Antimicrobial Stewardship at Kaweah Delta: An Overview

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Objectives

- Describe the clinical benefits, goals, and structure of the KD Antimicrobial Stewardship Program
- Highlight key distinctions between asymptomatic bacteriuria and true urinary tract infections
- Review appropriate diagnostic tests and cultures
- Select empiric therapy using hospital-approved PowerPlans
- Demonstrate the importance of antimicrobial de-escalation
- Select appropriate evidence-based durations of therapy

What is Antimicrobial Stewardship?

- “Coordinated interventions designed to improve and measure the appropriate use of [antibiotic] agents by promoting the selection of the optimal [antibiotic] drug regimen including dosing, duration of therapy, and route of administration.”

Barlam, TF. *Clin Infect Dis*. 2016;62(10):e51-e77.

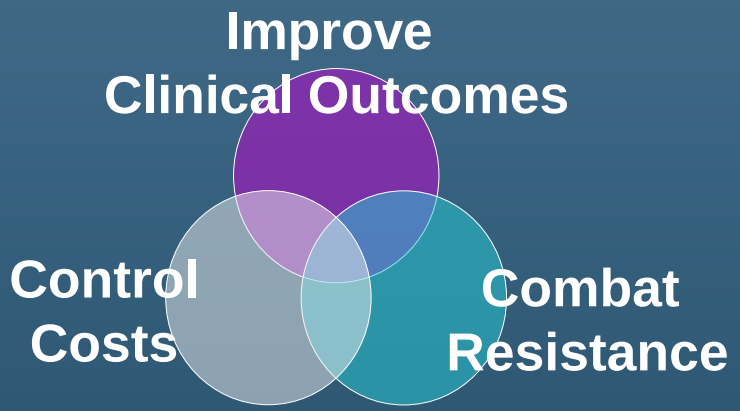
Why is Stewardship Important?

- 30-50% of antibiotic orders/treatment is unnecessary or inappropriate (possible underestimate)
- 142,000 ED visits in 2008 for antibiotic adverse events
- CDC estimates >2 million cases & 23,000 deaths/year from multi-drug resistant organism infections
  - ESBL, CRE, MRSA, VRE
  - Increased mortality, more difficult to treat, more costly medications
- CDC estimates 250,000 cases & 14,000 deaths/year from *C. difficile* infections
  - Directly related to antibiotic use
  - High risk medications include: clindamycin, fluoroquinolones, ceftriaxone, anti-pseudomonal β-lactams
- Unnecessary antibiotics increase hospital costs and contribute to longer lengths of stay

Antibiotic Resistance Threats in the United States, 2013. CDC. Originally online September 16, 2013. https://www.cdc.gov/medicationsafety/program_focus_activities.html
Owens RC. *Clin Infect Dis*. 2008;46(S1):S19-31.
Rao GG. *Drugs*. 1998;55(3):323-30.

Goals of Stewardship

- Primary goals
  - Optimize clinical outcomes through antimicrobial
    - Selection
    - Dosing
    - Route
    - Duration
  - Reduce resistance
  - Minimize toxicity
  - Reduce super-infections (e.g. *C. difficile*)
  - Reduce unnecessary antimicrobial use



- Secondary goal
  - Control costs

Dellit TH. *Clin Infect Dis*. 2007;44:159-177

Infectious Diseases Team

Daniel Boken, MD
Board Certified-Infectious Diseases
Stewardship Physician Leader

Benjamin Ereshefsky, PharmD, BCIDP
Stewardship Pharmacist Leader

Mina Raju, DO
Board Certified-Infectious Diseases

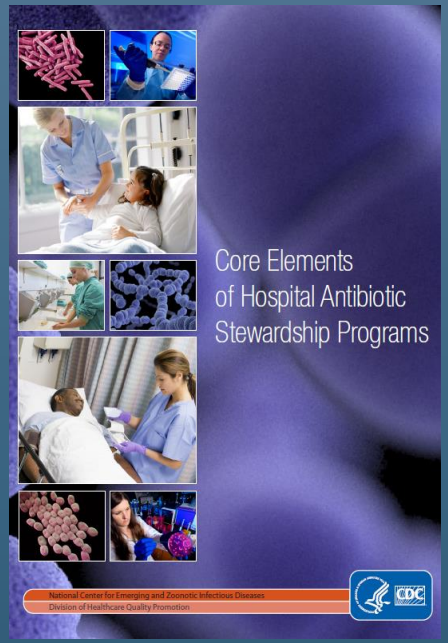
Infection Prevention Manager
Shawn Elkins, MPA, BSN, RN

Clinical Laboratory Director
Randy Kokka, MPH, CLS

Antimicrobial Stewardship Focus

- Detailed chart review of patients on antimicrobial therapy
  - Available 5 days a week (M-F 8:00 am – 5:00 pm)
  - Evaluation of cultures and susceptibilities
  - Recommendations for optimization or discontinuation of antimicrobials (e.g. "prospective audit and feedback")
- Development of institutional policies and protocols
  - Empiric antimicrobial use
  - Diagnostic testing
  - Infection prevention
- Education
- Track and review antimicrobial utilization and expenditures

Barlam, TF. *Clin Infect Dis*. 2016;62(10):e51-e77.



Broad Interventions

- Antibiotic time-out
- Restrictions or pre-authorization
- **Prospective audit with feedback**

Pharmacy-Driven Interventions

- **IV to PO interchange**
- **Renal adjustment protocol**
- **Pharmacokinetic monitoring (e.g., vanc, AMG)**
- **Dose optimization (e.g. extended-infusion Zosyn)**
- **Duplicate therapy alerts**
- **Automatic stop orders (e.g. 7 days for antibiotics)**

Diagnosis & Infection Specific Interventions

- CAP
- UTI
- SSTI
- Surgical Prophylaxis
- MRSA
- *C. difficile* infection
- Culture-positive infections

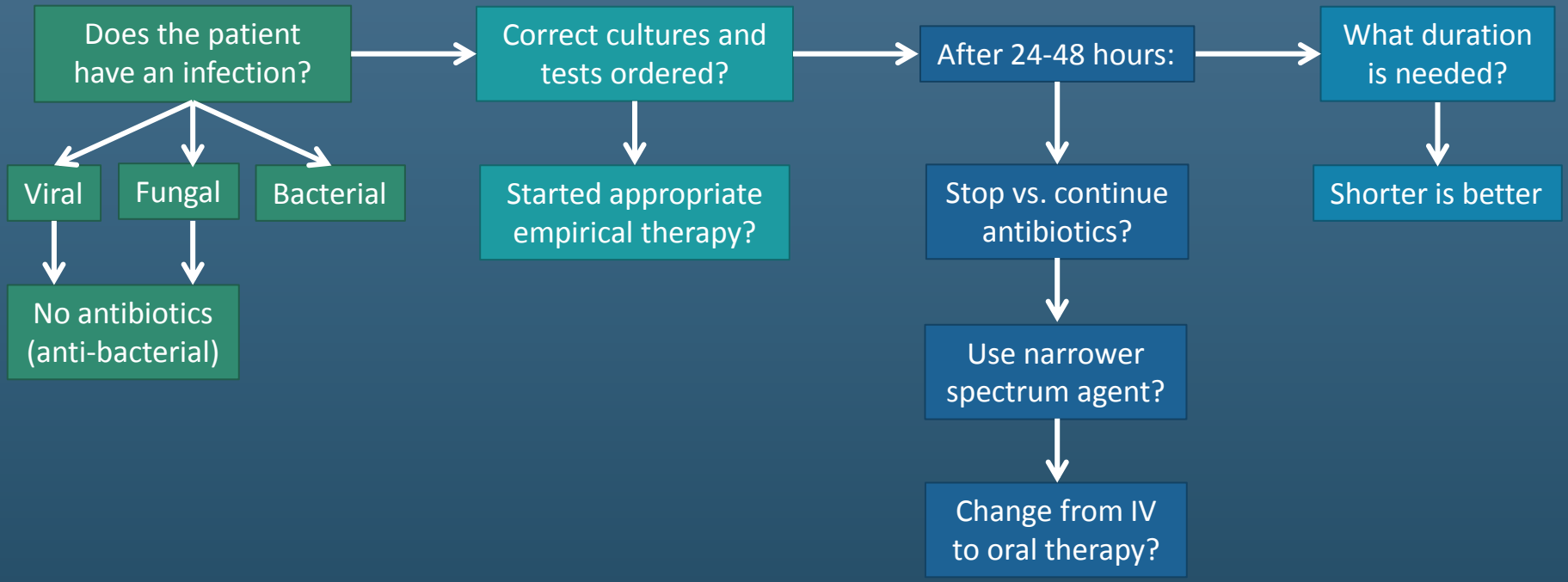
Other

- **Leadership support**
- **Physician and pharmacist leaders**
- **Monitor antimicrobial use**
- **Annual antibiogram**
- **Education to clinicians and other staff**

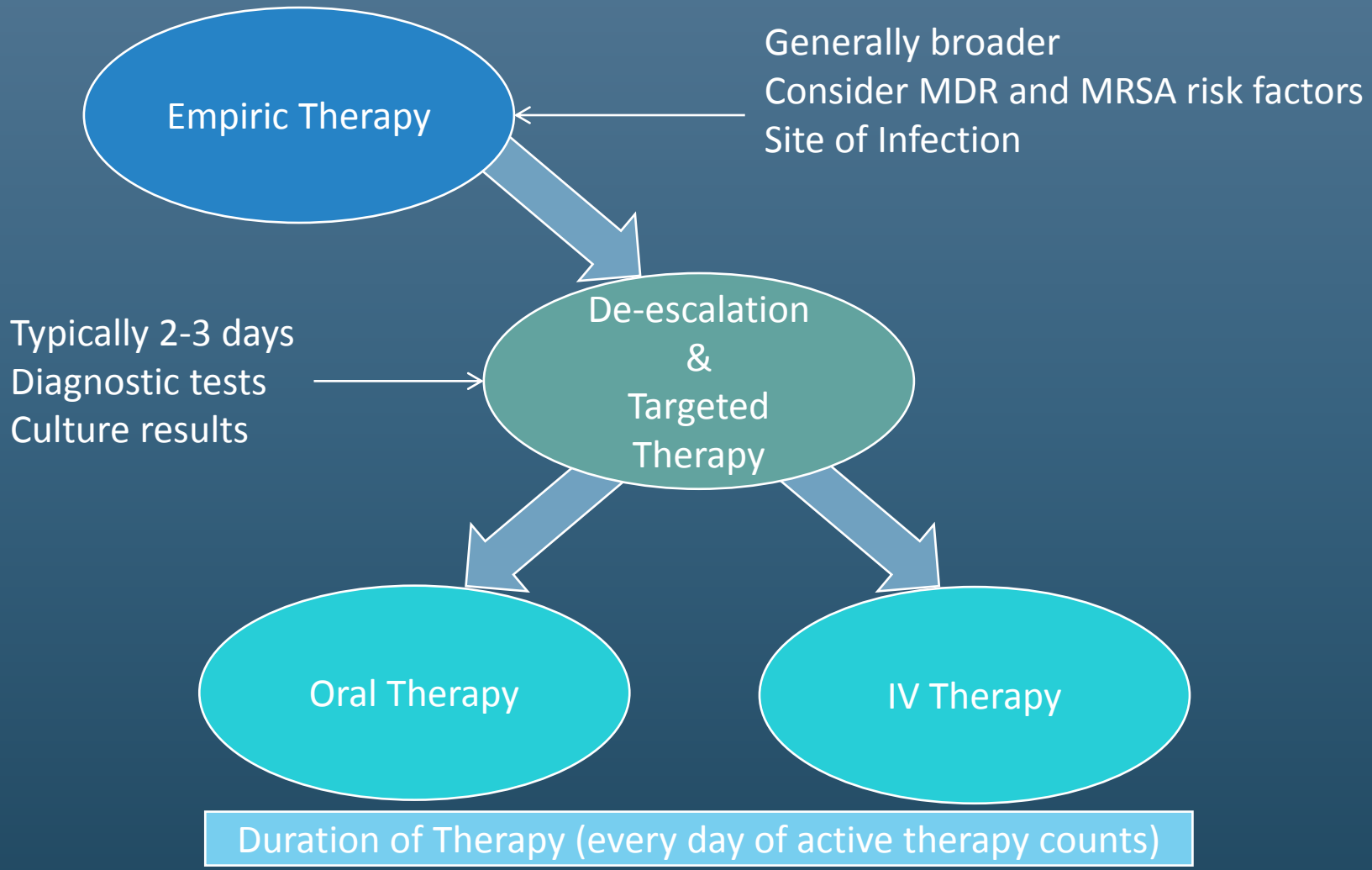
Stewardship Rounds

- Conducted Monday, Wednesday, and Friday
- Recommendations entered as “Stewardship Rounds” progress notes by Dr. Boken
- Stewardship review requests are always welcome
  - Contact ID pharmacist at x6606
  - Contact Dr. Boken via cellphone/text

The 4 Moments of Antibiotic Decision Making



Tama P. *JAMA*. 2019;321(2):139-140.
Wald-Dickler N. *Clin Infect Dis*. 2019.doi: 10.1093/cid/ciy1134.


Empiric Therapy
Generally broader
Consider MDR and MRSA risk factors
Site of Infection
Typically 2-3 days
Diagnostic tests
Culture results
De-escalation
&
Targeted
Therapy
Oral Therapy
IV Therapy
Duration of Therapy (every day of active therapy counts)

Determining Presence of Infection

Asymptomatic Bacteriuria (ASB)

- Definition

> "Asymptomatic bacteriuria (ASB) is the presence of 1 or more species of bacteria in the urine at specified quantitative counts ($\geq 10^5$ colony-forming units [CFU]/mL or $\geq 10^8$ CFU/L), irrespective of the presence of pyuria, in the absence of signs or symptoms attributable to urinary tract infection (UTI)."

- Not treating ASB is an important stewardship goal to reduce unnecessary antibiotic use

Nicolle. *Clin Infect Dis*. 2019. ciy1121, https://doi.org/10.1093/cid/ciy1121.

Asymptomatic Bacteriuria

- Do **NOT** screen for or treat ASB in:

  - Healthy premenopausal, non-pregnant women or healthy postmenopausal women
  - Older, community-dwelling adults with functional impairment
  - Older residents of long-term care facilities
  - Patients with diabetes
  - Patients with renal transplants >1 month after surgery
  - Patients with spinal cord injury
  - Patients with short-term and long-term indwelling urethral catheters
  - Patients undergoing elective non-urologic surgery

- Look for other cause of symptoms and observe:

  Older patients with functional and/or cognitive impairment with bacteriuria and without local GU symptoms or other systemic signs of infection (e.g. fever, hemodynamic instability) with
  - Delirium (acute mental status change, confusion)
  - Fall

Nicolle. *Clin Infect Dis*. 2019. ciy1121, https://doi.org/10.1093/cid/ciy1121.

Risk of Treating ASB

- *C. difficile* infection
- Antimicrobial resistance
- Symptomatic UTI
- Adverse drug effects from antibiotics

"Antimicrobial treatment did not confer any benefits."

Nicolle. *Clin Infect Dis*. 2019. ciy1121, https://doi.org/10.1093/cid/ciy1121.

UTI Symptoms: No Catheter

At least **ONE** of:
- Acute dysuria
- Acute pain, swelling, tenderness of testes, epididymis, or prostrate

OR

At least **ONE** of:
- Fever
- Leukocytosis

AND

At least **ONE** of:
- CVA pain or tenderness
- New/increased suprapubic tenderness
- Gross hematuria
- New/increased incontinence
- New/increased urgency
- New/increased frequency

OR **TWO** or more

Use “Suspected UTI PowerPlan to order UA with reflex culture if indicated

NHSN Long-term Care Facility Component Urinary Tract Infection. CDC. January 2017.

UTI Symptoms: Catheter Associated*

At least **ONE** of:

- Fever
- Rigors
- New onset hypotension, with no alternate cause
- New onset confusion/function decline (AMS) with no alternate diagnosis **AND** leukocytosis
- New CVA pain or tenderness
- New or increased suprapubic tenderness
- Acute pain, swelling, or tenderness of testes, epididymis, or prostate
- Purulent discharge from around catheter

*Bacteriuria rate: 3-5% per catheter day

Use “Suspected UTI PowerPlan to order UA with reflex culture if indicated

NHSN Long-term Care Facility Component Urinary Tract Infection. CDC. January 2017.

Ordering Tests, Cultures, Empiric Therapy

When and What to Culture?

- Obtain BEFORE starting antibiotics if possible
- Culture only sites where infection is suspected
  - Pan-culturing when a source is suspected can result in confounding information (contaminants or colonization)
  - Unnecessary urine cultures are #1 cause of colonization treatment
- NEVER culture/swab surface wounds
  - High rates of colonization
  - Results can mask the true pathogen
  - Deep or surgical cultures preferred

Blood Cultures

- If initial blood cultures are negative, repeats are unnecessary
- Repeating blood cultures in gram-negative rod bacteremia is largely unnecessary
- If initial blood cultures show coagulase-negative staphylococci contaminants, repeats are unnecessary
- In *S. aureus* bacteremia or candidemia, repeat blood cultures every 24-48 hours until first negative culture

BioFire Rapid Diagnostic Platform

- Multiplex PCR technology to rapidly detect a wide array of pathogenic organisms
- Samples include:
  - Nasopharyngeal swab (RP2 panel)
  - Cerebrospinal fluid (ME panel)
  - Blood cultures (BCID panel)
  - Deep respiratory secretions (Pneumonia panel)
  - Stool (GI Panel)
- For detailed usage and treatment guide go to:
  - KDNet→Manuals – Resources→Pharmacy→Pharmacy References→"BioFire Protocol"

C. difficile Testing Criteria

- Hospital policy: PC.255

Testing Inclusion Criteria:

- Three or more loose & watery stools in ≥24 hours
- Presence of at least one of the following
  - Abdominal cramping, tenderness, or pain
  - Temperature ≥38°C and no other source
  - Radiologic evidence of colitis

Positive test collected >3 days after admission

Testing Exclusion Criteria:

- Formed or semi-formed stool
- Laxative, stool softener, enema, or bowel prep within 24 hours
- Positive *C. diff* test in past **21 days**
- Negative *C. diff* test in past **7 days**

Do not send a stool sample for a test of cure!!!!

Hospital Antibiogram — 2018

			Aminoglycosides			Beta-lactam Antibiotics										Miscellaneous						Gram-Positive Antibiotics				
						Cephalosporins				Penicillins				Other												
	KDHC Antibiotic % Susceptibility Report 2018 Questions? Contact Microbiology x2638	**# Isolates Tested**	**Amikacin**	**Tobramycin**	**Gentamicin**	**Cefazolin**	**Cefuroxime-axetil**	**Ceftriaxone**	**Ceftazidime**	**Ampicillin**	**Amoxicillin/clavulanate**	**Ampicillin/sulbactam**	**Piperacillin/tazobactam**	**Meropenem**	**Aztreonam**	**Levofloxacin**	**Trimethoprim/sulfa**	**Nitrofurantoin**	**Tetracycline**	**Clindamycin**	**Fosfomycin**	**Vancomycin**	**Oxacillin (nafcillin)**	**Penicillin**	**Linezolid**	**Erythromycin (azithromycin)**
Gram-Negatives	**Acinetobacter baumannii**	**34**	-	100	100	-	-	12	82	-	-	100	85	97	-	88	97	-	100	-	-	-	-	-	-	-
	Citrobacter freundii	**79**	100	92	92	-	-	82	84	-	-	-	81	100	82	91	80	99	80	-	-	-	-	-	-	-
	Citrobacter koseri	**50**	100	100	100	98	57	100	100	-	100	-	100	100	100	100	100	76	100	-	-	-	-	-	-	-
	Enterobacter cloacae	**150**	100	99	99	-	-	85	85	-	-	-	85	98	85	97	93	38	94	-	-	-	-	-	-	-
	Escherichia coli	**4295**	100	90	89	83	82	93	93	49	80	56	96	100	93	80	71	95	73	-	-	-	-	-	-	-
	Klebsiella aerogenes	**107**	100	98	98	-	-	86	85	-	-	-	85	100	89	99	96	-	97	-	-	-	-	-	-	-
	Klebsiella oxytoca	**74**	100	100	99	62	91	97	100	-	92	76	92	100	95	100	95	78	91	-	-	-	-	-	-	-
	Klebsiella pneumoniae	**767**	100	97	98	92	91	95	94	-	95	85	95	100	95	97	92	26	86	-	-	-	-	-	-	-
	Morganella morganii	**63**	100	94	73	-	-	94	90	-	-	-	98	100	98	85	65	-	-	-	-	-	-	-	-	-
	Proteus mirabilis	**322**	100	84	82	94	97	99	99	72	92	78	100	100	99	75	70	-	-	-	-	-	-	-	-	-
	Pseudomonas aeruginosa	**406**	99	97	95	-	-	-	91	-	-	-	92	97	N/A	86	-	-	-	-	-	-	-	-	-	-
	Serratia marcescens	**76**	100	91	100	-	-	100	100	-	-	-	99	100	100	99	100	-	50	-	-	-	-	-	-	-
	Stenotrophomonas maltophilia	**32**	-	-	-	-	-	-	-	-	-	-	-	-	-	100	100	-	-	-	-	-	-	-	-	-
Gram-Positives	**Enterococcus faecalis**	**178**	-	-	-	-	-	-	-	99	-	-	-	-	-	-	-	98	18	-	-	99	-	99	96	-
	Enterococcus faecium	**40**	-	-	-	-	-	-	-	28	-	-	-	-	-	-	-	20	28	-	-	40	-	28	95	-
	Staphylococcus aureus	**1136**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	98	100	93	86	-	100	54	16	100	-
	CoNS	**206**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	64	100	85	63	-	100	43	10	100	-
	Streptococcus pneumoniae	**65**	-	-	-	-	-	98[b]	-	-	-	-	-	-	-	100	83	-	85	94	-	100	-	100[a]	100	74

[a] Penicillin G: pneumonia 100%; meningitis 80% [b] Ceftriaxone: meningitis 94%; non-meningitis 98%

Ceftriaxone Resistance: E. coli 7% K. pneumoniae 5% K. oxytoca 3% P. mirabilis 1%

MRSA Rate: 46% VRE Rate: 12%

Available online: KDCentral→Physicians→Antibiograms

β-Lactam Allergies

- Up to 90% of patients with a reported allergy are really not allergic
- Patients with allergies >10 years old have a high chance of losing their sensitivity
- Patients with reported allergies receive:
  - Broader-spectrum antibiotics
  - Less effective antibiotics
  - More harmful antibiotics
  - More expensive antibiotics

Rubin R. *JAMA*. 2018;320(18):1846-48.

Managing Patients With β-lactam Allergies

- Determine **what** the reaction was, **whether** rescue medications (e.g. epinephrine) were needed, **when** it occurred, **what** drug they received
- Ask about subsequent antibiotic use (ask a pharmacist to review previous inpatient and outpatient medications)
- Know the risk for cross-reactivity:
  - Mild reactions (e.g. rash) to penicillins usually indicate tolerance to cephalosporins
  - Cephalosporins like cefazolin, ceftriaxone, and cefuroxime have very low cross-reactivity with penicillin/amoxicillin
  - GI related reactions (e.g. nausea, vomiting, diarrhea) are **NOT** allergies so alternative therapies are not needed
- Assess risks and benefits of using alternative or 2nd line therapy

Serious Side Effects from Fluoroquinolones

Musculoskeletal & Peripheral Nervous System

- Tendinitis
- Tendon Rupture
- Numbness/Tingling in arms/legs
- Muscle Weakness
- Muscle Pain
- Joint Pain
- Joint Swelling

Central Nervous System

- Anxiety
- Depression
- Hallucinations
- Suicidal Thoughts
- Confusion
- **Hypoglycemic coma**

Other Body Systems

- Severe Diarrhea (*C. difficile*)
- Worsening of myasthenia gravis
- Skin Rash
- Skin Burn
- Abnormal, rapid, or strong heart beat
- **Aortic aneurysm rupture or dissection**

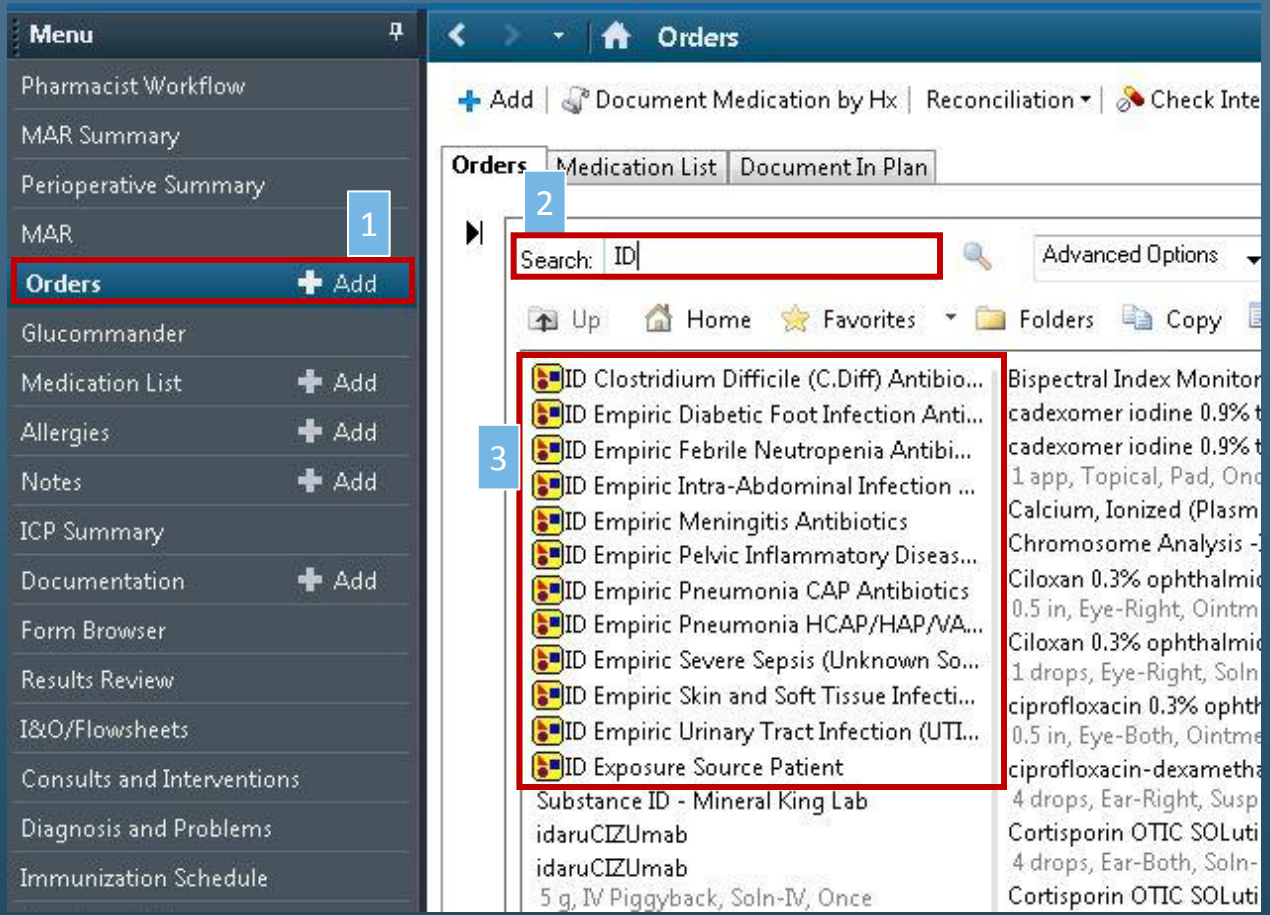
Risks generally outweigh the benefits for uncomplicated infections when other options are available

FDA Drug Safety Communication: FDA updates warnings for oral and injectable fluoroquinolone antibiotics due to disabling side effects. U.S. Food & Drug Administration. July 26, 2016. http://www.fda.gov/Drugs/DrugSafety/ucm511530.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery.
FDA News Release: FDA updates warnings for fluoroquinolone antibiotics on risks of mental health and low blood sugar adverse reactions. July 10, 2018. https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm612995.htm.
FDA Drug Safety Communication: FDA warns about increased risk of ruptures or tears in the aorta blood vessel with fluoroquinolone antibiotics in certain patients. December, 20, 2018. https://www.fda.gov/Drugs/DrugSafety/ucm628753.htm.

Using PowerPlans (Order Sets)

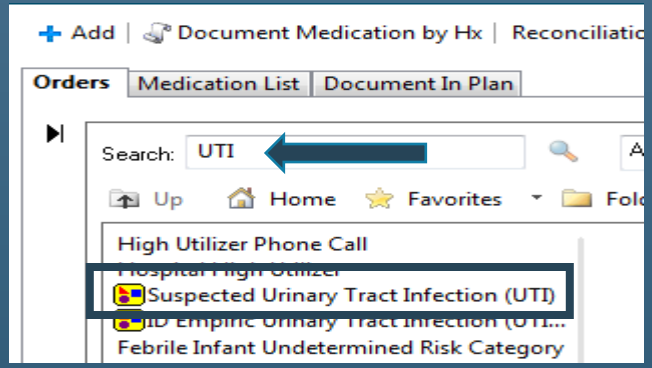
- Select the appropriate PowerPlan based on suspected source of infection
- Select treatment based on the criteria outlined in PowerPlan that fits patient presentation
- Treatment options for preferred or alternative (e.g. for allergies) therapy provided

Empiric Antibiotic PowerPlans

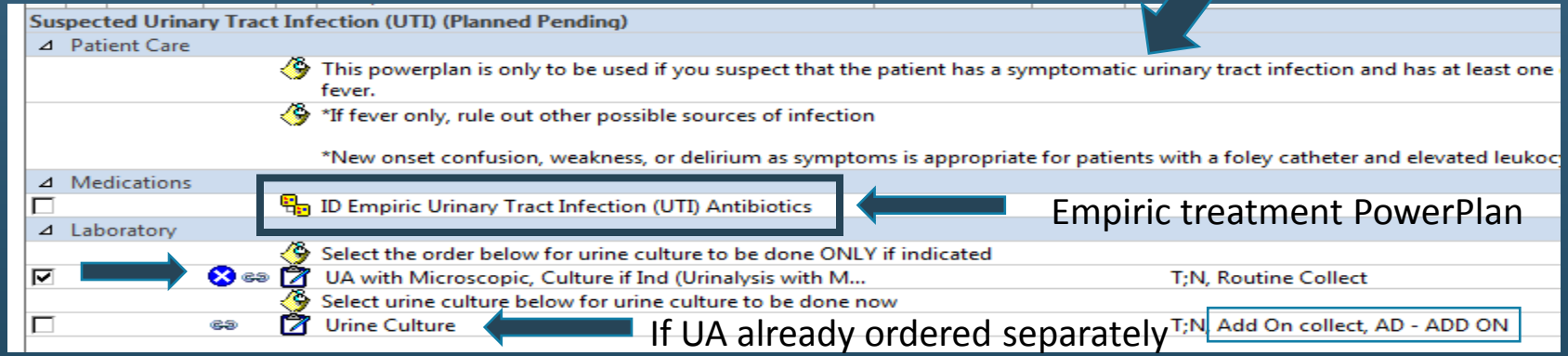


Suspected UTI PowerPlan

- Ordering



Urinary symptoms to assess **BEFORE** ordering



Empiric treatment PowerPlan

If UA already ordered separately

De-escalation and Discontinuing Empiric Therapy

Anti-Pseudomonal and Anti-MRSA Treatment

- Use empirically ONLY if patient has risk factors or if severe sepsis/shock
- MRSA risk factors
  - Hemodialysis
  - Necrotizing or cavitary community-acquired pneumonia
  - Purulent skin and soft tissue infection
  - Central lines
- *P. aeruginosa risk factors*
  - IV antibiotics in previous 90 days
  - Structural lung disease in community-acquired pneumonia
  - Severe immunocompromise (e.g. neutropenic fever)
  - Prolonged hospitalization

Admission from a nursing home alone is **NOT** a reason to start anti-pseudomonal or anti-MRSA treatment

Prolonged coverage for these organisms is inappropriate if not isolated from culture and no risk factors

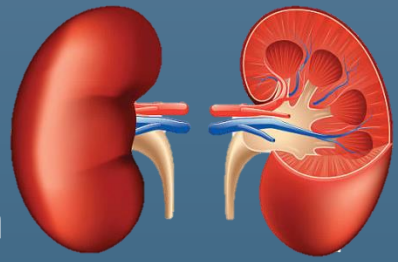
De-Escalation in Respiratory Infections

- MRSA nasal swab
  - >95% negative predictive value for MRSA pneumonia
  - Recommendation: discontinue vancomycin or linezolid with negative result
  - Found to decrease anti-MRSA treatment by ~2 days[1]

- Respiratory culture: "No MRSA or Pseudomonas detected"
  - Microbiology comment on cultures with normal flora[2]
  - Overuse of anti-MRSA and anti-pseudomonal treatment for HCAP and CAP
  - Recommendation: discontinue coverage for MRSA and *P. aeruginosa* and use a narrower spectrum agent if antibiotics still needed

[1]Baby N. *Antimicrob agent Chemother*. 2017;61(4):e02432-16.
[2]Musgrove MA. Open Forum Infect Dis. 2018 Jul 10;5(7):ofy162. doi: 10.1093/ofid/ofy162. eCollection 2018 Jul.

Avoid Patient Harm



- Vancomycin PLUS piperacillin/tazobactam has shown greater risk for acute kidney injury than:
- Vancomycin alone
- Piperacillin/tazobactam alone

If combination of vancomycin and piperacillin/tazobactam used empirically, DE-ESCALATE as quickly as possible, especially if other nephrotoxins present (e.g. contrast, NSAIDs, ACE inhibitors)

Rutter WC. *Antimicrob Agents Chemother*. 2018;62(7):pii: e00264-18. Mullins BP. *Ann Pharmacother*. 2018;52(7): Epub.
Anderson CW. *Mil Med*. 2017;182(9):e1773-e1778. Rutter WC. *J Hosp Med*. 2017;12(2):77-82. Navalkele B. *Clin Infect Dis*. 2017;64(2):116-123.
Hammond DA. *Clin Infect Dis*. 2017;64(5):666-674. Rutter WC. *Antimicrob Agents Chemother*. 2017;61(2):pii: e02089-16.
Giuliano CA. *Pharmacother*. 2016;36(12):1217-1228. Burgess LD. *Pharmacother*. 2014;34(7):670-676. Gomes DM. *Pharmaother*. 2014;34(7):662-669.

Prolonged Use of Anti-Pseudomonal β-Lactams

- Promotes increased risk for gram-negative resistant organisms
  - More difficult to treat (highly resistant GNR antibiotics non-formulary)
  - Higher rates of mortality
- Increases risk for *C. difficile* infection
  - Prolongs length of stay or leads to readmission
  - Significant morbidity or mortality, especially for elderly patients
  - Hospital-onset *C. difficile* infection rates are publicly reported

De-escalation is important to reduce patient harm!
Use the narrowest spectrum agent possible

Seddon MM. *Clin Infect Dis*. 2018 Oct 12. doi: 10.1093/cid/ciy863.
Teshome BF. *Pharmacother*. 2019;39(3):261-68.

Duration of Therapy

How Long to Treat? Shorter is Better

Infection	Short (days)	Long (days)
Community-acquired pneumonia	3-5	7-10
Hospital-acquired/ventilator-associated pneumonia	7-8	14-15
Pyelonephritis/complicated UTI	5-7	10-14
Post-operative intraabdominal infection	4	10
Gram-negative bacteremia	7	14
COPD exacerbation	≤5	≥7
Acute cellulitis/major abscess	5-6	10
Empiric neutropenic fever	72h (afebrile/stable)	72h (afebrile/ stable/ ANC >500 cells/µL

Wald-Dickler N. *Clin Infect Dis*. 2019 Jan 7. doi: 10.1093/cid/ciy1134. [Epub ahead of print].

Unnecessary/Inappropriate Antibiotic Use Increases Risk…

- Over 140,000 ED visits/year for adverse events from antibiotics (19%)[1]
- *C. difficile* infection[2]
  - Clindamycin
  - Fluoroquinolones
  - Ceftriaxone
  - Anti-pseudomonal β-lactams
- Antibiotic Resistant Organisms
  - ESBL, CRE (carbapenem-resistant enterobacteriaceae), MRSA, VRE[3]
  - More difficult to treat, more costly treatment
  - Increased mortality

[1]https://www.cdc.gov/medicationsafety/program_focus_activities.html
[2]Owens RC. *Clin Infect Dis*. 2008;46(S1):S19-31.
[3]Rao GG. *Drugs*. 1998;55(3):323-30.

How Long Should I Treat *S. aureus* Bacteremia?

Uncomplicated[1]
- No evidence of endocarditis
- No implanted prostheses
- Repeat blood cultures negative (2-4 days after initial positive)
- Defervescence within 72 hours of initiating treatment
- No evidence of metastatic sites of infection

Uncomplicated (CLABSI)[2]
- Not diabetic
- Not immunosuppressed
- Infected catheter removed
- No prosthetic devices
- No evidence of endocarditis
- No evidence of suppurative thrombophlebitis
- Fever and bacteremia resolve within 72 hours
- No evidence of metastatic infection

Duration: 2 weeks

Complicated[1,2]
- Do not meet uncomplicated criteria

Duration: 4-6 weeks
(consider 6 to ≥8 weeks if high-risk for recurrence in vertebral osteomyelitis[3])

Endocarditis[1,4]

Duration: 6 weeks
(consider ≥6 weeks if prosthetic valve involved)

[1]Liu C. *Clin Infect Dis*. 2001;52(3):e18-e55.
[2]Mermel LA. *Clin Infect Dis*. 2009;49:1-45.
[3]Park K. *Clin Infect Dis*. 2016;62(10):1262-9.
[4]Baddour LM. *Ciruclation*. 2015;132:1435-86.

S. Aureus Bacteremia: A Case for Process Improvement

- Repeat blood cultures every 1-2 days after initial positive culture in order to document clearance
- Echocardiogram (TEE > TTE) in all bacteremic patients
- Identify and eliminate the source of infection if possible
- Three Rs:
  - Right drug
  - Right dose
  - Right duration
- STRONGLY consider ID consult in *S. aureus* bacteremia (reduction in mortality, identification of source)

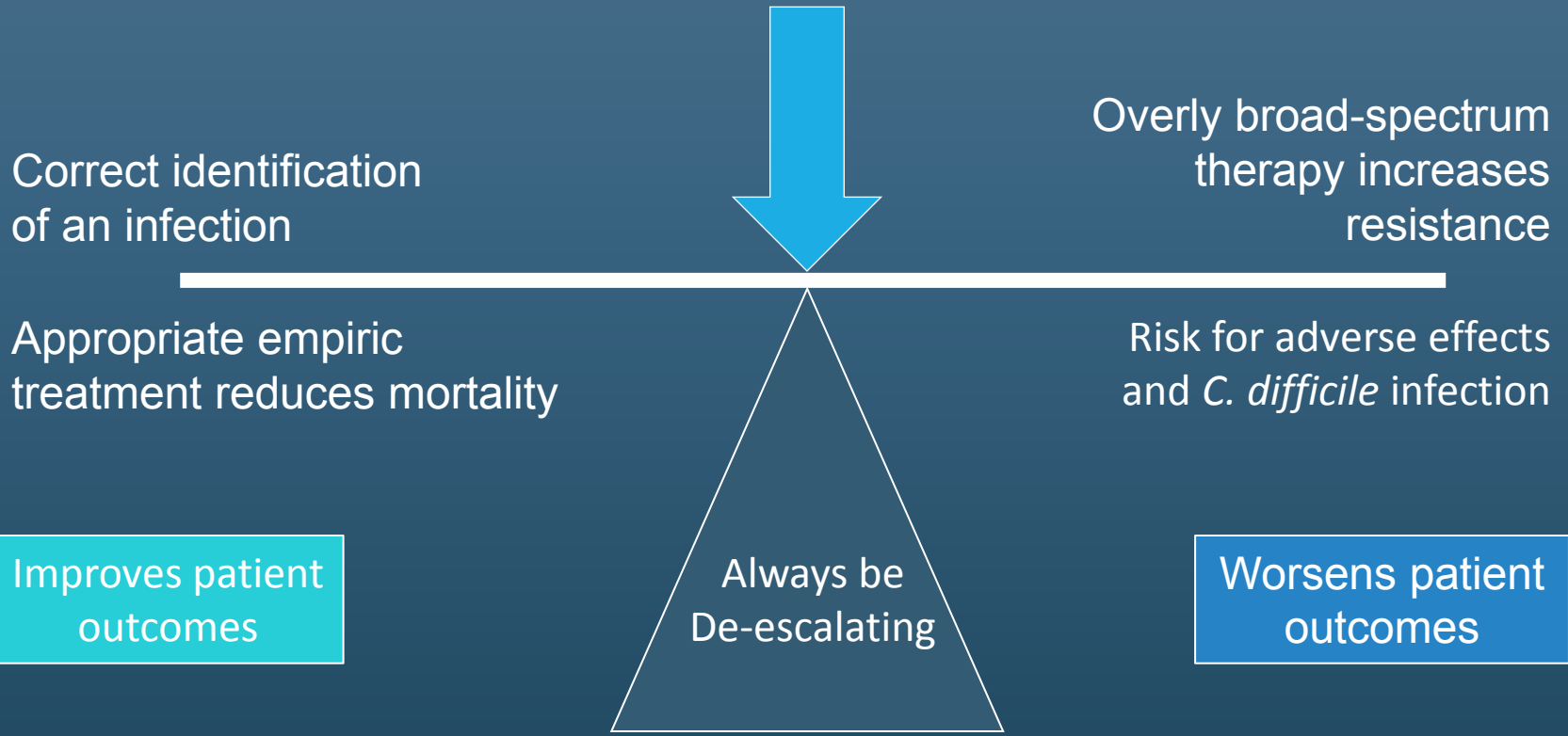
Liu C. *Clin Infect Dis*. 2001;52(3):e18-e55.
Tissot F. *J Infect*. 2014;69:226-34.

Treatment of MSSA Bacteremia

- Vancomycin is inferior to anti-staphylococcal β-lactams and result in greater mortality
  - Once blood culture identified as MSSA de-escalate
  - If β-lactam allergy assess patient ability to tolerate cefazolin or nafcillin
- Cefazolin has shown similar outcomes to nafcillin
  - Less adverse reactions and need to discontinue
  - Less expensive
  - Nafcillin advantage in CNS infection

The Critical Balance

Infection prevention



Conclusions

- Antimicrobial stewardship is designed to help with decisions about the best treatment for the patient
  - Improves clinical outcomes
  - Avoid harm to patients (e.g. *C. difficile*, resistance, adverse drug effects)
- PowerPlans and antibiogram aid in ordering empiric therapy
- De-escalate as soon as possible to the narrowest spectrum drug
- Contact the Antimicrobial Stewardship Team with any questions
  - Pharmacist contact: Ext 6606