Bugs & Drugs:
Basic ID Principles for the ICU

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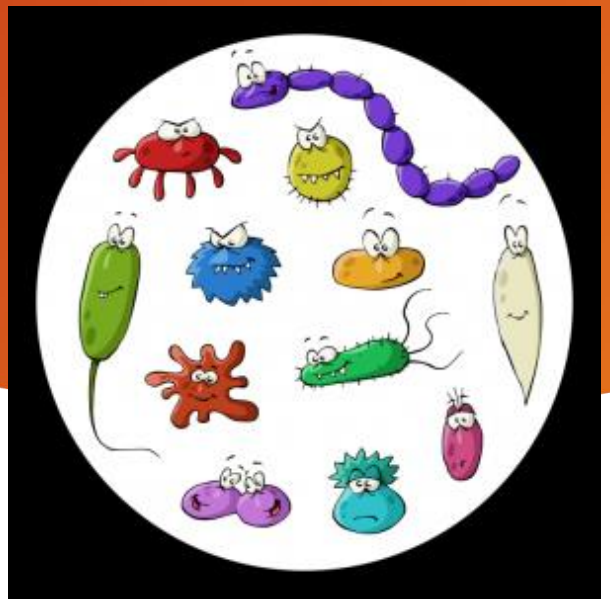

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DISCLAIMER

- Infectious disease is an immense topic
- This presentation is an overview of some common infectious disease states
- This presentation is about horses…not zebras
- Guidelines provide recommendations for populations with a given disease state. However, each patient is unique and the recommendations may be more or less applicable based on patient-specific factors

Objectives

- Review the general concepts of how antimicrobials eradicate infections
- Describe the common pathogens for frequently seen infections in hospitalized patients
- List appropriate empiric regimens for commonly encountered infections including how to find and use our institutional antibiogram
- Utilize a susceptibility report to appropriately de-escalate an antibiotic regimen
- Determine appropriate durations of therapy
- List appropriate prophylactic antimicrobial regimens

Why do we care?

- Infection is a common problem in hospitalized patients
  - It is the number 2 reason for hospital admission in the US
  - It is a common complication of admission for trauma
    - One study reporting that 37% of trauma admissions had an infection-related complication
- There are consequences to getting it wrong
  - The overall mortality rate for sepsis and septic shock is 16-33%
    - Mortality increases in patients with septic shock as time without appropriate antibiotic therapy increases

https://www.hcup-us.ahrq.gov/faststats/NationalDiagnosesServlet
Papia, G et al. **J of Trauma**. 1999;47(5):923- Volume 47 - Issue 5 - p 923
SSC Guidelines. Crit Care Med. 2021. 49;11:1063

Why do we care?

- There are also consequences to inappropriate antibiotic use
  - C. difficile infection
  - Increased development of antimicrobial resistance
  - Increased LOS and hospital costs
- Getting cultures helps reduce inappropriate use
  - Enables discontinuation and/or de-escalation
- The goal is to achieve maximal benefit with as little risk as possible

What it takes for an antibiotic to work

- The agent must have intrinsic activity against the organism
- The agent must be able to reach the site of infection
- The concentration at the site of infection must exceed the minimum inhibitory concentration of the organism
- The dosing regimen must utilize the pharmacokinetic and pharmcodynamic properties of the agent to maximize bacterial killing
- The source of the infection must be removed/controlled whenever possible
- The duration of therapy should be as short as possible to produce clinical cure

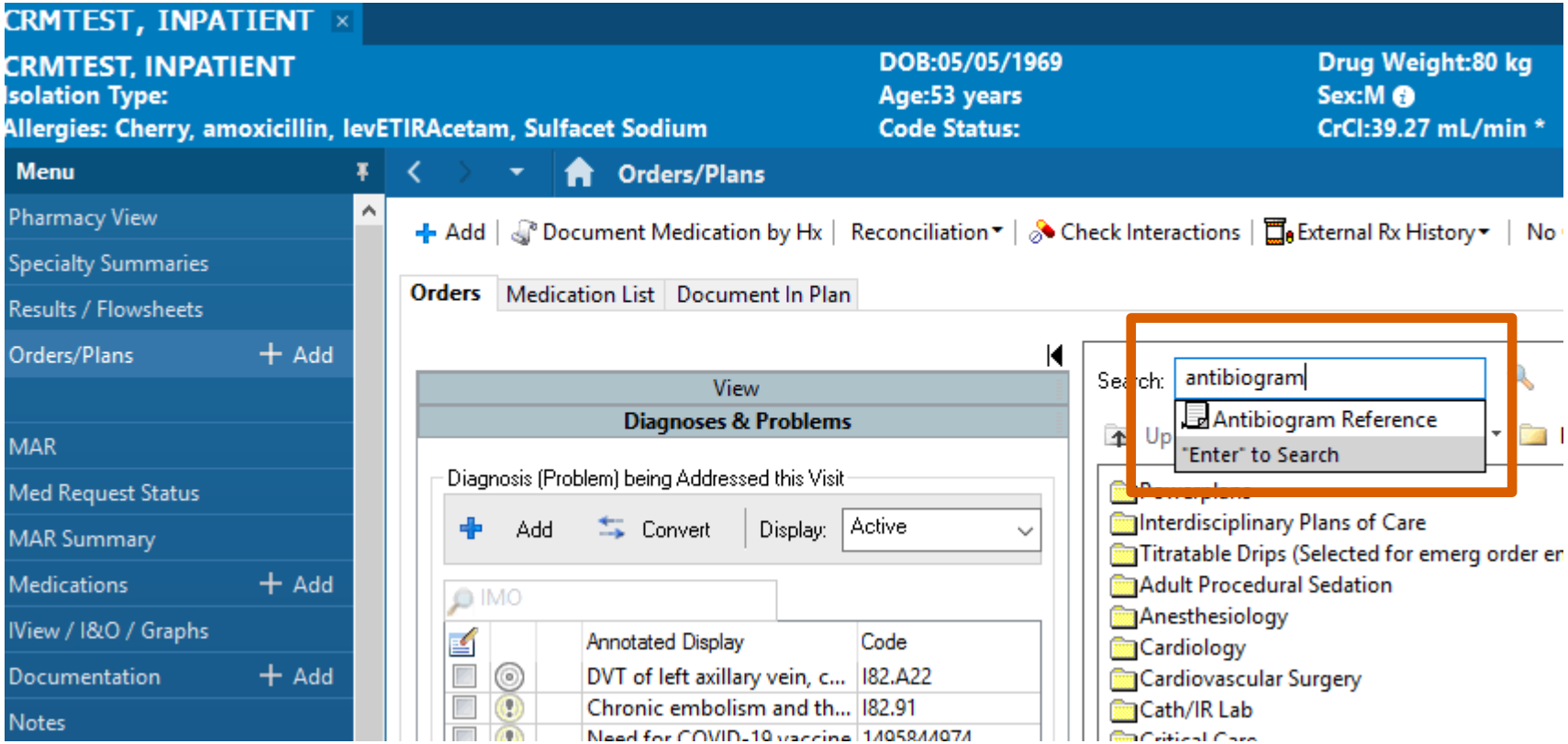
Bugs and Drugs

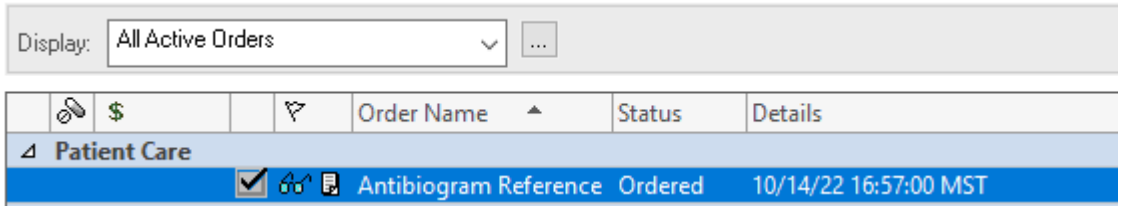
- Infectious disease is the number 1 area of weakness that I hear from most of my non-pharmacist colleagues
- It is not hard…but it does require a lot of memorization
- If you want to improve your ID skills two things are required
  1. Memorize what organisms most commonly cause infections in each organ system
  2. Memorize the spectrum of activity for all antibiotics

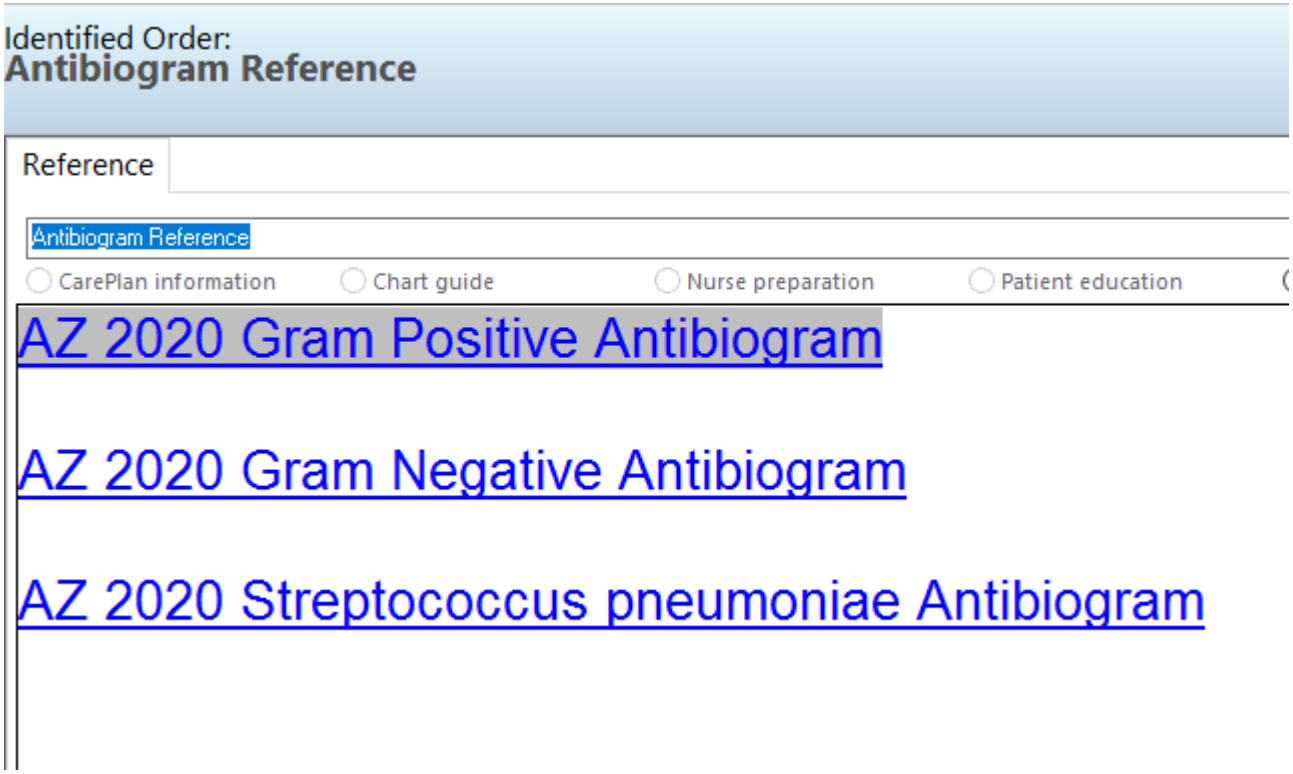
Clipped from my Sanford Guide App

Antibiograms

- Antibiograms give you information about institutional resistance patterns
- Once you have identified a likely source and the most common organisms to cause infection in that source, an antibiogram can help you select empiric therapies
- Agents with > 20% resistance should be avoided for empiric therapy
- The following slides will explain how to find our local antibiogram


CRMTEST, INPATIENT
CRMTEST, INPATIENT
Isolation Type:
Allergies: Cherry, amoxicillin, levETIRAcetam, Sulfacet Sodium
DOB:05/05/1969
Age:53 years
Code Status:
Drug Weight:80 kg
Sex:M
CrCl:39.27 mL/min *
Menu
Pharmacy View
Specialty Summaries
Results / Flowsheets
Orders/Plans + Add
MAR
Med Request Status
MAR Summary
Medications + Add
IView / I&O / Graphs
Documentation + Add
Notes
Orders/Plans
Add
Document Medication by Hx
Reconciliation
Check Interactions
External Rx History
Orders
Medication List
Document In Plan
View
Diagnoses & Problems
Diagnosis (Problem) being Addressed this Visit
Add
Convert
Display:
Active
IMO
Annotated Display
Code
DVT of left axillary vein, c...
I82.A22
Chronic embolism and th...
I82.91
Search:
antibiogram
Antibiogram Reference
"Enter" to Search
Interdisciplinary Plans of Care
Titratable Drips (Selected for emerg order er
Adult Procedural Sedation
Anesthesiology
Cardiology
Cardiovascular Surgery
Cath/IR Lab


Display:
All Active Orders
...
$
Order Name
Status
Details
Patient Care
Antibiogram Reference
Ordered
10/14/22 16:57:00 MST


Identified Order:
Antibiogram Reference
Reference
Antibiogram Reference
CarePlan information
Chart guide
Nurse preparation
Patient education
AZ 2020 Gram Positive Antibiogram
AZ 2020 Gram Negative Antibiogram
AZ 2020 Streptococcus pneumoniae Antibiogram

Gram negative Antibiogram

January 1, 2020 - December 31, 2020

Dignity Health.

Gram Negative Organisms
(%Susceptible)

		Penicillins/Beta-lactam Combinations			Cephalosporins					Aminoglycosides			Fluoro-quinolones		Carbapenems		Other			Urine Only		
					1st	Cepha-mycin	3rd		4th													
	Number of Isolates*	Ampicillin	Ampicillin-Sulbactam	Piperacillin-Tazobact	Cefazolin	Cefoxitin	Ceftazidime 3rd	Ceftriaxone 3rd	Cefepime 4th	Gentamicin	Tobramycin	Amikacin	Ciprofloxacin**	Levofloxacin**	Ertapenem	Meropenem	Aztreonam	Tetracycline	Trimethoprim-Sulfa	Nitrofurantoin#	Fosfomycin#!	Cefazolin Urine#@
AVERAGE OF ALL FACILITIES																						
Enterobacterales																						
Escherichia coli	7313	50	56	97	75	95	90	90	91	91	90	100	76	78	100	100	90	72	72	98	96	100
Klebsiella oxytoca	264		32	89	23	94	90	87	90	93	91	100	92	99	100	100	88	85	87	94		
Klebsiella pneumoniae	2007		77	91	80	90	89	89	90	95	92	100	88	95	99	99	89	79	86	63		100
Proteus mirabilis	614	73	85	99		97	94	89	93	93	92	99	68	70	100	100	93		76			100
ampC Mediated Resistance																						
Citrobacter amalonaticus complex	42			100					100	95	95	100	74	74	100	100		88	76	62		
Citrobacter freundii complex	169			79					95	93	90	99	83	90	99	99		80	79	94		
Citrobacter koseri	126			98					99	100	99	100	96	96	99	100		98	99	54		
Enterobacter cloacae complex	526			77					88	95	94	100	89	92	92	98		85	85	35		
Klebsiella aerogenes	262			76					93	99	98	100	95	98	98	98		92	97	52		
Morganella morganii	126			95					98	83	87	99	65	74	98	98		56	69			
Providencia stuartii	29			83					86			97	25	29	100	100			93			
Serratia marcescens	140			93					99	98	89	99	97	98	99	99			95			
Non-Enterobacterales																						
Achromobacter species	58			95			48							38		100			95			
Acinetobacter baumannii/calcoaceticus complex	110		59	44			51	36	51	55	87	90	47	52		53		53	55			
Pseudomonas aeruginosa	1385			86			88		90	94	97	98	80	79		90	75					
Stenotrophomonas maltophilia	137						43							75					98			
CRMC																						
Enterobacterales																						
Escherichia coli	1530	52	58	97	74	93	89	88	89	93	92	100	73	76	100	100	89	75	74	98	97	100
Klebsiella oxytoca	78		32	92	21	91	95	95	95	96	94	100	94	99	100	100	95	90	92	92		
Klebsiella pneumoniae	566		77	91	81	92	90	91	91	95	92	100	89	97	99	99	91	79	86	63		100
Proteus mirabilis	182	73	88	98		97	93	91	93	95	93	100	65	68	99	100	93		75			100
ampC Mediated Resistance																						
Citrobacter freundii complex	50			78					92	96	94	100	86	93	100	100		82	86	96		
Citrobacter koseri	30			100					97	100	97	100	92	92	97	100		93	97	53		
Enterobacter cloacae complex	148			82					93	97	97	100	96	97	95	100		89	90	34		
Klebsiella aerogenes	70			69					94	100	99	100	94	98	96	96		91	96	46		
Morganella morganii	45			98					100	82	84	100	62	76	98	98		60	71			
Serratia marcescens	52			98					100	98	88	100	98	100	100	100			98			
Non-Enterobacterales																						
Acinetobacter baumannii/calcoaceticus complex	30		57	45			53	30	53	57	83	100	50	53		53		80	53			
Pseudomonas aeruginosa	415			90			90		92	94	99	100	79	79		92	79					
Stenotrophomonas maltophilia	41						45							85					100			

*The actual number of isolates may be lower than listed total. **Fluoroquinolones values are for patients >16 years of age. # For urinary tract infections only. #! For urinary tract infections involving multi-drug resistant Escherichia coli only. Blank spaces indicate intrinsic resistance or a clinically ineffective agent versus the specific organism. Isolate numbers less than 30 are not statistically significant and are included for informational purposes only.

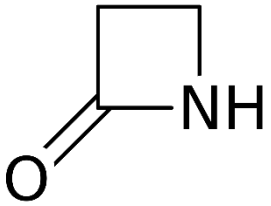
Organisms listed in bold italics have the potential to have ampC mediated resistance.

The breakpoints for Ciprofloxacin and Levofloxacin susceptibilities have been lowered by CLSI. For 2021, expect up to 10% lower susceptibility in comparison to the data presented in this table.

Ertapenem and Meropenem susceptibilities are only reported on multidrug resistant organisms.

Aztreonam and tetracycline are reported by request only.

Cefazolin Urine#@ - The CLSI breakpoints used to calculate these percentages only apply to urine isolates of *Escherichia coli, Klebsiella pneumoniae, & Proteus mirabilis* causing cystitis.



Our Workhorse β-Lactams

Ceftriaxone
- Covers Strep spp, MSSA, enteric GNB
- Does not cover Pseudomonas, Enterobacter, MRSA, enterococcus, anaerobes, or atypicals
- Good CNS penetration

Cefepime
- Covers Strep spp, MSSA, more Gram negatives than ceftriaxone, including Enterobacter and Pseudomonas
- Does not cover MRSA, enterococcus, anaerobes, or atypicals
- Good CNS penetration, can cause neurotoxicity

Pip/Tazo (Zosyn)
- Covers same as cefepime PLUS anaerobes and susceptible enterococcus spp
- Does not cover MRSA
- Bad CNS penetration, cannot be used in true PCN allergy

Meropenem
- Covers the same as pip/tazo but with enhanced activity against resistant species including ESBL
- Does not cover MRSA
- Good CNS penetration, should be reserved for Gram negative failure or proven resistance

Other Frequently used Antimicrobials

Vancomycin	• Covers Gram positive species (staph, strep, enterococcus) • Enteral or rectal formulations effective against C. difficile • Requires more intensive monitoring
Metronidaozle	• Covers anaerobic bacteria including Clostridia spp and parasites (protozoa, amoeba) • Can cause multiple CNS side effects (encephalopathy, aseptic meningitis, peripheral neuropathy)
Amp/Sulbactam (Unasyn)	• Also a β-lactam, covers some enteric GNB (resistance is a problem), MSSA, susceptible enterococcus, and anaerobes • Has a niche role in aspiration pneumonia and prophylaxis in oro-facial fractures

Uncomplicated Urinary Tract Infection

- Defined as >1000 cfu/ml of bacteria isolated from a midstream urine/clean catch sample in a SYMPTOMATIC patient
  - A urinalysis with >10 WBC and presence of bacteria will be reflexed for culture
  - Urine cultures usually take 24-48h to finalize
- Usually caused by Gram negative organisms (E. coli most common)
- Empiric therapy
  - Ceftriaxone 1gm IV daily x 3 days
  - TMP/SMX DS 1 tab PO BID x 3 days
  - Levofloxacin 250 mg IV/PO x 3 days

IDSA 2011 https://doi.org/10.1093/cid/ciq257[14]

Asymptomatic Bacteriuria

- Defined as >100,000 cfu/ml of bacteria isolated from a midstream urine/clean catch sample in a patient WITHOUT urinary symptoms or other signs of systemic infection
- Asymptomatic bacteriuria DOES NOT NEED TREATMENT

V. In an older, functionally or cognitively impaired patient, which nonlocalizing symptoms distinguish ASB from symptomatic UTI?

1. In older patients with functional and/or cognitive impairment with bacteriuria and delirium (acute mental status change, confusion) and without local genitourinary symptoms or other systemic signs of infection (eg, fever or hemodynamic instability), we recommend assessment for other causes and careful observation rather than antimicrobial treatment *(strong recommendation, very low-quality evidence)*.
2. In older patients with functional and/or cognitive impairment with bacteriuria and without local genitourinary symptoms or other systemic signs of infection (fever, hemodynamic instability) who experience a fall, we recommend assessment for other causes and careful observation rather than antimicrobial treatment of bacteriuria *(strong recommendation, very low-quality evidence)*. **Values and preferences:** This recommendation places a high value on avoiding adverse outcomes of antimicrobial therapy such as *Clostridioides difficile* infection, increased antimicrobial resistance, or adverse drug effects, in the absence of evidence that such treatment is beneficial for this vulnerable population. **Remarks:** For the bacteriuric patient with fever and other systemic signs potentially consistent with a severe infection (sepsis) and without a localizing source, broad-spectrum antimicrobial therapy directed against urinary and nonurinary sources should be initiated.

IDSA 2019 https://doi.org/10.1093/cid/ciy1121

How are CAUTIs different?

- CA-UTI is >1000 cfu/ml of at least 1 bacteria species in patient with an indwelling urethral or suprapubic catheter, intermittent catheterization, or who has had an indwelling catheter in the last 48 hours AND is symptomatic
  - New or worsening fever, rigors, AMS, malaise, or lethargy without other identifiable cause in addition to traditional symptoms of CVA tenderness, acute hematuria, pelvic discomfort, dysuria, urgency/frequency, and suprapubic pain
- CA-ASB is also a thing if a urine culture reveals at least 100,000 cfu/ml of a bacterial species in a patient with a catheter who is asymptomatic

IDSA 2010 , https://doi.org/10.1086/650482

How are CAUTIs different?

- Catheters should be replaced prior to culture if feasible when the catheter has been in place for > 2 weeks
- CA-UTIs are more frequently polymicrobial and more likely to grow hospital acquired (aka, more resistant) bacteria
- Empiric therapy should consider severity of illness
  - Mild illness
    - Ceftriaxone 1gm IV Q24 or Levofloxacin 500 mg IV Q24h x 5-7 days
  - Severely ill
    - Cefepime 2gm IV Q12h x 7 days + Vancomycin if patient is in shock
    - Aminoglycoside or aztreonam for cephalosporin allergy

IDSA 2010 , https://doi.org/10.1086/650482

PUBLIC SERVICE ANNOUNCEMENT

- This is where the use of ceftriaxone 1gm IV Q24 ends!!!
- If you are using ceftriaxone to treat *anything* other than the UTIs previously discussed the dose is

2 GRAMS

Pulmonary Infections

Type of Pneumonia	Causative Organisms	Empiric Treatment
CAP	Strep pneumo, H. Flu, GAS, M. Cat, Atypicals	Ceftriaxone 2 gm IV Q24 + Azithromycin 500 mg IV/PO daily x 5 days Add vanco if MRSA risk factors
HAP/VAP	Enteric GNB, Psuedomonas, MRSA	Cefepime 2 gm IV Q8h or Pip/Tazo 3.375 gm IV Q8h x 8 days PLUS vancomycin
Community acquired AP	Strep pneumo, H. flu	Good oral health: ceftriaxone 2gm IV Q24h x 5 days Bad oral health: unasyn 3g IV Q6h Bowel obstruction: cefepime or pip/tazo
Hospital acquired AP	E. coli, Klebsiella, Pseudomonas	Cefepime 2 gm IV Q8h or Pip/Tazo 3.375 gm IV Q8h x 7 days PLUS vancomycin, order MRSA nasal swab!

IDSA 2010 , https://doi.org/10.1086/650482
IDSA 2016 https://doi.org/10.1093/cid/ciw353
Longo DL. NEJM 2019;380:651

Intra-abdominal Infections (IAI)

Community Acquired	Mild to Moderate Severity	High-Risk or Severity
Empiric Single-agent Regimens	Cefoxitin 2gm IV Q6	Pip/Tazo 3.375gm IV Q8h Meropenem 1gm IV Q8h
Combination Regimens	Ceftriaxone 2gm IV Q24h + Metronidazole 500 mg IV Q8h	Cefepime 2gm IV Q8h + Metronidazole 500 mg IV Q8h + Vancomycin
Use high risk regimens for biliary infections beyond uncomplicated cholecystitis		
Add vancomycin to high-risk regimens for hospital acquired IAI		

- Duration is 4 days post source control for most cases without ongoing shock
- Risk factors for source control failure
  - >24h delay in initial intervention
  - Advanced age
  - Degree of peritoneal involvement/peritonitis
  - Poor nutritional status, low albumin
  - High severity of illness/degree of organ dysfunction

IDSA 2010 https://doi.org/10.1086/649554

What do you do when you have culture results?

- When just the organism has been identified (without the susceptibility report) you can go back to the antibiogram to check your odds…consider your patient's response to therapy before making changes
- Molecular tests like the Verigene for blood cultures can tell you if resistance markers are present before the final sensitivity report is available…easy to interpret for Gram positive isolates, seek expert help if there are Gram negative resistance markers
- Once you have a sensitivity report, you can de-escalate to the most narrow-spectrum effective agent

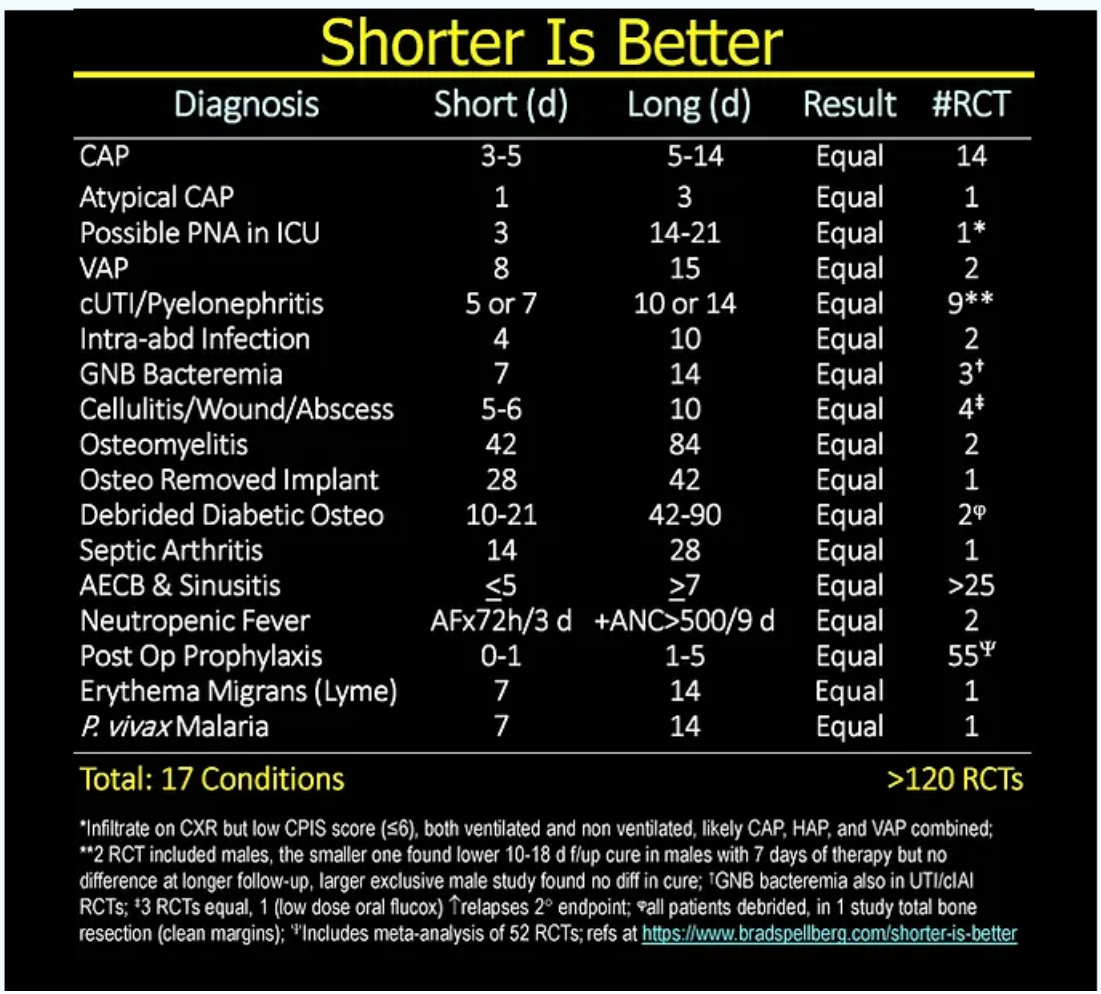
Sensitivity Report Pro Tips

- The micro lab utilizes “Cascade Reporting” when releasing sensitivity reports
  - They report the sensitivities for the most narrow, sensitive antibiotics
  - Sensitivities for broader agents are hidden in an effort to increase the use of more narrow antibiotics
  - Just because an antibiotic does not appear on a sensitivity report DOES NOT mean it is resistant
    - If you want confirmation, call the lab and ask them to unshield the antibiotic you are looking for
  - Any antibiotic that has intrinsic activity but is resistant in a particular isolate will appear in the report as resistant
  - The numbers in a sensitivity report are the microdilution concentration of the antibiotic required to kill the bacteria
    - There are established thresholds at which concentrations are determined sensitive, dose-dependent sensitive, intermediate, or resistant

Interpreting Susceptibility Reports

	Pseudomonas aeruginosa		Escherichia coli		Klebsiella aerogenes	
Drug	MINT	MDIL	MINT	MDIL	MINT	MDIL
Amoxicillin/Clavulanate			R	>16/8		
Ampicillin			R	>16		
Ampicillin/Sulbactam			R	>16/8		
Aztreonam					R	>16
Cefazolin			R	8		
Cefepime	S	4			S	<=1
Cefoxitin			I	16		
Ceftazidime	S	4				
Ceftriaxone			S	<=1		
Ciprofloxacin	S	<=0.25	S	<=0.25	S	<=0.25
Gentamicin	S	<=2	S	<=2	S	<=2
Levofloxacin	S	1	S	<=0.5	S	<=0.5
Piperacillin/Tazobactam	S	8/4			R	>64/4
Tobramycin	S	<=2	S	<=2	S	<=2
Trimethoprim/Sulfa			S	<=0.5/9.5	S	<=0.5/9.5

Durations of Therapy



Shorter Is Better

Diagnosis	Short (d)	Long (d)	Result	#RCT
CAP	3-5	5-14	Equal	14
Atypical CAP	1	3	Equal	1
Possible PNA in ICU	3	14-21	Equal	1*
VAP	8	15	Equal	2
cUTI/Pyelonephritis	5 or 7	10 or 14	Equal	9**
Intra-abd Infection	4	10	Equal	2
GNB Bacteremia	7	14	Equal	3†
Cellulitis/Wound/Abscess	5-6	10	Equal	4‡
Osteomyelitis	42	84	Equal	2
Osteo Removed Implant	28	42	Equal	1
Debrided Diabetic Osteo	10-21	42-90	Equal	2φ
Septic Arthritis	14	28	Equal	1
AECB & Sinusitis	≤5	≥7	Equal	>25
Neutropenic Fever	AFx72h/3 d	+ANC>500/9 d	Equal	2
Post Op Prophylaxis	0-1	1-5	Equal	55Ψ
Erythema Migrans (Lyme)	7	14	Equal	1
P. vivax Malaria	7	14	Equal	1

Total: 17 Conditions >120 RCTs

*Infiltrate on CXR but low CPIS score (≤6), both ventilated and non ventilated, likely CAP, HAP, and VAP combined; **2 RCT included males, the smaller one found lower 10-18 d f/up cure in males with 7 days of therapy but no difference at longer follow-up, larger exclusive male study found no diff in cure; †GNB bacteremia also in UTI/cIAI RCTs; ‡3 RCTs equal, 1 (low dose oral flucox) ↑relapses 2° endpoint; φall patients debrided, in 1 study total bone resection (clean margins); ΨIncludes meta-analysis of 52 RCTs; refs at https://www.bradspellberg.com/shorter-is-better

https://www.bradspellberg.com/shorter-is-better

Antimicrobial Prophylaxis

- Duration beyond 72 hours is no longer prophylaxis…it is empiric treatment
- There is pretty good data for orthopedic indications…beyond that it’s a data-free or data-ignored zone
- In general, durations beyond 24h have no additional benefit on reducing eventual infections

Antibiotic Prophylaxis – Orthopedic Indications

Gustilo Grade I	• Open fx with clean wound less than 1 cm long • Cefazolin 2gm IV Q8h • Continue for 72h or for 2 doses post soft tissue coverage
Gustilo Grade II	• Open fx with wound > 1cm long without extensive soft tissue damage • Cefazolin 2gm IV Q8h • Continue for 72h or for 2 doses post soft tissue coverage
Gustilo Grade III, subtypes a,b,c	• IIIa adequate coverage of bone despite extensive soft tissue damage • IIIb extensive soft tissue loss, exposed bone, usually highly contaminated • IIIc open fx with associated arterial injury requiring repair • Ceftriaxone 2gm IV Q24h + Metronidazole 500 mg IV Q8h for IIIb • Continue for 72h or for 24h post soft tissue coverage

https://www.east.org/education-career-development/practice-management-guidelines/archived/open-fractures-prophylactic-antibiotics[26]

Antibiotic Prophylaxis – CNS Indications

- Data does not support the use of prophylactic antibiotics for the prevention of meningitis in basilar skull fractures
- Antibiotics have no effect on rates of CNS infections in penetrating brain injuries
- If antibiotics are given use the dosing below and limit duration to 72 hours total or for 24h after operative intervention

Type of Injury	Prophylatic Regimen
Open skull fracture	Ceftriaxone 2gm IV Q12h
Survivable penetrating injury without gross contamination	Ceftriaxone 2gm IV Q12h + Vancomycin
Survivable penetrating injury with gross environmental contamination (soil/grass)	Cefepime 2gm IV Q8h + Metronidazole 500 mg IV Q8h or Meropenem 2gm IV Q8h + Vancomycin

Batial DO, et al. Cochrane Database Syst Rev 2015 Apr 28:(4):CD004884
Harmon LA, et al. J Trauma Acute Care Surg 2019;87(1):67[27]

Questions?

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