CHI Memorial

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Clinical Use Criteria for IV Vancomycin

June 2020

Updated vancomycin dosing guidelines

- Trough-only monitoring is no longer recommended for serious MRSA infections due to increased nephrotoxicity and limited efficacy data

- In patients with suspected or definitive serious methicillin resistant *S. aureus* (MRSA) infection, target AUC/MIC_{BMD} ratio of 400-600
  - Assume MIC_{BMD} of 1mg/L

- Limited evidence at this time to recommend trough-only or AUC-guided dosing for noninvasive MRSA or infections caused by other gram-positive organisms

/ Rybak MJ et al. Am J Health Syst Pharm. 2020;77(11):835-64.

Overuse of IV vancomycin

- Adverse reactions
  - Infusion related reactions (ex: Red man syndrome)
  - Nephrotoxicity
  - Less frequently – neutropenia, ototoxicity (?)

- Drug resistance
  - VRE
  - VISA, VRSA

- Pharmacist time (dose optimization)

- Cost (drug cost & monitoring)

Antimicrobial Stewardship Pharmacist

- Unable to review all patients receiving IV vancomycin
- Theradoc alerts built around positive cultures
  - If no cultures sent or negative cultures, no alert
- Duration report
  - Usually Day 5 (maybe Day 4)
  - But, dose changes can affect duration report – some patients may still be missed

General thoughts

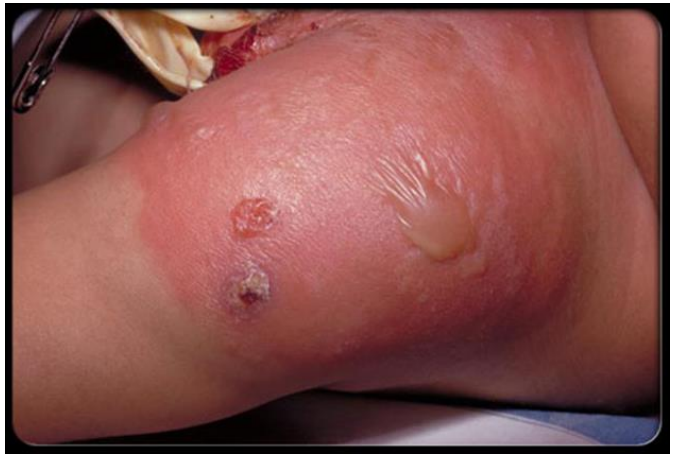
- If high suspicion of *S. aureus* - empiric IV vancomycin appropriate
- Should be discontinued if culture data do not indicate need for definitive therapy
- Few situations when continued use of vancomycin is appropriate in the absence of relevant positive cultures
- Consider source of infection

ABSSSI

Empiric	Recommend D/C in 48-72 hrs.
• Abscess • Diabetic foot/ peripheral vascular disease ulcer • Surgical site infection • Necrotizing fasciitis	• Patient clinically stable & • No microbiologic evidence of drug resistant gram positive infection

Not acceptable:

- Cellulitis - No purulent focus of infection



Bone & Joint Infections

Empiric	Recommend D/C in 48-72 hrs.
• Suspected osteomyelitis or septic arthritis	• Good quality specimen indicates growth of an organism for which vancomycin is not the drug of choice

- Aim for dosing frequencies that are easy for transition into outpatient setting (ex: q12, q24)

Bacteremia

Empiric	Recommend D/C in 48-72 hrs.
• ≥ 2 sets of blood cultures positive for GPC • ≥ 1 set of blood culture positive for GPC in a moderately or severely ill patient	• BioFire results an organism for which vancomycin is not the drug of choice (ex: S. aureus mecA not detected, GBS)

- If MRSA identified via BioFire, aim for dosing frequencies that are easy for transition into outpatient setting (ex: q12, q24)

Table 2: FilmArray™					
Genus	**Species**	**Resistance**		**DOC**	**Action Plan**
Staphylococci	*S. aureus*	-mecA & -vanA/B	MSSA	Cefazolin or Nafcillin	• ID consult per hospital policy • Recommend stopping unnecessary gram negative/antifungal agents if unlikely to be from polymicrobial source • Recommend narrowing to DOC
		+mecA	MRSA	Vancomycin (ALT: Daptomycin)	
		+vanA/B	VRSA	Daptomycin (ALT: Linezolid)	
	Staphylococcus spp.	-mecA		Cefazolin or Nafcillin	• Staph spp. that is not aureus is most often a contaminant (exception: central line or prosthetic implants) • Review objective ID parameters (fever, WBC count etc.) for true infection and determine if patient has prosthetic implants or central line • If most likely a contaminant, notify MD and recommend stopping antibiotics
		+mecA		Vancomycin	
Streptococci	*S. agalactiae* (GBS)			Penicillin, Cefazolin (ALT: Vancomycin)	• Recommend stopping unnecessary gram negative/antifungal agents if unlikely to be from polymicrobial source • Recommend narrowing therapy to DOC • If 1 of 2 Streptococcus spp. (not GBS, S. *pneumoniae*, or GAS) and patient does not seem clinically infected, consider stopping antibiotics as this is most likely a contaminant
	S. pneumoniae			Pneumonia: Ceftriaxone (ALT: Levofloxacin, Vancomycin for patients with severe allergy) Meningitis: Ceftriaxone plus Vancomycin	
	S. pyogenes (GAS)			Penicillin, Cefazolin (ALT: Vancomycin) If pt is severely ill, consider adding clindamycin (↓ toxin production)	
	Streptococcus spp.			Vancomycin, Ceftriaxone	
Enterococci	*Enterococcus spp.*	-vanA/B	VSE	Vancomycin	• Recommend stopping unnecessary gram negative/antifungal agents if unlikely to be from polymicrobial source • Recommend narrowing therapy to DOC • If plan to recommend linezolid, screen for DDIs
		+vanA/B	VRE	Linezolid, Daptomycin (8mg/kg)	

Severe Sepsis of Unclear Source

Empiric	Recommend D/C in 48-72 hrs.
• Known MRSA colonization • Indwelling hardware/ catheter • Transfer from LTCF • Injection drug use • Recent hospitalization or current prolonged hospitalization • Hemodynamically unstable	• Patient clinically stable & • If source identified, use source related guidance to recommend vancomycin D/C or • If no source identified, and no microbiologic evidence of drug resistant gram positive infection

Endocarditis/meningitis

	Empiric	Recommend D/C in 48-72 hrs.
Endocarditis	• Suspected endocarditis	• Blood culture (BioFire) results an organism for which vancomycin is not the drug of choice
Meningitis	• Suspected meningitis	• CSF fluid analysis (normal) • If CSF fluid abnormal & BioFire results an organism for which vancomycin is not the drug of choice (ex: *N. meningitidis*, *L. monocytogenes*, *H. influenzae*)

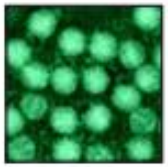
- Endocarditis: if MRSA identified via BioFire, aim for dosing frequencies that are easy for transition into outpatient setting (ex: q12, q24)

FilmArray® Meningitis/Encephalitis Panel

1 Test. 14 Targets. All in about an hour.

Bacteria

Escherichia coli K1
Haemophilus influenzae
Listeria monocytogenes
Neisseria meningitidis
Streptococcus agalactiae
Streptococcus pneumoniae



Viruses

Cytomegalovirus (CMV)
Enterovirus
Herpes simplex virus 1 (HSV-1)
Herpes simplex virus 2 (HSV-2)
Human herpesvirus 6 (HHV-6)
Human parechovirus
Varicella zoster virus (VZV)

Fungi

Cryptococcus neoformans/gattii

Table 1. Typical Lumbar Puncture CSF Findings

Measure	Normal	Viral Meningitis	Bacterial Meningitis
Opening pressure (mmH_2O)	<180	<180	>180
Protein (mg/dL)	<40	Normal or <100	>100-200
Glucose (nmol/L)	≥2.5	≥2.5	<2.2
CSF glucose/serum glucose	≥0.6	≥0.6	<0.4
WBC (count/mm^3)	≤5	<1,000	>1,000
WBC differential	70% lymphocytes, 30% monocytes	MNLs	Mainly PMNLs
Gram stain (%)	None	NA	75-90
Positive culture (%)	None	NA	>70-85
PCR	NA	EVs, HSV, VZV, EBV	Test for *N meningitidis*, *S pneumoniae*, *H influenzae*; technique needs refinement

Biliary Tract Infections

Cholecystitis

- Inflammation of gallbladder & ducts
- Localized signs/ symptoms

Cholangitis

- More severe manifestation, includes more diffuse inflammation & systemic signs of infection

Usually MONOmicrobial

- Consider site of acquisition, anatomic defects, severity of illness

Intra-abdominal infection - primary peritonitis

Infection of the peritoneal space without identifiable source or injury

- Spontaneous Bacterial Peritonitis (SBP)

- Risk factors:

  - **Acute gastrointestinal hemorrhage**, for 7 days after the start of the hemorrhage

  - Ascites along with impaired liver or renal function & elevated protein level

Primary Peritonitis

MONOmicrobial

- 70% aerobic gram negative bacilli
  - ***Proteus, E. coli,* and *Klebsiella***.
  - *Streptococcus* species, such as *Streptococcus pneumoniae* and viridans group streptococci
- Anaerobes RARE

Secondary Peritonitis

Infection resulting from an identifiable source

- Trauma, surgery, perforation
- Bowel necrosis
  - Obstruction, vascular compromise
- Severe inflammation
  - Appendicitis, pancreatitis

POLYmicrobial

- Empirically cover aerobic & anaerobic gram-negative bacilli +/- targeted pathogens
  - *Pseudomonas*, *Enterococcus*, *Staphylococcus*, *Candida*
  - Consider setting of acquisition, severity of illness

Intra-abdominal infections

Empiric	Recommend D/C in 48-72 hrs.
• Healthcare-associated secondary peritonitis *Known colonizer of MRSA *Recent abdominal surgery *Recent broad spectrum antibiotic use • Severe secondary peritonitis *Patient hemodynamically unstable • Peritoneal dialysis related peritonitis	• Patient clinically stable & • No microbiologic evidence of drug resistant gram positive infection

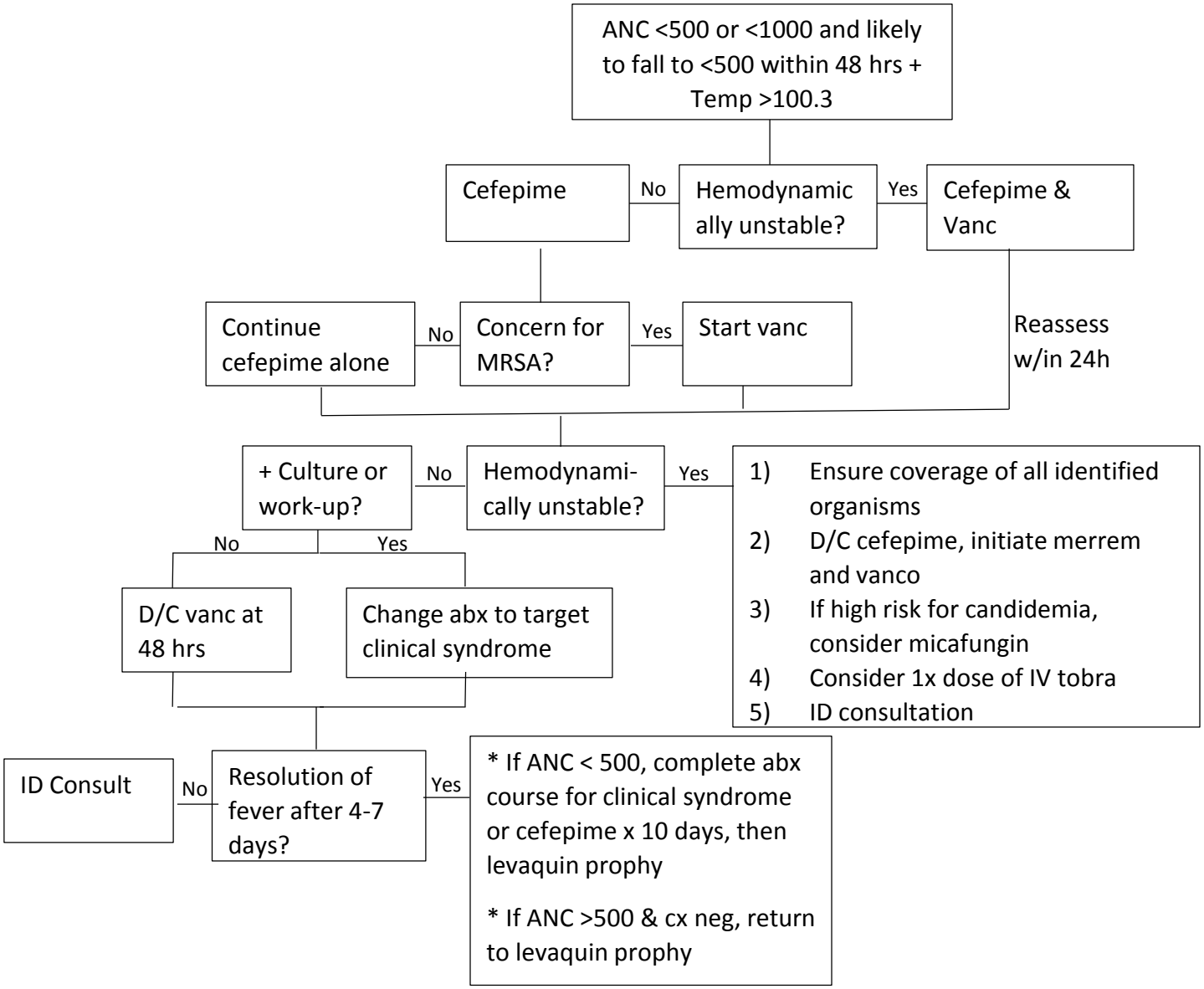
Not acceptable:

- Primary peritonitis (SBP)
- Biliary tract infection
- Uncomplicated community-acquired intra-abdominal infection

Neutropenic Fever

Empiric	Recommend D/C in 48-72 hrs.
Suspected • Catheter-related infection • Skin or soft-tissue infection • Pneumonia Hemodynamic instability	• Patient clinically stable • No microbiologic evidence of drug resistant gram positive infection

- If cultures positive w/ a suspected pathogen, antibiotics should be targeted at that organism
- If clinically stable, good quality cultures completed but negative – consider stopping IV vancomycin


ANC <500 or <1000 and likely to fall to <500 within 48 hrs + Temp >100.3
Cefepime
No
Hemodynamically unstable?
Yes
Cefepime & Vanc
Continue cefepime alone
No
Concern for MRSA?
Yes
Start vanc
Reassess w/in 24h
+ Culture or work-up?
No
Hemodynamically unstable?
Yes
1) Ensure coverage of all identified organisms
2) D/C cefepime, initiate merrem and vanco
3) If high risk for candidemia, consider micafungin
4) Consider 1x dose of IV tobra
5) ID consultation
No
Yes
D/C vanc at 48 hrs
Change abx to target clinical syndrome
ID Consult
No
Resolution of fever after 4-7 days?
Yes
* If ANC < 500, complete abx course for clinical syndrome or cefepime x 10 days, then levaquin prophy
* If ANC >500 & cx neg, return to levaquin prophy

Pneumonia – HAP/VAP

- Hospital acquired PNA (HAP):
  - >48h after admission, not incubating at the time of admission
  - ~ 5-10 cases/1000 admissions

- Ventilator-associated PNA (VAP):
  - Subset of HAP that develops >48-72h after intubation
  - ~6.5-10 cases/1000 ventilator-days

- Add MRSA agent if:
  - Patients being treated in units where >20% of *S. aureus* isolates are methicillin resistant **OR**
  - Use of IV abx in the past 90 days **OR**
  - High risk of mortality: Requiring ventilator support due to pneumonia and septic shock

Richards MJ, et al. Crit Care Med 1999; Richards MJ, et al., ICHE 2000; Chastre and Fagon Am J Resp Crit Care Med 2002; Klevens RM, et al. Public Health Rep. 2007 Mar-Apr; 122(2): 160–166.

Healthcare-associated pneumonia

- Any one of the following risk factors:
  - Residence in a nursing home and other long-term care facilities
  - Hospitalization for ≥ 2 days in last 90 days
  - Home infusion therapy
  - Chronic dialysis
  - Home wound care
  - Family member with a known antibiotic-resistant pathogen

CAP guidelines & DRP risk factors

Inpatient PNA	Standard regimen	Prior Resp. Isolation of MRSA or *P. aeruginosa* within the prior year	Recent hospitalization (90 days) & IV antibiotics & locally validated risk factors for MRSA & *P. aeruginosa*
Nonsevere	β-lactam + macrolide OR respiratory quinolone	Add coverage against MRSA or P. aeruginosa and obtain cultures and/or nasal MRSA PCR(if anti-MRSA drug added) to allow for de-escalation	Obtain cultures and/or nasal PCR (MRSA) but initiate treatment only if culture results are positive
Severe	β-lactam + macrolide OR β-lactam + respiratory quinolone		Add coverage against MRSA or P. aeruginosa and obtain cultures and/or nasal MRSA PCR (if anti-MRSA drug added) to allow for de-escalation

Respiratory cultures both campuses (Jan-Oct 19)

- Total inpatient respiratory cultures submitted: 1576
  - MRSA: 92/1576 (6%)
  - *P. aeruginosa*: 93/1576 (6%)
  - Ceftriaxone R gram negative: 135/1576 (9%)

- Total number of cultures set up for ID and sensitivity: 349 (22%)
  - MRSA: 92 (26%)
  - *Pseudomonas aeruginosa*: 93 (27%)
  - Ceftriaxone R gram negative: 135 (39%)

*Same patients could have had MRSA &/or *P. aeruginosa* &/or ceftriaxone R gram negative

"HCAP" at Memorial

- Many patients receiving vancomycin & cefepime/pip-tazo do not need it

- No validated scoring system
  - Available systems may not be a good fit for our patient population

- The most consistently strong individual risk factors for respiratory infection with MRSA or *P. aeruginosa* are:
  - Prior isolation of these organisms, especially from the respiratory tract, and/or
  - Recent hospitalization and exposure to parenteral antibiotics

CAP at Memorial

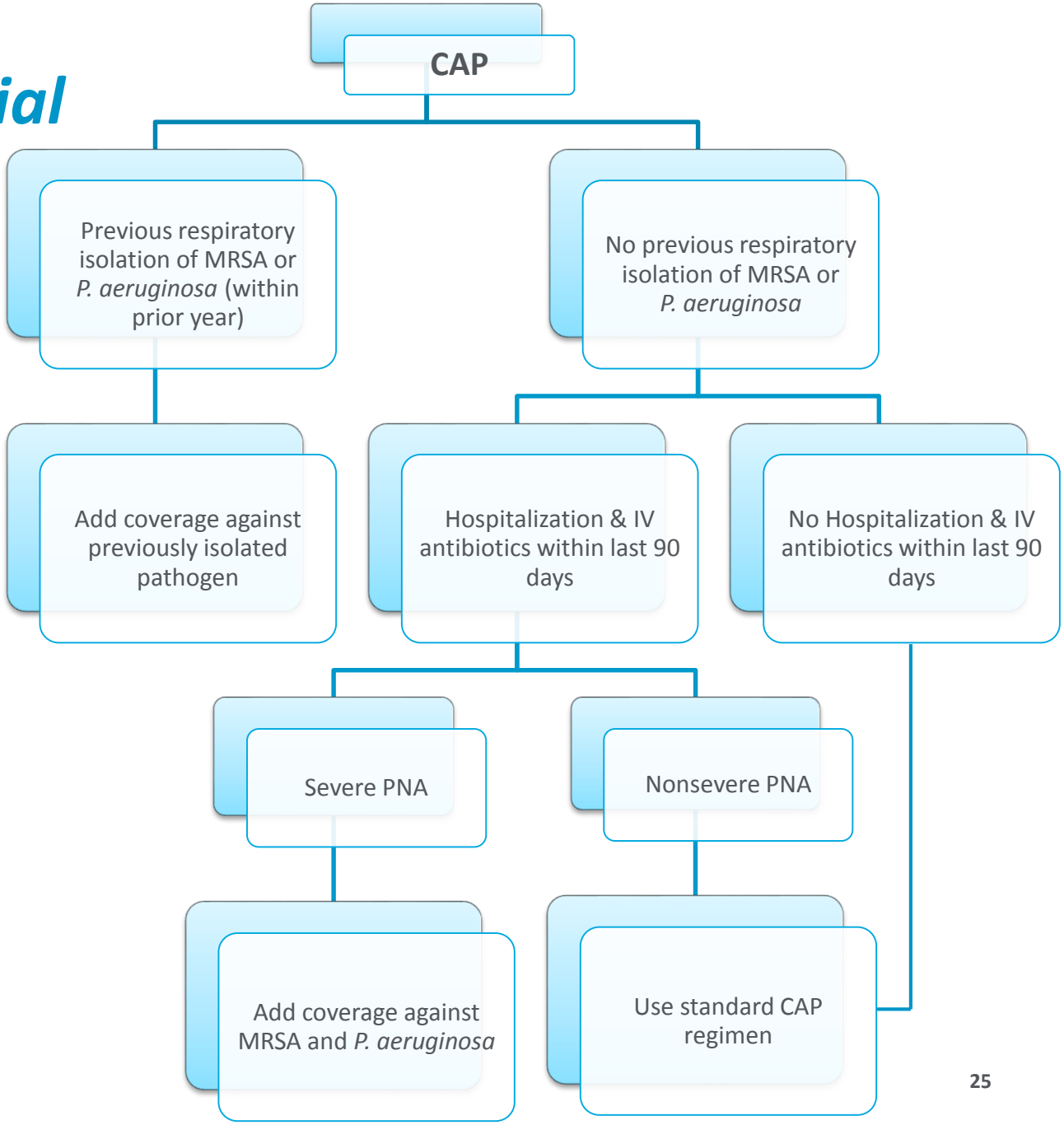
Severe PNA: 1 major criterion or ≥ 3 minor criteria

Major:
- Septic shock w/ vasopressor need
- Resp failure requiring mechanical ventilation

Minor:
- Respiratory rate ≥ 30 breaths/min
- PaO2/FiO2 ratio ≤ 250
- Multilobar infiltrates
- Confusion/disorientation
- Uremia (BUN level ≥ 20)
- Leukopenia (WBC < 4k)
- Thrombocytopenia (Platelet <100k)
- Hypothermia (temp <36°C)
- Hypotension requiring fluid resuscitation

If anti-MRSA drug initiated:
- MRSA nasal PCR
- Sputum & blood cultures

If anti-pseudomonal agent initiated:
- Sputum & blood cultures



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De-escalation from empiric IV vanco - PNA

- MRSA nasal PCR
  - Parente, DM, et al. Meta-analysis published in CID (2018)
  - 22 studies; n=5163
  - CAP & “HCAP” – NPV: 98.1% & PPV: 56.8%
  - VAP – NPV: 93.7% & PPV: 40.3%

- P&T approved – pharmacists can order MRSA nasal PCR on patients who are empirically started on IV vancomycin for pneumonia

Parente DM, et al. *Clin Infect Dis.* 2018; 67(1):1-7.

Pneumonia

Empiric	Recommend D/C in 48-72 hrs.
• HAP, VAP • CAP in patients with previous (within 1 year) respiratory isolation of MRSA • Severe CAP in patients with hospitalization & IV antibiotics in past 90 days • CAP in patients with necrotizing or cavitary infiltrates, empyema	<u>Respiratory cultures obtained</u> • Good quality respiratory culture growing alternate (non-MRSA) organism • Good quality respiratory culture within 48 hrs of antibiotics with no growth <u>No respiratory culture obtained</u> • Patient clinically improving • MRSA nares swab negative within 48 hours of antibiotics & prior to mupirocin decolonization • Chest imaging – not suggestive of empyema or cavitary infiltrates

Acceptable definitive use of vancomycin

- Proven infection with beta-lactam resistant organisms
  - MRSA
  - Methicillin-resistant Coagulase-Negative Staphylococcus
  - Ampicillin-resistant Enterococcus spp.
  - Ceftriaxone-resistant Streptococcus spp.

- Treatment of infections caused by gram-positive organisms in patients who have serious allergies to β-lactam agents

Daily review of IV vancomycin's clinical appropriateness

- Vancomycin ***continuation*** smart text will be updated to include a clinical evaluation section
- First shift pharmacist performing kinetics monitoring would be expected to complete this and make necessary recommendations to providers
  - Stewardship pharmacists will be more than happy to help you with any cases you'd like to discuss!
- Second & third shift will not be expected to perform this review or make interventions
- Once everyone is trained, Jeff will update this in EPIC and I will send out an e-mail

Daily review of IV vancomycin's clinical appropriateness

- Vancomycin continuation note updates: *Please use this as a guideline and feel free to modify as it fits your particular patient*
  - Empiric/Definitive (select one) therapy for *** (free text source of infection)
  - If source is pneumonia: MRSA nasal PCR ordered/detected/not-detected (select one)
  - Plan to recommend d.c. ~ 48 hours if *** (free text, ex: blood cultures negative, MRSA nasal PCR not detected etc.)
  - If IV vancomycin appropriate definitive therapy: Expected duration of therapy (days) = ***
  - Maintenance dose and plan (levels, f/u, etc): ***
  - Pharmacy will continue to follow

Daily review of IV vancomycin's clinical appropriateness

- Vancomycin continuation note example:
  - Empiric therapy for Pneumonia
  - MRSA nasal PCR ordered
  - Plan to recommend d.c. if MRSA nasal PCR not detected and no cultures with a drug resistant gram positive organism (feel free to remove this statement from the posted note piece if you're not comfortable with it; would keep it in the ivent so next pharmacist is aware of your plan)
  - Maintenance dose and plan: 1g IV q12h
  - Pharmacy will continue to follow

Cases

- BH is a 45 year old obese male with a PMH significant for hyperlipidemia who presents to the ER with a 3 day history of a hot to touch, red, swollen left lower leg. He reports bumping it on a metal table a week ago. He wasn't able to visualize if it had broken the skin at that time, but because the pain had quickly gone away he had actually forgotten that he bumped it. BH has no other comorbidities.

- The erythema is measuring ~ 5 cm long and wraps around his whole lower leg and the patient reports that it has been getting worse over the past day and a half. He cannot bear weight very much without extreme pain.

- The ER draws some blood to send for chemistries, CBC and blood cultures.
- His temperature is: 100.5 F BP=125/80 HR=80 RR=12 Pain (resting) =3/10 Pain (bearing weight) =8/10 WBC = 17K

Cases

1. What is the source of infection for this patient?

2. Would we use IV vancomycin in this patient? If not, what would be the drug of choice?

3. Do we order the MRSA nasal PCR if IV vancomycin was empirically started?

Cases

1. What is the source of infection for this patient?
    1. Non-purulent cellulitis

2. Would we use IV vancomycin in this patient? If not, what would be the drug of choice?
    1. No, this is most likely to be caused by strep. Drug of choice is ancef

3. Do we order the MRSA nasal PCR if IV vancomycin was empirically started?
    1. No, MRSA nasal PCR has been the most well studied in pneumonias and we should only be ordering it in patients with a pneumonia who are started on IV vanco

Cases

CA is an 80 yo male with a history of HTN, DM who presents from a nursing home with fevers and cough. In the ED he is intermittently confused. His vitals/labs in the ED: T 101F, WBC 14.2, HR 110, RR 31, O2 sat 93% of 4L NC. His CXR shows a LLL infiltrate. He reports no allergies to antibiotics. He is admitted to the medical floor of the hospital.

Based on the new IDSA pneumonia guidelines, what antibiotics would you recommend for CA?

Cases

Ceftriaxone & azithromycin. We would not recommend IV vancomycin & cefepime despite the fact that patient is coming from a nursing home because this is no longer a risk factor that the IDSA guidelines recommend using to determine need for anti-MRSA/anti-Pseudomonal therapies

Cases

Regardless of what you recommend, patient is empirically started on IV vancomycin and cefepime. Sputum culture is ordered but patient is unable to produce sputum so none collected.

What would you do at this time?

Cases

Regardless of what you recommend, patient is empirically started on IV vancomycin and cefepime. Sputum culture is ordered but patient is unable to produce sputum so none collected.

What would you do at this time?

Order the MRSA nasal PCR and recommend d.c vancomycin if negative!

Cases

AS is a 56 year old male who was admitted 13 days ago for coronary artery bypass surgery. Post CABG the patient had slow recovery and remained in the ICU. Two days ago, AS developed a fever (Tmax: 101.5F), hypoxemia requiring intubation, WBC= 14.2, abundant purulent tracheal secretions, and a CXR revealing localized infiltrate in RLL. Scr 1.8mg/dL, Weight = 98kg. A BAL has been sent to the lab. The team would like to initiate empiric antibacterial therapy.

What do you recommend?

How can we de-escalate?

Cases

- Cefepime and IV vancomycin (empiric VAP therapy)

- Although you could order the MRSA nasal swab for this patient, remember that the negative predictive value of this test in patients with VAP is lower (~93%). Since you already have a BAL culture that is pending, would await those results and recommend de-escalation if negative for MRSA.

Cases

RG is a 42 year-old patient who presents to the ED with a history of poorly controlled diabetes. He presents with acute pain from a right foot chronic ulcer, increased purulent foul smelling drainage and the ulcer has gotten wider and deeper in the last few weeks. Recently completed a course of Augmentin as an outpatient with no improvement. He is admitted to the hospital for management of a severe diabetic foot infection and workup of potential osteomyelitis.

What regimen would you recommend empirically?

How can we de-escalate?

Cases

- Vancomycin/zosyn (Chronic infected diabetic foot ulcer s/p outpatient antibiotic therapy)

- De-escalation/stopping IV vancomycin depends on plans for debridement or other surgical intervention. If debridement, we'll need to wait for cultures. If they amputated the source due to osteo and achieved clean margins – you can actually recommend stopping abx 48 hours post surgery

Cases

LB is a 76 year old male who is admitted to CVICU after a cardiac arrest and prolonged resuscitation. Upon admission to the unit, his procalcitonin is 40, WBC is 15, Tmax 100.0 and he has developed hypotension refractory to fluid resuscitation. His chest X-ray shows edema & blood cultures/ a UA with reflex to urine culture has been ordered. The intensivist empirically begins antibiotic treatment with IV vancomycin and zosyn.

How can we de-escalate?

Cases

- At 48 hours, review culture data, imaging data, & provider notes. If no source of infection identified and no positive cultures with a resistant gram positive organism, recommend d/c vancomycin. If a source has been identified, use source specific guidance for de-escalation.

Thank You!

Questions?