit T, et al. *Clin Infect Dis.* 2007;44:159-177.

Appropriate Antimicrobial Therapy

- Matches antibiotic susceptibilities of the organism to the antibiotic used

"S" = Success

Improved Outcomes = Reductions in:



- Hospital and infection-related mortality
- Infection-related morbidity
- Length of hospital stay
- Days of antimicrobial therapy
- Cost of hospitalization

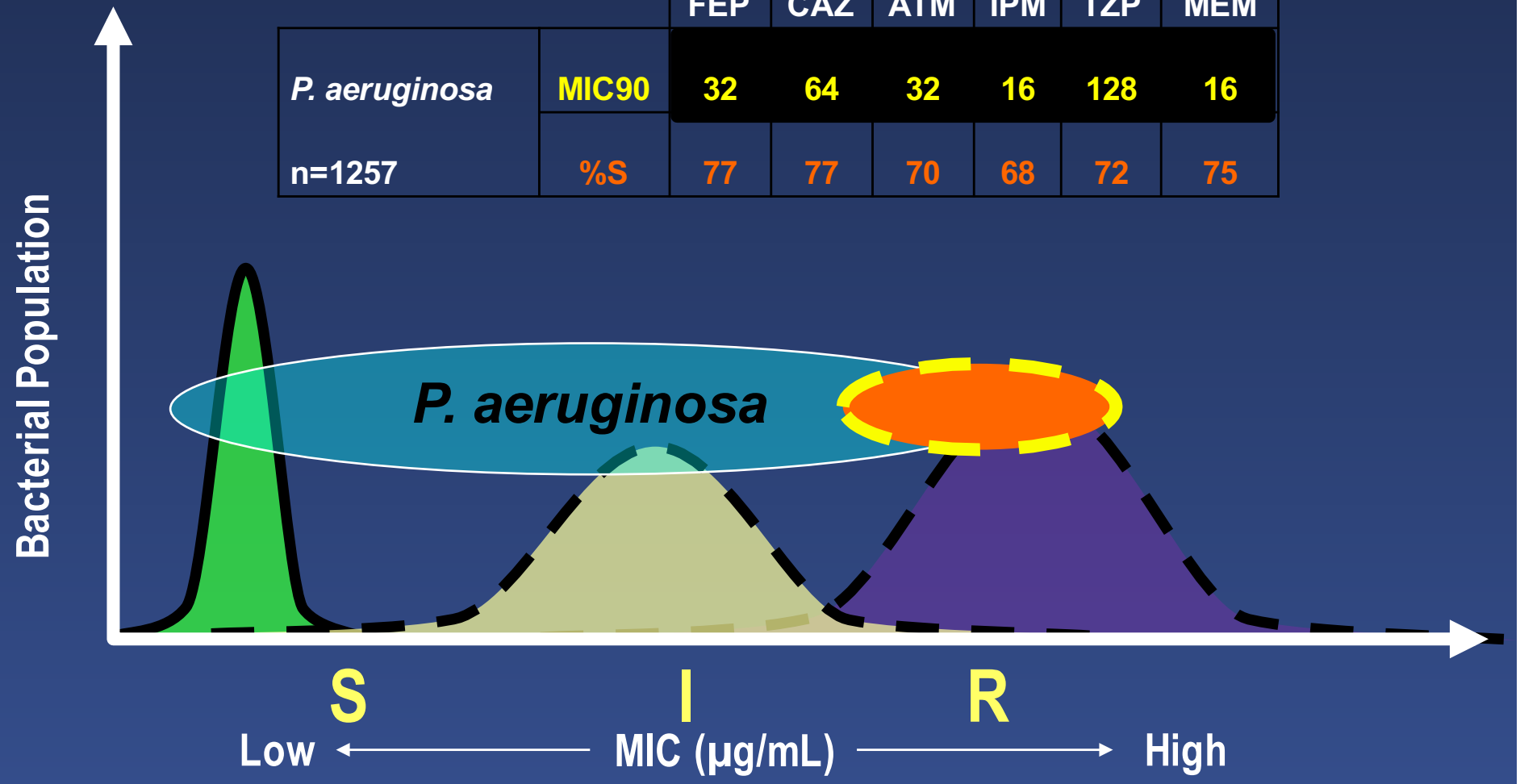
Kollef, et al. *Chest*. 1999; 115:462-474.
Engemann, et al. *Clin Infect Dis*. 2003; 36:592-598.
Lodise, et al. *Clin Infect Dis*. 2002; 34:922-929.
24:251-256.
Toubes, et al. *Clin Infect Dis*. 2003; 36:724-730.
Pelz, et al. *Intensive Care Med*. 2002. 28:692-697.
Song, et al. *Infect Control Hosp Epidemiol*. 2003;

Antimicrobial Stewardship Programs: Interventional Opportunities

- **Intervention**
  - Avoidance of discordant therapy (i.e., **inappropriate** therapy based on *in vitro* susceptibility)
    - » Prescribe → BROAD SPECTRUM EMPIRIC
    - » Interventions → Appropriate USE

Impact of Resistance Mechanism on *In Vitro* Potency → MIC Distributions

		FEP	CAZ	ATM	IPM	TZP	MEM
P. aeruginosa	MIC90	32	64	32	16	128	16
n=1257	%S	77	77	70	68	72	75



Sutherland CA, Nicolau DP. *Clinical Therapeutics* 2015;37(7):1564-1571

Implementing Antibiotic Stewardship

Microbiology and Laboratory Diagnostics

- Advocate for:
  - » **Stratified** antibiograms (i.e., location, age)
    - Increasing need to have pathogen specific MICs for pharmacodynamic optimization

Barlam TF, et al. Clin Infect Dis Advance Access Published April 13, 2016

Implementing Antibiotic Stewardship

Microbiology and Laboratory Diagnostics

- Advocate for:
  - » **Stratified** antibiograms (i.e., location, age)
  - » **Selective** or **Cascade** reporting of AST results
    - Laboratory provides susceptibility information suggestive of using the most narrow spectrum antibiotic(s) and provides information on broad spectrum agents only for more resistant pathogens

Barlam TF, et al. Clin Infect Dis Advance Access Published April 13, 2016

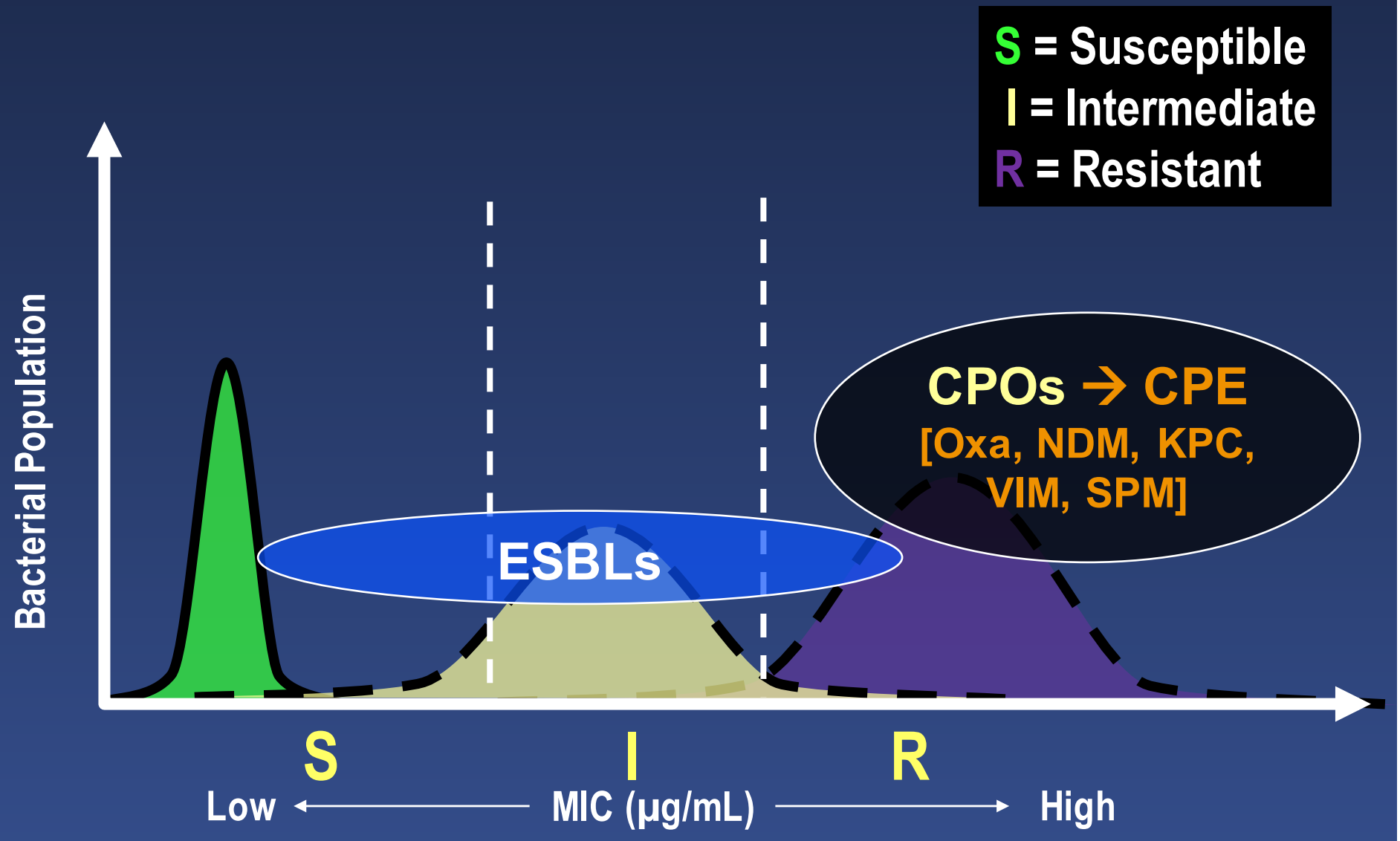
Implementing Antibiotic Stewardship

Microbiology and Laboratory Diagnostics

- Advocate for:
  - » **Stratified** antibiograms (i.e., location, age)
  - » **Selective** or **Cascade** reporting of AST results
  - » **Rapid viral testing** for **respiratory pathogens**
  - » **Rapid diagnostic testing** on **Blood** specimens
  - » **Nonculture-based fungal markers** in **hematology malignancy** patients at risk for invasive fungal disease

Barlam TF, et al. Clin Infect Dis Advance Access Published April 13, 2016

The Evolution of Enterobacteriaceae



CPOs = Carbapenemase producing organisms

Handling and Interpretation Issues with CarbaNP

CarbaNP Test, based on hydrolysis, used for detecting the presence or absence of carbapenemases

Benefits

- Accessible to most labs
- Low reagent cost
- Fast results

Potential sources for ambiguous or erroneous results

- Hands on, multi-step testing procedure
- Visually reading of color based results can be subjective
- CarbaNP cannot differentiate between various carbapenemases
- Reproducibility of results is an issue due to variable levels of carbapenemase activity, especially OXA-48 like carbapenemases.
- Results must be manually entered and communicated to clinical and infection control staff

J. Clin. Microbiol. 2010;48(4):1323-1332

Molecular Testing for Carbapenemase

Test Name/ Manufacturer	Approved Specimens	Key Advantages	Disadvantages
FilmArray® BCID Panel Biofire Dx	**Blood** Culture	**Detects the most prevalent CP in US – KPC** Comprehensive 27 target panel for most common causes of blood stream infections	**Does not detect NDM, VIM, OXA-48, IMP** Not cost effective for carbapenemase detection and routine use Limited in sample throughput
Verigene® System Nanosphere, Inc.	**Blood** Culture	Comprehensive panel **detects most common carbapenemases and CTX-M ESBL**	**Limited in sample throughput** Not cost effective for routine use
Xpert CarbaR Cepheid, Inc.	Resistant culture isolates from **blood, urine, sputum, rectal/peri-rectal swabs**	**Rapid – 48 min. to result** Comprehensive – 91 gene targets for carbapenemase producing organisms - **KPC, NDM, VIM, IMP, OXA-48**	Higher cost than culture / phenotypic methods. Specific for carbapenemases **Does not detect ESBLs**

http://jac.oxfordjournals.org/content/early/2014/03/26/jac.dku083.full.pdf

Double Carbapenem Therapy for Carbapenemase-Producing *K. pneumoniae*

Mechanism of Action

- **Ertapenem preferentially hydrolyzed by KPC carbapenemases & since only so many units of enzyme produced per unit time this effectively neutralized hydrolysis of 2nd compound → thus effective activity**
  - Bulik and Nicolau. Antimicrob Agents Chemother 2011;55(6):3002-3004

- **Characterization of Porin Expression in *Klebsiella pneumoniae* Carbapenemase (KPC)-Producing *K. pneumoniae* Identifies Isolates Most Susceptible to the Combination of Colistin and Carbapenems**
  - Hong et al. Antimicrob. Agents Chemother. 2013, 57(5):2147-2153

Double-Carbapenem Regimen for Carbapenemase-producing Pandrug-resistant *Klebsiella pneumoniae Infections: Is it really effective in humans?*

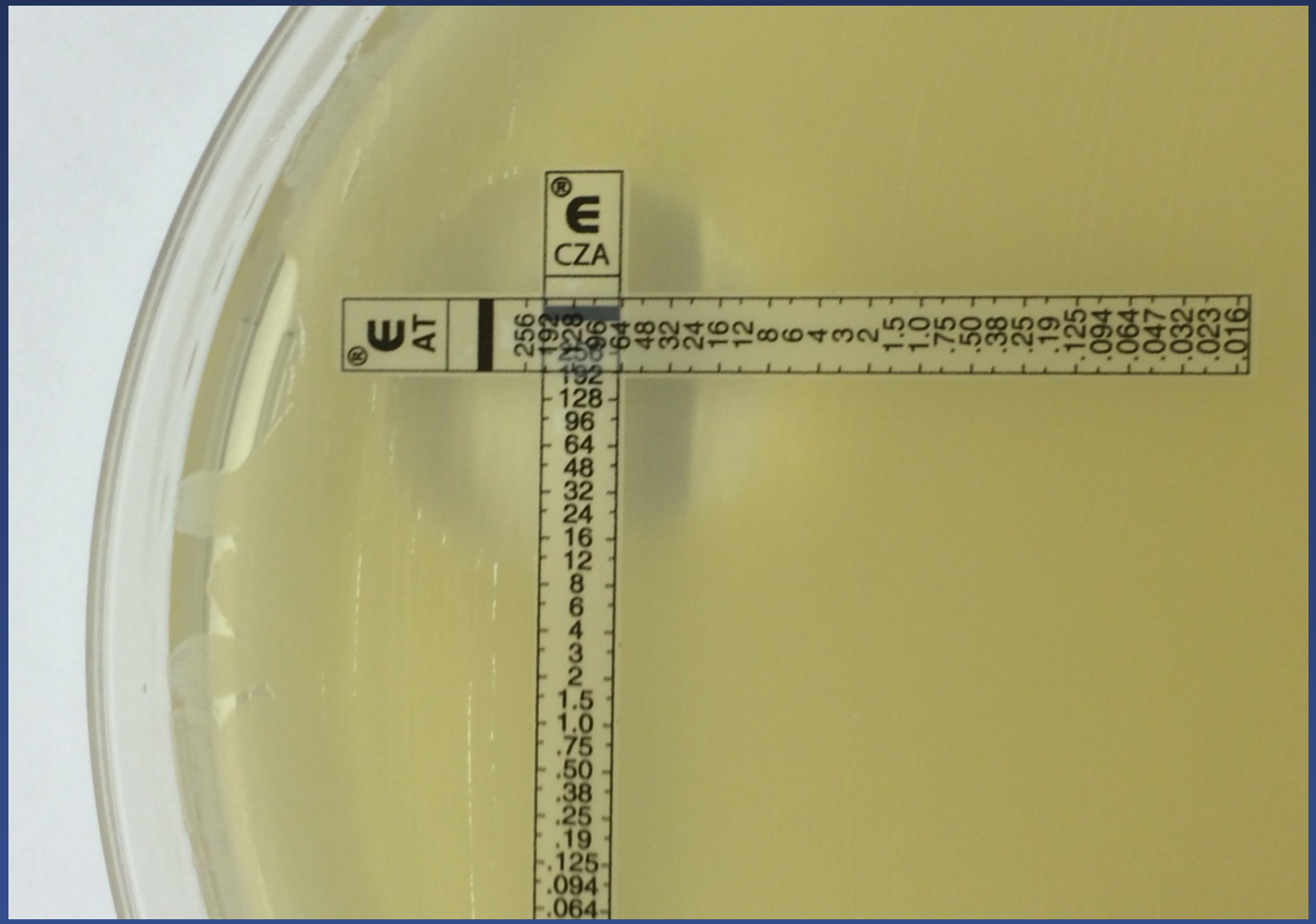
- Three patients suffering from PDR 16 KPC-2 positive *Klebsiella pneumoniae bacteremia (2) and UTI (1).*
- Failed conventional therapy including colistin
- Ertapenem plus doripenem or meropenem administered for 10-20 days
- *All patients responded with out relapse*

Giamarellou H , et al. AAC 2013;57(5):2388-2390

XDR *K. pneumoniae*

NDM, Oxa-48, CTX-M

CAZ/AVI >128; ATM >64, MER >64; CST > 16, Tig 1



Changing the Paradigm of How We Steward: Syndrome-Based Stewardship

"Disease State Management"

- Don't focus on components of care (i.e, medicines or a test) and lose sight on the process of care → Quality
  - » Process measure: DDD or days of therapy
  - » Outcome measure: length of stay, overall cost of care
- Can broaden impact of interventions to appropriate diagnostics, imaging, time to therapy, etc.
- Easier to provide education and gather meaningful evidence for a specific infectious indication
- Focused message facilitates provider learning
  - – Intervention seen as educational compared with broader stewardship methods
  - – Learning = sustainable change

DDD, defined daily dose

Barlam TF, et al. Clin Infect Dis Advance Access Published April 13, 2016

Hartford Hospital: VAP Pathway
Diagnostic and Treatment Algorithm

- **Syndrome Based Approach**
  - Derived from 1 yr prospective observational period with microbiology, ABX use & patient outcomes
  - Program implementation included pathway process:
    - » Diagnosis
    - » Initial antimicrobial therapy
      - Appropriate agent → "susceptible"
      - Adequate agents → "optimal exposures"
    - » Early assessment – Clinical & BAL culture
      - Stop Therapy
      - Continue → Same Regimen, Escalate or De-Escalate
    - » Duration of therapy

Nicasio AM, et al. *J Crit Care* 2010;25:69-77; Kuti & Nicolau *J Crit Care* 2010;25:152-153

Antimicrobial Stewardship: BEST PRACTICE

- **Intervention:**
  - **Antibiotic Modification**
  - **Clinical Stability - Discontinue antibiotic therapy if no evidence of infection (bronchoalveolar lavage samples negative)**
    - Raman K, Nailor MD, Nicolau DP, et al. Early Antibiotic Discontinuation in Patients with Clinically Suspected Ventilator Associated Pneumonia and Negative Quantitative Bronchoscopy Cultures. *Crit Care Med* 2013;41(7):1656-1663

Antimicrobial Stewardship: BEST PRACTICE

- **Intervention:**
  - **Clinical Success → De-escalation**
    - » Optimizing choice of agent, dose and dosing interval based on the "S" of the organism
    - » Timely intervention → 48-96 hrs from start of Tx
  - Added Importance of:
    - » Obtaining culture
    - » Rapid susceptibility testing - phenotypic profiling
    - » Rapid molecular diagnostics - genotypic profiling
    - » INTERPRET / COMMUNICATE these data to the clinician

Antimicrobial Stewardship: BEST PRACTICE

- **Intervention:**
  - Antibiotic Modification
  - **Clinical Failure** - Re-evaluate
    - » Resistant pathogen
    - » Source control
    - » Non-infectious process
    - » Insufficient antibiotic exposure

Antimicrobial Stewardship Programs: Interventional Opportunities

- **Intervention**
  - Avoidance of discordant therapy (i.e., inadequate therapy low exposures due to insufficient dose and / or regimen)
    - » Increased body weight
    - » Augmented renal function
    - » Therapeutic interventions (i.e., CRRT, cardiac bypass pump)
    - » High MIC organisms
    - » Poor penetration to site of infection

Appropriate Antimicrobial Therapy
An Increasing Challenge

- Impact of previous ABX therapy on outcomes of Gram-negative sepsis
  - ABX therapy in previous 90 days, patients = 310
  - Organisms
    - *E. coli* 31%
    - *Klebsiella pneumoniae* 23%
    - *Pseudomonas aeruginosa* 18%
  - ABX use: Cefepime > Cipro > imipenem
  - Patients with prior ABX higher RESISTANCE to cefepime, Pip/tazo, carbapenems, Cipro & gentamicin
  - Patients with prior ABX higher INAPPROPRIATE THERAPY and MORTALITY compared with patients without ABX exposure

Johnson MT, et al. Crit Care Med 2011;39(8):1859-1865

Appropriate Antimicrobial Therapy
An Increasing Challenge

- **Impact of ESBLs on Clinical and Economic Outcomes in Patients with Urinary Tract Infection**
  - **55 ESBL (cases) & matched controls (non-ESBL UTI)**
    - » Failure of initial antibiotic regimen (62% vs. 6%; *P*<0.001) & time to appropriate therapy (51 vs. 2.5 hours; *P*<0.001) were greater in ESBLs
    - » Median cost of care was greater (additional $3,658; *P*=0.02) and median length of stay (LOS) was prolonged for ESBLs (6 vs. 4 days; *P*=0.02)
    - » **Antimicrobials comprised less than 1% of cost of care**
  - **Cost of care & LOS with ESBLs were 1.5 times those caused by non-ESBL UTIs; this resulted in net hospital loss of $3,200 per ESBL UTI**

MacVane SH, Tuttle LO, Nicolau DP. *Journal of Hospital Medicine* 2014:9(4);232-238

Antimicrobial Stewardship: Does the Name Fit Task

- Focus on "BEST PRACTICE" processes → optimal delivery of care

- Best Practice in…… Management of UTIs
  - Initial assessment - Colonization v. Infection
  - Need for culture → rapid diagnostics
  - Need for ABX therapy
  - Etiology of disease → Urology consult

Antimicrobial Stewardship Programs: Interventional Opportunities

- Intervention
  - Avoidance of unnecessary therapy
    - Excessive duration of therapy
      - "Concept of treat to response"
    - Role of Biomarkers
      - C-reactive protein (CRP)
      - Procalcitonin

Adverse Ecological Effects

- *"Collateral Damage"*
  - a term used to refer to ecological adverse effects of antibiotic therapy:
    - » Selection of resistance in TARGET organism
    - » Unwanted development of colonization or infection with NEW [RESISTANT] organism

- Antibiotic classes commonly linked to collateral damage: Cephalosporins, Fluoroquinolones → Carbapenems

Paterson DL. *Clin Infect Dis*. 2004;38(suppl 4):S341-S345.

Strategies to Optimize Clinical & Microbiologic Outcomes

- **Best Practice …..**
  - Appropriate Use of Cultures
  - Appropriate Initial Therapy
    - » Right DRUG(s)
      - Rapid diagnostics → ID; pheno / geno profile
    - » Optimize Exposures (PD profile)
  - De-escalation → Narrow Spectrum
  - Reduce Duration of Therapy (Biomarkers)
  - Economic considerations:
    - » Cost of ABX & Lab tests v. Cost of Care