Antimicrobial Overview

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Outline

1. Address the Role of Antimicrobial Stewardship (ASP)
2. Briefly review the interpretation of culture and sensitivity report
3. Evaluate indication, dosing and monitoring of common antibiotic classes used in the hospital setting
4. Discuss disease states where short courses of antibiotics may be given

Klebsiella pneumoniae				
	MDIL	MINT	EDIL	EINT
Ampicillin	>=32	R		
Amoxicillin/Clavulanate	>32	R		
Piperacillin/Tazobactam	>=128	R		
Cefazolin	>=64	R		
Ceftriaxone	>=64	R		
Cefepime	>=64	R		
Ertapenem	>4	R		
Meropenem	8	R		
Amikacin	16	S		
Gentamicin	>=16	R		
Tobramycin	>=16	R		
Ciprofloxacin	>=4	R		
Levofloxacin	>=8	R		
Trimethoprim/Sulfa	>=320	R		

Definitions

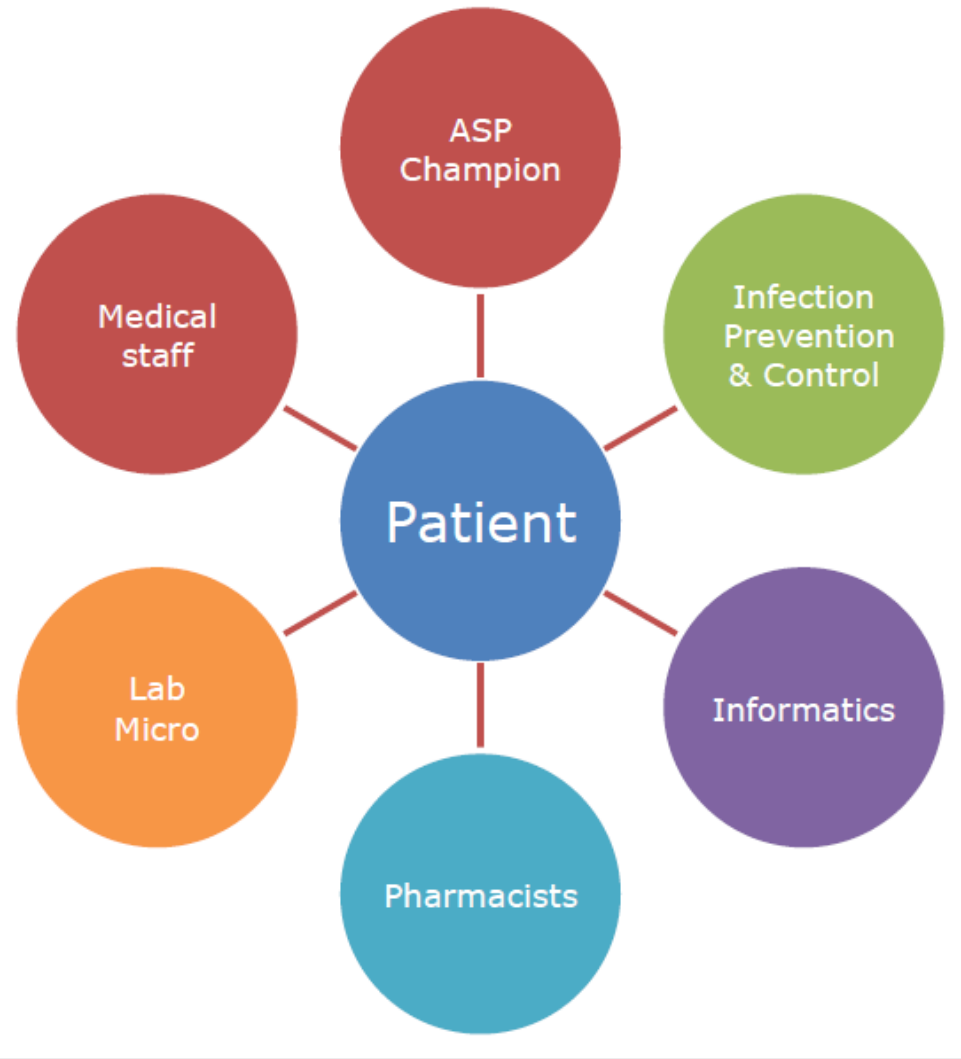
- **Stewardship**: the conducting, supervising, or managing of something; *especially*: the careful and responsible management of something entrusted to one's care

- **Antimicrobial Stewardship**: coordinated interventions designed to improve and measure the appropriate selection, dosing, route and duration of antimicrobial therapy while optimizing clinical outcomes, while minimizing unintended consequences of antimicrobial use

The Role of Antimicrobial Stewardship Programs (ASPs)

- Growing body of evidence demonstrates that ASPs dedicated to improving antibiotic use
  - Improve the quality of patient care and patient safety
    - Increase infection cure rates
    - Reduce treatment failures
    - Reduce adverse events associated with antimicrobial therapy
  - Decrease antibiotic resistance
    - Significantly reduce hospital rates of (*Clostridium difficile* infections) (CDI)
  - Provide hospitals with opportunity for cost savings
- 2014 CDC recommended that all acute care hospitals implement ASPs
- 2017 CMS standards established
- ASPs can be implemented effectively in a wide variety of hospitals
  - SUCCESS is dependent on defined leadership and a coordinated multidisciplinary approach

ASP is a Multidisciplinary Approach



Dellit TD, et al. Clin Infect Dis 2007;44:159-77
Drew RH, et al. Pharmacotherapy 2009;29:593-607

Banner Health

Banner Health Pharmacy and Therapeutics Clinical Consensus Group
Restricted Antimicrobials
Last Updated April 2020

Medication	Restriction Criteria

Amikacin	▪ Short-term empiric therapy
	  ○ Severe, life-threatening infections when Nocardia species, Mycobacterium, or gram-negative organism with suspected MDRO or patient with history of MDRO
	▪ Treatment:
	  ○ Severe, life-threatening infections for Nocardia or Mycobacterium species
	  ○ Gram negative MDRO organisms not susceptible to other aminoglycosides (i.e. gentamicin/tobramycin)

Aztreonam	▪ Treatment of GNR infection in cases with severe PCN allergy (Anaphylaxis, which may manifest as hypotension, shock, swelling of tongue or throat, difficulty breathing, Steven Johnson Syndrome (SJS), Drug Reactions with Eosinophilia and Systemic Symptoms (DRESS), or Toxic Epidermal Necrolysis (TEN) reactions with previous PCN use) ▪ If allergy to ceftazidime or cefiderocol avoid aztreonam use

Ceftaroline (Teflaro)	▪ MRSA (ceftaroline-susceptible):
	  ○ Severe infection* AND vancomycin failure** or allergy/intolerance***
	  ○ Can be used for synergistic combination therapy with daptomycin for refractory MRSA bacteremia****
	▪ *Streptococcus pneumoniae* (ceftaroline-susceptible): severe infection* AND ceftriaxone resistance, intolerance or contraindications AND vancomycin failure** or allergy/intolerance***
	▪ *Enterococcus* spp.: severe infection* for synergistic combination therapy (documented ceftaroline susceptibility not required)
	If patient does not meet above criteria, consider alternative therapy options such

Restricted Antimicrobial Agents

Formulary

- Amikacin
- Aztreonam
- Ceftaroline
- Colistin
- Daptomycin*
- Ertapenem
- Fidaxomicin
- Fosfomycin
- Isavuconazole
- Linezolid
- Meropenem
- Micafungin
- Moxifloxacin
- Polymyxin B
- Posaconazole
- Tigecycline*
- Voriconazole

Non-Formulary*

- Ceftazidime/avibactam
- Ceftolozane/tazobactam
- Eravacycline
- Imipenem-Cilastin
- Imipenem-cilastin-relebactam
- Meropenem/vaborbactam

*Patient may receive first dose to avoid delays in care, for future doses ID consult is expected

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Microbiology: Understanding the Pitfalls of a Culture and Sensitivity Report

What do the categorical values and which antibiotic(s) would you use to treat this infection?

Trach Aspirate: *Pseudomonas aeruginosa*

	Sensitive
Ceftriaxone	R
Cefepime	S
Ciprofloxacin	I
Meropenem	S
Gentamicin	S
Tobramycin	S
Aztreonam	S
Piperacillin/tazobactam	S

“Susceptibility testing is an in vitro phenomenon and does not necessarily reflect or predict in vivo efficacy. Susceptibility testing is subject to great variability depending on pathogen tested, media used, conditions of incubation, and method of accessing bacterial growth”

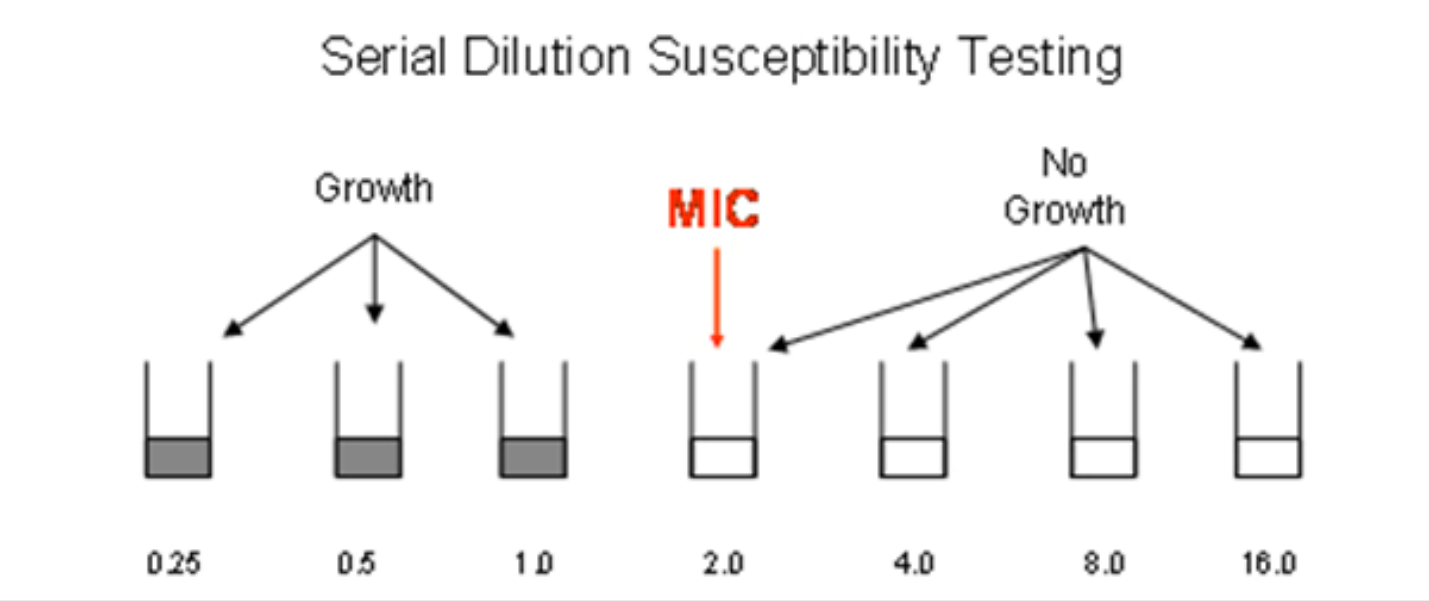
Take Home Message: Do not just look for the “S”

Burke A Cunha

Medical Clinics of North America; Vol 84. No 6: Nov 2000. Pp 14071429

MIC definition

- Minimum Inhibitory Concentration
- The **lowest** antimicrobial concentration that prevented **visible** growth of an organism after 24 hours of incubation



What do the numbers mean and which antibiotic(s) would you use to treat this infection?

Trach Aspirate: *Pseudomonas aeruginosa*

	Sensitive	MIC/ml
Ceftriaxone	R	>32
Cefepime	S	4
Ciprofloxacin	I	≤1
Meropenem	S	≤1
Gentamicin	S	2
Tobramycin	S	≤1
Aztreonam	S	8
Piperacillin/tazobactam	S	16

What do the numbers mean and which antibiotic(s) would you use to treat this infection?

Trach Aspirate: *Pseudomonas aeruginosa*

	Sensitive	MIC/ml	CLSI Breakpoint (mcg/mL)
Ceftriaxone	R	>32	8
Cefepime	S	4	8
Ciprofloxacin	I	≤1	0.5
Meropenem	S	≤1	4
Gentamicin	S	2	4
Tobramycin	S	≤1	4
Aztreonam	S	8	8
Piperacillin/tazobactam	S	16	16

Summary: Interpreting a C/S Report

1. WHAT IT TELLS YOU
    1. Identifies bacteria present: Does not identify infection vs colonization vs contamination
    2. Sensitivity results based on IN VITRO data (pH, amount of protein, inoculum, oxygenation)
2. WHAT IT DOES NOT TELL YOU
    1. Which antibiotic should be used to treat an infection
    2. That needs your interpretation of the C/S report

Case

1. AT is a 49-year-old female (No hx of MDROs) with uncontrolled diabetes is hospitalized with significant flank pain, chills, and a temperature of 101.3°F (38.5°C). She is very uncomfortable because of flank pain, and her vital signs are blood pressure 140/95 mm Hg, heart rate 105 beats/minute, and respiratory rate 23 breaths/minute. Her laboratory test results are remarkable only for a WBC of 11.3 x 10^3 cells/mm^3. She has no history of renal insufficiency. Which one of the following is best to recommend for this patient?

A. Ampicillin/sulbactam 3 g intravenously every 6 hours
B. Ceftriaxone 1 g intravenously every 24 hours
C. Aztreonam 1 g intravenously every 8 hours
D. Levofloxacin 750 mg intravenously every 24 hours

Sepsis Adult IP [pp], Sepsis Urosepsis Antimicrobials [sub-p] (Initiated Pending)				
Medications				
		Severe PCN reaction defined as: anaphylaxis (hypotension, shock, swelling of throat/tongue, difficulty breathing), Steven-Johnson Syndrome (SJS), Drug Reactions with Eosinophilia and Systemic Symptoms (DRESS), Toxic Epidermal Necrolysis (TEN) with prior PCN use		
		When administered concomitantly, vancomycin and piperacillin may have additive nephrotoxic effects. Clinical and laboratory monitoring of renal function is recommended.		
No MDR risk factors				
☐		cefTRIAXone	1 Gm, IV Piggyback, Soln-I...	
		For penicillin anaphylactic reaction		
☐		tobramycin	5 mg/kg, IV Piggyback, Sol...	Pharmacy t...
		May consider use in patients that aminoglycosides are contraindicated.		
☐		ciprofloxacin	400 mg, IV Piggyback, Soln...	
MDRO Risk				
		Choose one of the three options below		
☐		cefepime	2 Gm, IV Piggyback, Soln-I...	
		Zosyn for CrCL above 20 ml/min or CRRT/SLED		
☐		piperacillin-tazobactam (piperacillin-tazobactam (Zos...	4.5 Gm, IV Piggyback, Soln...	4.5 gm bolu...
☐		piperacillin-tazobactam (piperacillin-tazobactam (Zos...	3.375 Gm, IV Piggyback, So...	Maintenanc...
		Zosyn for CrCL below 20 ml/min or Peritoneal/Hemodialysis		
☐		piperacillin-tazobactam (piperacillin-tazobactam (Zos...	2.25 Gm, IV Piggyback, Sol...	2.25 gm bol...
☐		piperacillin-tazobactam (piperacillin-tazobactam (Zos...	3.375 Gm, IV Piggyback, So...	Maintenanc...
		For penicillin anaphylactic reaction		
☐		aztreonam	2 Gm, IV Piggyback, Soln-I...	
☐		tobramycin	5 mg/kg, IV Piggyback, Sol...	Pharmacy t...

Hospital Antibiogram

Case

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Antimicrobial Class Review

Beta Lactam Antibiotics

- Includes your penicillins (PCN) and extended PCN, cephalosporins, and carbapenems
  - PCN VK/G
  - Nafcillin/oxacillin
  - Ampicillin or Unasyn(ampicillin/sulbactam)
  - Piperacillin or Zosyn(piperacillin/tazobactam)
  - Cephalosporins: cefazolin, cefotetan, cefuroxime, cefotaxime/ceftriaxone, ceftazidime, cefepime, ceftaroline
  - Carbapenems: Imipenem/cilastain, Meropenem, Ertapenem, Doripenem
- Narrow-broad spectrum coverage
- Time dependent killers, so we care how frequently/closely together we administer these agents
- MOA: work by inhibiting cell wall biosynthesis in the bacterial organism
  - Bactericidal
  - Alter the main site of action Penicillin binding proteins (PBPs)
- MOR: Bacteria often develop resistance to β-lactam antibiotics by synthesizing a beta lactamase or a penicillanase, an enzyme that attacks the β-lactam ring

Beta lactam antibiotics: PCN-G, Nafcillin, Ampicillin/Sulbactam

- Narrow spectrum
- Pen G hits all Strep species
- Nafcillin preferred Staph (MSSA) as the agents are “cidal”
  - Yes-better than vanco for MSSA!!!
- Unasyn has extended coverage for gram negatives and (most)anaerobes
  - b/c of the sulbactam it is good for beta lactamase producing g-
  - Covers *Bacteroides fragilis (~80%)*
- Metabolized and cleared by the kidneys
- Generally well tolerated
- AE (Nafcillin): maculopapular rash/hypersensitivity rxn, neutropenia, interstitial nephritis, transaminitis/hyperbilirubinemia

Zosyn®-piperacillin/tazobactam

- **Work horse, #2 most used abx at BUMCP**
- Should be consider first line for nosocomial infections
- BUMCP uses hospital wide extended infusion protocol (administered as 4.5g x1, then 3.375g q8h over 4 hours)
- Broad spectrum coverage:
  - excellent *Strep/Enterococcus*
  - good *Staph*(MSSA)
  - Good gram negative-including *Pseudomonas (82% per BUMCP antibiogram)*
  - Anaerobic-including Bacteroides (~96%)

- FDA Approved for both CAP,HAP, intra-abdominal infections, SSTI-including diabetic foot infections
- ADE: phlebitis at infusion site, drug fever, leukopenia/thrombocytopenia, interstitial nephritis, rare cases of hepatitis

Cephalosporins-general principals to apply

- 1st Generation vs. 2nd generation vs. 3rd generation vs 4th Generation vs. 5th Generation
- Early generations are best for Strep and Staph (MSSA), No Enterococcus
- Later generations (3-5th) have improved gram negative coverage, some with added Pseudomonas coverage
- Most cephalosporins are considered safe during pregnancy (category B)
- Most are primary metabolized and eliminated via kidneys
  - Except ceftriaxone
- Consequences:
  - Highly associated with emergence of resistance primarily in g(-)
  - Selects for VRE
  - Associated with *C. difficile*
- Cross reactivity w/ PCN is low with higher generation cephs as they are structurally different enough from PCN
  - True IgE mediated avoid cephalexin, cefadroxil and cefazolin
  - Safe to administer cefopodoxime, cefdinir, ceftriaxone, ceftazidime and cefepime

Case

E.M. is a 45-year-old man who is started on empiric vancomycin for osteomyelitis of the radius after a traumatic injury. Five days later, E.E.'s culture grows MSSA. He has no history of renal insufficiency.

Wound Culture - Accession: 000012020201003746
Result Status - Auth (Verified)

Micro Reports | **Susceptibilities** | Specimen | Comments | Action List

	A	B	C
1	Staphylococcus aureus		
2		MDIL	MINT
3	Ox/Nafcillin	<=0.25	S
4	Erythromycin	>=8	R
5	Clindamycin	>=4	R
6	Trimethoprim/Sulfa	<=10	S

Which one of the following is best to recommend for E.M.?

A. Continue vancomycin 15mg/kg intravenously q12h for duration of therapy.
B. Add rifampin 300mg BID to vancomycin intravenously 15mg/kg q12h for duration of therapy.
C. De-escalate to cefazolin 2g intravenously every 8 hours for duration of therapy.
D. De-escalate to nafcillin 2g intravenously every 4h for duration of therapy.

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Which one of the following is best to recommend for E.M.?

A. Continue vancomycin 15mg/kg intravenously q12h for duration of therapy.
B. Add rifampin 300mg BID to vancomycin intravenously 15mg/kg q12h for duration of therapy.
C. Change to cefazolin 2g intravenously every 8 hours for duration of therapy.
D. Change to nafcillin 2g intravenously every 4h for duration of therapy.

First Generation Cephalosprin: Cefazolin

- Excellent gram positive coverage
  - Consider first line, along with Nafcillin/Oxacillin for *Strep* and *Staph*(MSSA)
- Preferred cephalosporin for *S. aureus*(MSSA)
- Some gram negative coverage for susceptible Ecoli
- 3 main FDA indication-prostatitis or epididymitis & surgical prophylaxis
- Can dose escalate by weight
  - 80 kg use 1 gm
  - >80 kg use 2 gm
- AE: generally very well tolerated with rare reports of eosinophilia, CNS-confusion, disorientation, hallucinations

2nd Generation-cefotetan, cefoxitin & cefuroxime

- Moderate gram negative and gram positive coverage including Strep and Staph (MSSA)
  - Covers anaerobes but should be confirmed by susceptibility testing first
    - Cefuroxime better for head/neck anaerobes
    - Cefotetan has increasing resistance in the Bacteroides group
- Cefuroxime is only in this generation available IV/PO
- Mostly indicated for UTIs, Lower RTI, SSTI, Gyn infections
- Used for surgical prophylaxis in abdominal/colorectal surgeries
- Can dose escalate in obesity
  - 80kg use 1 gm
  - >80 kg use 2 gm (1.5 gm cefuroxime)

3rd generation: Ceftriaxone & ~~Cefotaxime~~

- Brother/sister drugs
- Identical spectrums of activity include:
- Excellent Strep, coverage
  - Will need to keep a close eye on resistant (reported at 3-5%)
- Good Staph (MSSA) coverage
- Good g(-) coverage (no pseudomonas)
- Maintain particularly good coverage for Ecoli (98%)
  - WARNING-MORE with Enterobacteriaceae (SPICE organisms), inducible resistance
  - AmpC-lactamases are active-site serine enzymes that are primarily cephalosporinases
- Niches:
- Identical spectrums, can use interchangeably
  - Ceftriaxone Q12 vs. 24hr
  - First line agents for CNS infections-high dose 2 gm IV q12H
- AE: relatively safe drug profile, interstitial nephritis
  - Ceftriaxone can cause biliary sludge-dose dependent AE

3rd Gen Ceftazidime & 4th Gen Cefepime

- Ceftazidime primarily gram negative, including Pseudomonas (80%)
    - Does not have good *Strep pneumoniae* sensitivity
    - Lacks adequate Staph coverage
    - Good CNS penetration, but not preferred first line
- Cefepime
    - Addition of good Strep (including *Strep pneumoniae*) Staph (MSSA) coverage
    - Gram positive coverage is comparable to ceftriaxone/cefotaxime
    - Does not get hydrolozed by AmpC-lactamase produced by SPICE organisms
    - Can dose escalate both for CNS dosing-2gm
        - Dosing for Pseudomonas is always 2g q8h!
    - Renally eliminated
    - ADE: SZ if not renally adjusted

Case

1. A 54-year-old man with a history of worsening hepatic insufficiency and significant ascites is admitted for suspected intra-abdominal infection. His ascitic fluid is sent for analysis and returns suggestive of spontaneous bacterial peritonitis. He is initiated on empiric Zosyn therapy while cultures are pending. On day 2 ascitic fluid cultures reveal E. coli.

Micro Reports | **Susceptibilities** | Specimen | Comments | Action List

	A	B	C
1	Escherichia coli		
2		MDIL	MINT
3	Ampicillin	>=32	R
4	Amoxicillin/Clavulanate	>32	R
5	Piperacillin/Tazobactam	8	S
6	Cefazolin	8	R
7	Ceftriaxone	<=1	S
8	Cefepime	<=1	S
9	Gentamicin	<=1	S
10	Tobramycin	<=1	S
11	Ciprofloxacin	<=0.25	S
12	Trimethoprim/Sulfa	<=20	S

Which one of the following is best to recommend for this patient?

A. Ertapenem 1 g 24h intravenously QD

B. Ampicillin/sulbactam 3g q6h intravenously

C. Ciprofloxacin 500mg PO BID

D. Ceftriaxone 1g intravenously QD

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PHARMACOTHERAPY accp

Duration of Exposure to Antipseudomonal β-Lactam Antibiotics in the Critically Ill and Development of New Resistance

Besu F. Teshome,[1,2] Scott Martin Vouri,[3,4] Nicholas Hampton,[5] Marin H. Kollef,[6] and Scott T. Micek[1,7,*]

[1]Department of Pharmacy Practice, St. Louis College of Pharmacy, St. Louis, Missouri; [2]John Cochran Division, VA St. Louis Health Care System, St. Louis, Missouri; [3]Department of Pharmaceutical Outcomes and Policy, University of Florida College of Pharmacy, Gainesville, Florida; [4]University of Florida Health Physicians, Gainesville, Florida; [5]Center for Clinical Excellence, BJC Healthcare, St. Louis, Missouri; [6]Division of Pulmonary and Critical Care Medicine, Washington University School of Medicine, St. Louis, Missouri; [7]Center for Health Outcomes Research and Education, St. Louis College of Pharmacy, St. Louis, Missouri

Study Objective Minimizing the duration of broad-spectrum antimicrobial exposure in the critically ill is a commonly used strategy aimed at preventing resistance. Our objective was to correlate the duration of exposure to antipseudomonal β-lactam antibiotics with the development of new resistance in critically ill patients.

Design Single-center, retrospective cohort study.

Setting A large, academic, tertiary care hospital.

Patients A total of 7118 adults with a discharge diagnosis of severe sepsis or septic shock who received at least one dose of cefepime, meropenem, or piperacillin-tazobactam during their hospitalization between 2010 and 2015.

Measurements and Main Results Cohort entry was defined as the first day of any antipseudomonal β-lactam initiation, and exposure was defined as the cumulative days of any antipseudomonal β-lactam exposure during the 60-day follow-up period. The primary outcome was development of new resistance to any antipseudomonal β-lactam > 3 days after cohort entry. New resistance was defined as detection of resistance to any antipseudomonal β-lactam not identified within 180 days before cohort entry. Patients without an outcome (i.e., did not develop new resistance) or who died by day 60 were censored. Cox proportional hazards models were performed to assess the risk of development of new resistance to any antipseudomonal β-lactam with each additional day of exposure. Analyses of each individual antipseudomonal β-lactam were evaluated as secondary outcomes. Each

Results:

4% increased risk of new resistance for each additional day of anti-pseudomonal β-lactam exposure:

- Cefepime 8%
- Zosyn 8%
- Meropenem 2%

5th Gen- Ceftaroline

- Broad spectrum
  - Gram positive coverage includes MRSA, VISA, vanco-resistant *S. aureus,* methicillin-resistant *S. epidermidis,* penicillin-resistant *S. pneumoniae,* and VRE (not *E.faecium).*
  - Gram negative coverage, (comparable to 3rd generation cephalosporins) but does not include ESBL producing or AmpC-derepressed Enterobacteriaceae or most non-fermenting gram negative bacilli.
- Indications for CAP and complicated skin and skin-structure infections
- Dose adjustments necessary for renal dysfunction
- Place in therapy unclear
  - Possible alternative for patients intolerant or unresponsive to other regimens.
  - Could provide broad spectrum monotherapy instead of other complex regimens.
  - Synergy exists with daptomycin – combination often used after vancomycin failure in pSAB
- Dosing is 600mg q8-12h
- ADE- neutropenia develops with q8h dosing with long term use

Carbapenems

- IMIPENEM/CILASTATIN
- MEROPENEM
- ~~DORIPENEM~~
- ERTAPENEM

Carbapenems--general principals to apply

- AKA “Gorillacillins”
  - These should be reserved for MDROs
- Broadest spectrum of the Beta lactam class
  - Gram positive includes: Strep/Enterococcus*, Staph (MSSA), no MRSA, g+ anaerobes
  - Gram negative coverage includes: all Enterobacteriaceae, Pseudomonas, Acinetobacter, and Extended Spetrum Beta Lactamase(EBSL) g-bacteria (Ecoli, Klebsiella)
  - Excellent anaerobic coverage both g (+) and g (-)
- First line, DOC (drug of choice) for ESBL
- MOR: carbapenemase enzymes exist (KPC, OXA-48, NDM)
  - Famously stable to AmpC β-lactamases and extended-spectrum-β-lactamases
- Low cross reactivity in PCN allergic patients (reported <2%)
- AE: seizures (elderly, h/o seizures (0.2% vs 33%), higher doses and not renally adjusted, bone marrow suppression, infusion related hypotension
- Major DDI (drug-drug interactions): CYP p450 (Valproic Acid-decreased levels, increasing risk for seizures; select alternative abx or anti-SZ agent)

Meropenem & Imipenem/Cilastin

- Meropenem is our formulary carbapenem of choice
- We do alternative dosing strategy of 500 mg IV Q6H
- FDA approved for meningitis, 2 gm IV Q8hr
- For MDRO's or patients with obesity dose escalate to 1g q6h

- Imipenem/cilastin (Non-formulary)
- Approved by BUMCP pharmacy for Nocardia, Acinetobacter, and Mycobacterium species.
- Degraded by dehydropeptidase so must be administered with cilastatin
- Slightly better positive activity of carbapenems (primarily Enterococcus)

Ertapenem

- Spectrum of coverage very similar to Mero/imipenem:
  - exception of Pseudomonas and Enterococcus(30-50% resistance reported)
- Still covers ESBL gram-
- Excellent anaerobic coverage
- Should be considered over meropenem when Pseudomonas coverage is not needed
- FDA approved for CAP and complicated DM foot infections
- Q24hr dosing (easy dosing but reserve for ESBLs)
- May need higher doses in obesity, studies have not recommended dose.
  - Recommend picking alternative carbapenem

Fluoroquinolones – general principles

- Drug of choice for CAP & complicated UTIs
- Spectrum of coverage:
  - Moderate Gram negative: due to local resistance poor empiric agent to start with
  - Good Strep coverage, Levofloxacin and Moxifloxacin are preferred for Strep but are not be best choice for *S. aureus* (MSSA and MRSA). Cipro lacks GPC coverage
  - Anaerobes: Moxifloxacin provides coverage. No anaerobic coverage for Cipro or levo (add metronidazole).
  - Atypicals: Good coverage
- Drug interactions:
  - Divalent or trivalent cations(antacids, sucralfate, minerals) interfere with absorption
  - Avoid oral administration w/ Tube Feeds (use IV formulation)
  - Avoid other QTc prolonging drugs (amiodarone, procainamide, propafenone, flecainide, etc), or in pts with hypokalemia/hypomagnesia, bradycardia, or cardiomyopathy

FDA Warning on FQ Antibiotic use

- FDA states the risk of serious side effects with fluoroquinolones generally outweigh benefits for patients with:
  - Acute bacterial sinusitis
  - Acute exacerbation of chronic bronchitis
  - Uncomplicated UTI

Fluoroquinolone Boxed Warning	
July 2008	• increased risk of tendinitis and tendon rupture
February 2011	• increased risk of exacerbating muscle weakness related to Myasthenia gravis
August 2013	• increased potential risk for irreversible peripheral neuropathy
July 2016	• increased CNS effects ((i.e. anxiety, depression, hallucinations, suicidal thoughts, confusion)
July 2018 (new labeling change)	• new mental health side effects updated to include disturbances in attention, disorientation, agitation, nervousness, memory impairment and delirium • serious blood sugar disturbances, particularly risk of coma with hypoglycemia
January 2019	• Increased risk for ruptures or tears in the aorta

Case

1. BT is a 54-year-old woman with a history of worsening renal insufficiency, aortic dissection, A-fib (on amiodarone/warfarin) is admitted with dysuria and flank pain. She is initiated on empiric Zosyn therapy while cultures are pending. On day 2 urine cultures reveal E. coli.

Micro Reports | **Susceptibilities** | Specimen | Comments | Action Lis

	A	B	C
1	Escherichia coli		
2		MDIL	MINT
3	Ampicillin	>=32	R
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9	Gentamicin	<=1	S
10	Tobramycin	<=1	S
11	Ciprofloxacin	<=0.25	S
12	Trimethoprim/Sulfa	<=20	S

Which one of the following is the best antibiotic de-escalation strategy for this patient?

A. Ampicillin/sulbactam 3g intravenously QD

B. Ciprofloxacin 500mg PO BID

C. Ceftriaxone 1g intravenously QD

D. Trimethoprim/Sulfa 1 DS PO twice daily and reduce warfarin dose by 50%

Case

1. BT is a 54-year-old woman with a history of worsening renal insufficiency, aortic dissection, A-fib (on amiodarone/warfarin) is admitted with dysuria and flank pain. She is initiated on empiric Zosyn therapy while cultures are pending. On day 2 urine cultures reveal E. coli.

Micro Reports | **Susceptibilities** | Specimen | Comments | Action Lis

	A	B	C
1	Escherichia coli		
2		MDIL	MINT
3	Ampicillin	>=32	R
4	Amoxicillin/Clavulanate	>32	R
5	Piperacillin/Tazobactam	8	S
6	Cefazolin	8	R
7	Ceftriaxone	<=1	S
8	Cefepime	<=1	S
9	Gentamicin	<=1	S
10	Tobramycin	<=1	S
11	Ciprofloxacin	<=0.25	S
12	Trimethoprim/Sulfa	<=20	S

Which one of the following is the best antibiotic de-escalation strategy for this patient?

A. Ampicillin/sulbactam 3g intravenously QD

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Aminoglycosides

- Gentamicin
- Tobramycin
- Amikacin

Aminoglycosides –general principles

- Pharmacy to dose Aminoglycosides at BUMCP – providers enter consult
- Use as adjunctive therapy for serious gram negative infections
  - Pseudomonas, E. coli, Enerobacter, Klebsiella, Proteus, Morganella, Providencia, and Serratia
- Gram positive:
  - Gentamicin used synergistically against some *Strep & Enterococci bugs.*
- No activity against anaerobes or atypicals
- Use Concentration dependent bactericidal activity.
  - Efficacy predicted by peak/MIC ratio
  - Dosed once daily to maximize peak levels
  - Do not use QD dosing in patients with unstable renal function, CrCl<30 ml/min, meningitis, or increased Vd (pregnancy, ascites, edema).
- Produce prolonged post antibiotic effects
  - Antibiotic is bacteriostatic for 30-60 min after the concentration decreases below the MIC
- Toxicities commonly include nephrotoxicity (reversible) and ototoxicity (irreversible)

Anti-MRSA Agents

- VANCOMYCIN
- LINEZOLID
- DAPTOMYCIN

Vancomycin

- **Work Horse: #1 used antibiotic at BUMCP**
- Spectrum of activity: Strep, Staph (including MSSA/MRSA), and some gram positive anaerobes
  - Higher rates of failure when MRSA MIC is at breakpoint of 2
- Dosed by Pharmacy Consult
  - Goals troughs 12-18 mcg/mL
- ADE:
  - Infusion related AE is Redman's syndrome, usually avoided by slowing the infusion to 120 minutes (standard is 30-60 min)
  - Redman's: flushing over chest/face/trunk, +/-hypotension & pruritis
    - +/-Benadryl pre-med
  - When used alone nephrotoxicity is associated with >4g daily dose & >7 day duration of therapy
    - Can be nephrotoxic in combo with other drugs such as high dose Zosyn, aminoglycosides, diuretics etc

Linezolid

- Spectrum of activity
  - Primarily gram positive bacteria including MRSA and VRE
  - Active against penicillin resistance Strep pneumoniae
  - Can be used in some of the drug resistant mycobacteria(non-TB) infections
- Don’t use to treat complicated Staph bacteremia; FDA approved for VRE bacteremia
- MOA: Inhibits protein synthesis at the 50s ribosome
  - Bacteriostatic(most bacteria including Staph)
  - Bacteriocidal(Streptococci/enterococci)
- IV and PO available-100% bioavailable
- ADE:
  - Major DDI w/ SSRI can cause serotonin syndrome
  - AE: severe thrombocytopenia (14d), usually reversible at discontinuation, optic neuritis and peripheral neuropathy

Daptomycin

- Similar spectrum of activity to linezolid and needs to be reserved for documented resistant infections
  - MRSA, VRE or VISA/VRSA
- Daptomycin 10 mg/kg needed for VRE with MIC of 4
- Primary indications: complicated SSSI and non-resolving bacteremia
  - Daptomycin is FDA approved for R sided endocarditis
- Requires baseline CK level and weekly monitoring
- Bactericidal activity against Staph
- Daptomycin is inactivated by lung surfactants and should NOT be used to treat PNA
- ADE: myopathy, eosinophilic PNA (rare)

Case

G.P. is a 57-year-old man who has received a diagnosis of osteomyelitis of the tibia after a traumatic injury. The surgical bone culture reveals MRSA susceptible to all antimicrobials on the test panel (other than oxacillin). The vancomycin is S (MIC is 2 mcg/mL). G.P. has no known drug allergies.

Which one of the following is best to recommend for G.P.?

A. Levaquin 750mg QD x 8 weeks.
B. Continues Vancomycin 15 mg/kg intravenous q12 hours x 8 weeks.
C. Escalate to Daptomycin 6 mg/kg intravenous x1 dose & consult ID provider.
D. Escalate to Linezolid 600 mg intravenous twice daily twice daily x 8 weeks

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D. Linezolid 600 mg intravenous twice daily plus rifampin 300 mg orally twice daily x 8 weeks

Antimicrobial Duration of Therapy

The New Antibiotic Mantra- "Shorter is Better"

Diagnosis	Treatment Days Short (d)	Treatment Days Long (d)	Result	# RCTs
CAP	3-5	7-10	Equal	10
VAP	≤8	15	Equal	2
Pyelonephritis	5 or 7	10 or 14	Equal	7
Acute Exacerbation Chronic Bronchitis	≤5	≥7	Equal	>20
Cellulitis	5-6	10	Equal	4

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Banner University Medicine

Thank you

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