Staphylococcus aureus

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Infectious Disease Attending
BUMC-P

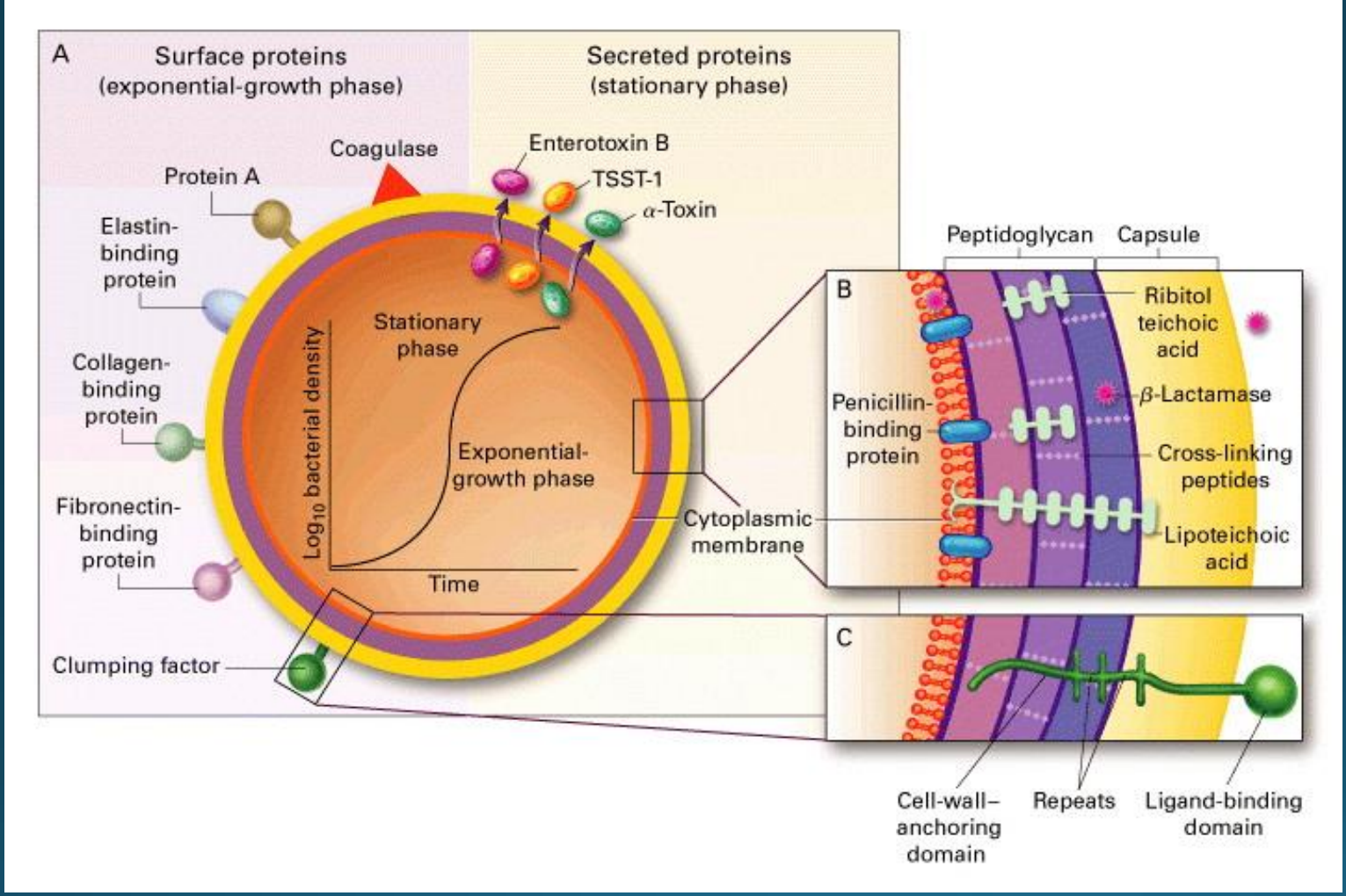
Staphylococcus aureus

- Microbiology /pathogenesis
- Case presentation
- Teaching points
- Updates

Staphylococcus aureus

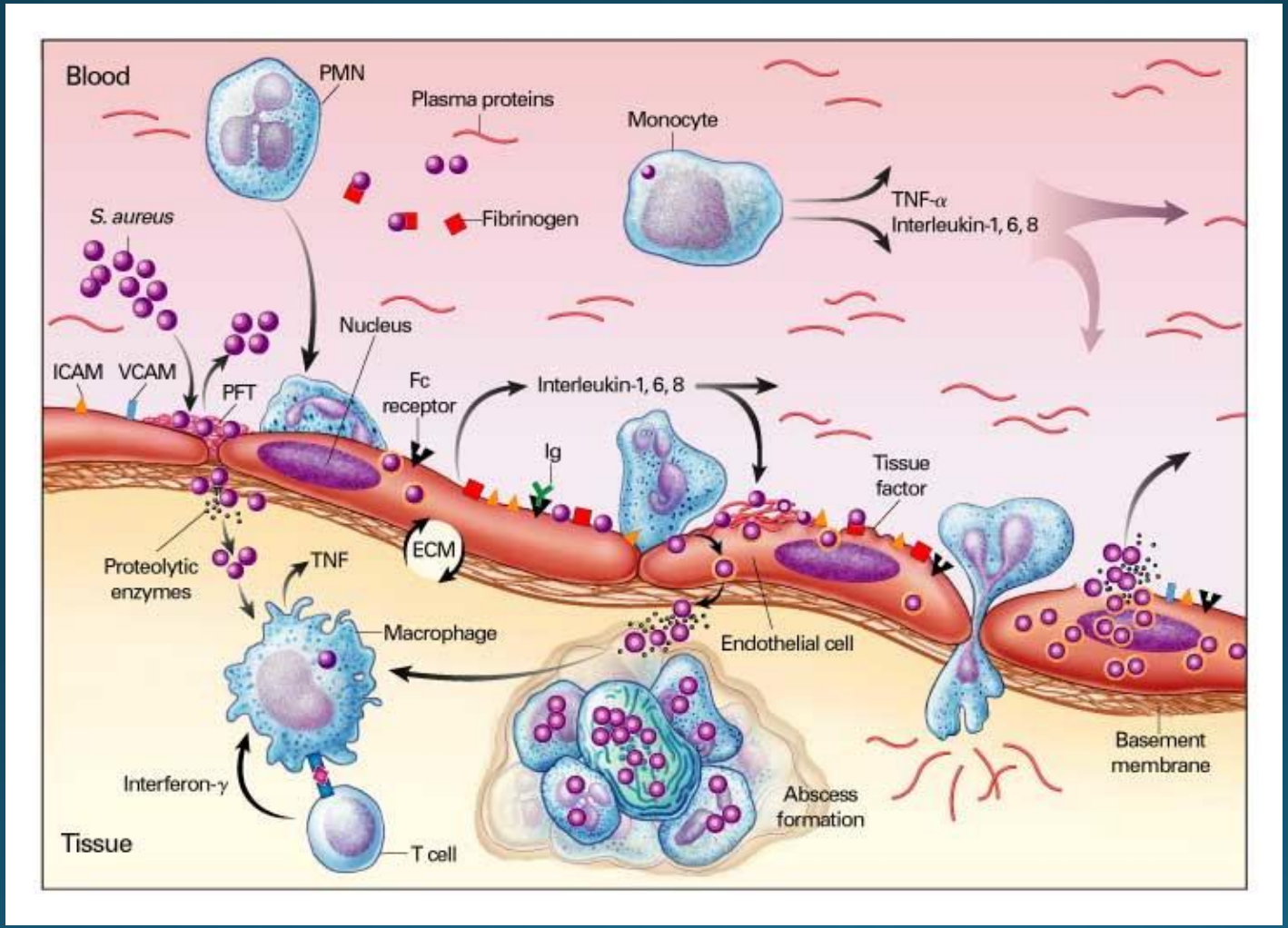
- Gram positive cocci in clusters
- Catalase and coagulase positive
- Frequent colonizer asymptomatic carriers -20-40% normal population in anterior nostrils
- Responsible for both pyogenic and toxin related diseases
- Primary cause of community and hospital acquired blood stream infections
- First cause of many invasive infections including infective endocarditis and osteomyelitis

Structure of *S. aureus*.



Lowy FD. N Engl J Med 1998;339:520-532.

Pathogenesis of Staphylococcal Invasion of Tissue.



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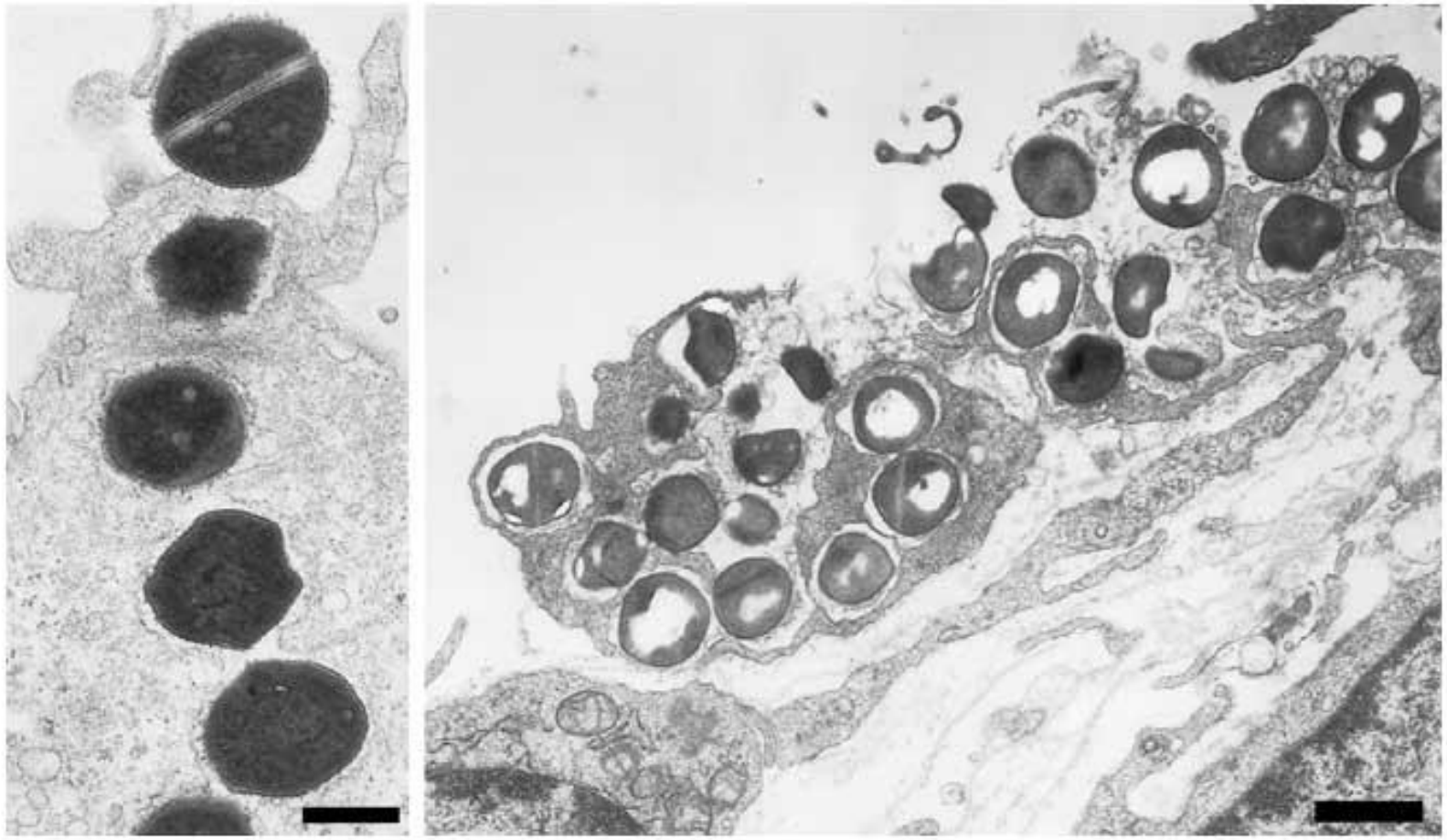
The NEW ENGLAND JOURNAL of MEDICINE

Endothelial-Cell Phagocytosis of *S. aureus* in Vitro.



Lowy FD. N Engl J Med 1998;339:520-532.

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Case presentation

67-year-old woman , history of lupus erythematosus diagnosed over 10 years ago on prednisone and Humira was admitted to an outside hospital where she presented complaining of abdominal pain and right arm swelling.

At baseline she was able to do basic ADLs she worked as a first grade teacher at school has been having right arm pain and weakness about 3 weeks before presentation and also noted that she was dragging her right leg around a reported new lower back pain the abdominal pain started the day of admission about 30 minutes before breakfast.

Remarkable medical history SLE osteoarthritis right total knee replacement in June 2017 uses daily prednisone and Humira

At an outside facility her vitals were 36.8 temperature heart rate 82 respiratory rate 18 blood pressure 128/76 labs included glucose 234 sodium 124 potassium 4.2 bicarbonate 18 chloride 93 albumin 2.2 globulin 4.9T bili 1 BUN 20 creatinine 1.0 AST 30 ALT 13

WBC 21.7 hemoglobin 8.3 platelets 285

ST elevation MI on the EKG

CT head with contrast no intracranial bleed chronic age-related small vessel ischemic change no territorial infarct

CT angiography chest no PE dissection or aneurysm in the chest

CT abdomen and pelvis with contrast: kidney and spleen infarcts.

Outside blood cultures growing gram-positive cocci in clusters

Received a dose of vancomycin and Zosyn and transferred to Banner University Medical Center for higher level of care

QUESTION
What antibiotic would you use?

If patient would have reported allergy to nafcillin and cefazolin itching. Attempted to rechallenge , intense itching after a few minutes

1	Staphylococcus aureus		
2		MDIL	MINT
3	Ox/Nafcillin	<=0.25	S
4	Tetracycline	<=1	S
5	Erythromycin	0.5	S
6	Clindamycin	0.25	S
7	Trimethoprim/Sulfa	<=10	S
8	Vancomycin*	2	S

CID, vol 52,Issue 3, 1 February 2011, pages e18-e55

QUESTION
Our patient was not allergic to PCN

- What antibiotic would you have used.

  Nafcillin or cefazolin ?

Inoculum effect-overwhelming MSSA use nafcillin

- The Cefazolin Inoculum Effect is Associated With Increased Mortality in MSSA Bacteremia. Miler et al. Open Forum Infectious Diseases,Vol 5,Issue 6,June 2018, ofy 123
- McDaniel et al. Comparative Effectiveness of cefazolin Versus Nafcillin or Oxacillin for treatment of MSSA Infections Complicated by Bacteremia: A Nationwide Cohort Study. CID, Vol 65, Issue 1, 1 July 2017, pages 100-106
- Comparative Evaluation of Tolerability of Cefazolin and Nafcillin for Treatment of MSSA Infections in the outpatient setting. Yougster et al. CID, Vol 59,Issue 3,August 2014, Pages 369-75

Cefazolin (Ancef) vs. Nafcillin Utilization in MSSA Infections

Historically for MSSA infections, anti-staphylococcal penicillins (ASP) such as nafcillin have traditionally been the first line antibiotic therapy for MSSA infections including bacteremia.[1,2] Studies have demonstrated that cefazolin has similar efficacy compared to ASP with a better tolerability profile. Based upon a drug-utilization evaluation (DUE) completed at our facility, approximately 55% of patients were eligible to receive cefazoline as a first line agent.

Cefazolin is an appropriate **first line agent** for MSSA infection for patients **without** the following:

- CNS involvement
- Deep-seated infection (Epidural abscess/Endocarditis) – inoculum effect has been documented in vitro/vivo when cefazolin used
- Cephalosporin allergy

Pros/Cons for Administration of Cefazolin

Pros	Cons
Better side effect profile, nafcillin associated with • Hypokalemia • Transaminitis/hyperbilirubinemia	Inoculum effect- limited data for deep-seated infections
Less frequent dosing Cefazolin: 2gm IV q8h vs. Nafcillin 2gm IV q4h or continuous infusion	Poor CNS penetration
Ready-to-use bag, less time for medication preparation	

MIC Interpretation

- When cultures return for an MSSA infection with susceptibility to oxacillin/nafcillin, this also means cefazolin can be used for treatment. If contraindications do not exist, cefazolin can be used for MSSA infections.

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

	A	B	C
1	Staphylococcus aureus		
2		MDIL	MINT
3	Ox/Nafcillin	0.5	S
4	Erythromycin	>=8	R
5	Clindamycin		R
6	Trimethoprim/Sulfa	<=10	S

References:

1. Li, J, Echevarria KL, Traugott KA. Beta-lactam therapy for methicillin-susceptible staphylococcus aureus bacteremia: a comparative review of cefazolin versus antistaphylococcal penicillins. Pharmacotherapy 2017;37:346-360.

2. McDanel JS, Roughmann MC, Perencevich EN et al. Comparative effectiveness of cefazolin versus nafcillin or oxacillin for treatment of methicillin-susceptible staphylococcus aureus infections complicated by bacteremia: A nationwide cohort study.

3. Miller WR, et al. The Cefazolin Inoculum Effect is Associated with Increased Mortality in Methicillin Susceptible Staphylococcus aureus Bacteremia. OFID;5:1-8.

Case presentation

- Blood cultures 4/4 Staphylococcus aureus. MSSA
- MRI brain Demonstrated extensive small to moderate acute patchy cerebral and left cerebellar infarcts with possible petechial hemorrhage consistent with septic emboli
- At arrival BUMCP physical exam. Patient alert oriented ×3 tachycardic 112 blood pressure 93/60 temperature 37.4 O2 sat 98% on 2 L
- Eyes with normal conjunctivae HEENT poor dentition with dentures in place. Neck supple
- Lungs clear to auscultation cardiovascular tachycardic +murmur
- Abdomen diffusely soft nontender musculoskeletal swelling of the right upper extremity with severe tenderness to palpation in the area of the wrist. Encephalopathic, Janeway lesions in bilateral palms and soles neurologic encephalopathic following commands inconsistently

QUESTION

- Is this complicated vs uncomplicated bacteremia?. Why?
- TTE vs TEE?

Complicated vs Uncomplicated Bacteremia- Duration of Treatment

- Uncomplicated bacteremia

-Neg blood cultures 2-4 days

-Exclusion of endocarditis

-No implanted prosthesis

-Follow up blood cultures obtained 2-4 days after initial set that do not grow MRSA

-Defervescence within 72 h of initiating effective therapy

-No evidence of metastatic infection

*clinical assessment to identify source and extent of infection

SOURCE CONTROL

- Complicated bacteremia

-Patients with positive blood cultures who do not criteria for uncomplicated bacteremia

CID 2011:52 (1 February)

Echocardiography

- TEE is preferred in adults with SA bacteremia because of its superiority , compared with TTE, for detection of vegetations and identification of complications (intra cardiac abscess and valvular complication)

Fowler VG Jr. et al. Role of echocardiography in evaluation of patients with staphylococcus aureus bacteremia: experience of 103 patients .J Am Coll Cardiol 1997;30:1072-8

Sullenberger AL et al . Importance of trans esophageal echocardiography I the evaluation of Staphylococcus bacteremia. J Heart Valve Dis 2005;14:23-8

Abraham et al. Staphylococcus aureus bacteremia and endocarditis: the Grady Memorial Hospital experience with methicillin sensitive S. aureus and methicillin resistant S. aureus bacteremia. Am Heart J 2004; 147:536-9

Reynolds HR et al. Sensitivity of transthoracic versus trans esophageal echocardiography for detection of native valve vegetations in the modern era. J. Am Soc Echocardiogr 2003; 16:67-70

Echocardiography

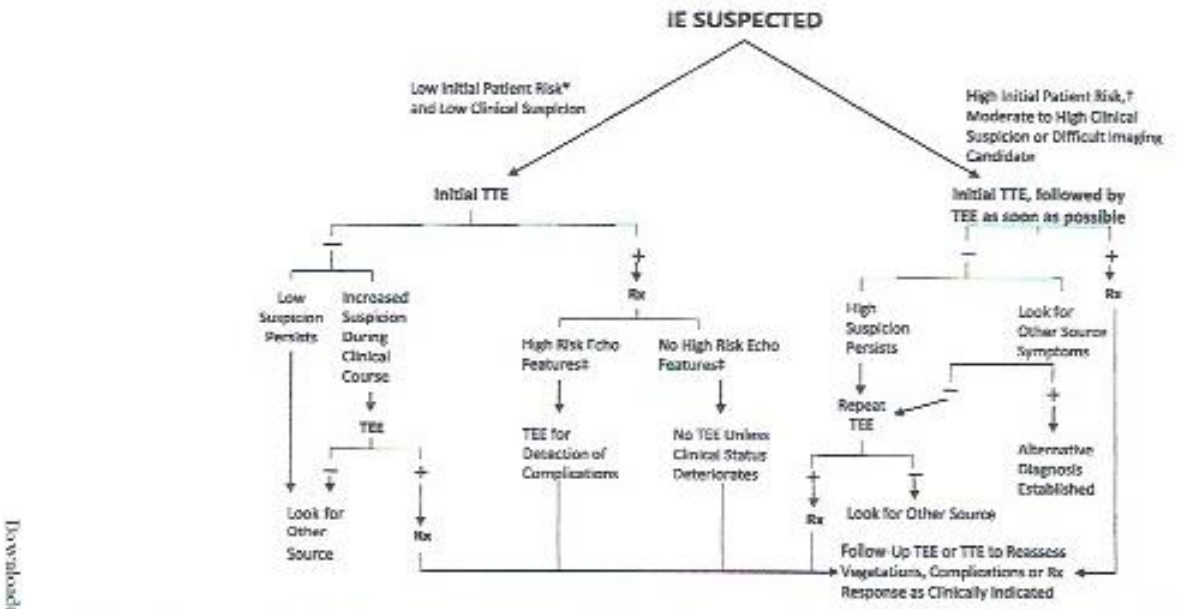


Figure. An approach to the diagnostic use of echocardiography (echo). Rx indicates prescription; TEE, transesophageal echocardiography; and TTE, transthoracic echocardiography. *For example, a patient with fever and a previously known heart murmur and no other stigmata of infective endocarditis (IE). †High initial patient risks include prosthetic heart valves, many congenital heart diseases, previous endocarditis, new murmur, heart failure, or other stigmata of endocarditis. ‡High-risk echocardiographic features include large or mobile vegetations, valvular insufficiency, suggestion of perivalvular extension, or secondary ventricular dysfunction (see text). Modified from Baddour et al.[12]

Endocarditis management Circulation; 2015; 132:1-53

Case presentation

- Cardiac cath showed possible mitral valve and aortic valve endocarditis and high suspicion for septic emboli there was a distal LAD clot- underwent thrombectomy

- TTE showed an LV ejection fraction 50-55% grade 1 diastolic dysfunction moderate calcification of the mitral valve leaflets small filament echodensity visualized on the mitral valve moderate mitral stenosis moderate mitral regurgitation

- A TEE with mitral valve and aortic valve vegetations. Normal LV function moderate mitral regurgitation, moderate TR. Mitral valve in anterior 0.4 x 0.5 cm leaflet and string filament-like material and posterior leaflet 1.1 cm x 0.2 cm vegetations visualized. Mild aortic insufficiency observed. Presence of string filament-like vegetation visualized in the left coronary cusp. No PFO

Case presentation

The cardiac cath was consistent with an acute occlusion of distal LAD status post aspiration thrombectomy ×2 with aspiration of white particular matter and the plan was for IV antibiotics no anticoagulation given risk of hemorrhagic conversion no indication given septic emboli .It was thought to be a septic emboli and not a thrombotic occlusion

Patient was bacteremic for 4 -5 days orthopedic team evaluated the patient and debrided bedside an I&D of the right elbow septic olecranon bursa .Culture bursa + MSSA , aspiration of the right wrist, cell count was not consistent with infection. Patient's mental status improve cardiothoracic surgery examined her determined that she was not a surgical candidate orthopedic team also recommended a conservative management

Cardiothoracic surgery consult?-surgery indications?

Surgical indications Native valve endocarditis

Complex decision and depend on many clinical and prognostic factors

-Valve dysfunction resulting in signs/symptoms of heart failure

-IE caused by fungi or highly R organisms

-IE complicated by heart block, annular or aortic abscess

-Persistent infection (5-7d)provided that other sites infection excluded

-IE + recurrent emboli and persistent or enlarging vegetations despite appropriate ATB

-Severe valve regurgitation and mobile > 10 mm vegetations

-mobile vegetations > 10 mm, particularly when involving anterior leaflet MV and associated with other relative indications for surgery

- Timing of surgery following stroke

- ICH. Surgery delayed one month

-Ischemic stroke. Surgery does not need to be delayed if there are indications for surgery

Circulation. 2015, 132:1435-1486
NEJM 2012. 366:2466-2473

Hospital course

- Hospital Day 5-7 : Continues to be febrile, WBC 20 K encephalopathic. Day number 5 weaned off pressors. Repeat head CT with new areas of infraction L frontal and R posterior circulation
- Blood cx + MSSA Day number 4. At Day #4/ 5 added daptomycin to nafcillin
- Neurology, ID recommending re evaluation CTS although unlikely to be able to withstand open heart surgery given co morbidities. Patient initially declined blood products

QUESTION

What is persistent bacteremia?what options for treatment?

- Add gentamicin?
- add daptomycin?
- Add rifampin?

Persistent bacteremia

- Positive blood cultures > 7 days after initiation of vancomcyin (1)
- Positive blood cultures at or after 3-4 days bacteremia

1. CID 2011:52 (1 February)
2. CID 2007;44(12):1453
   CID 2006;43 (5)e 42
   J Antimicrob Chemother.2016;71 (3):576
   CID. 2014;59(10):1455
   CID 2019 ciz257 https://doi.org/10.1093/cid/ciz257

Persistent bacteremia

What is persistent bacteremia? Options for treatment?

- Add rifampin?
- Add gentamicin?
- ***add daptomycin***

Geriak et al. Clinical Data on Daptomycin plus cefatroline versus Standard of Care Monotheraoy in the Treatment of MRSA bacteremia .Antimicrob Agents Chemother 63 e 02482-18. May 2019

Sakoulas et al. Antimicrobial salvage therapy for persistent staphylococcal bacteria using daptomycin plus ceftaroline Clinical Therapeutics 36;10,2014 1317-33

Dhand et al .Daptomycin in combination with other antibiotics for the treatment of complicated MRSA bacteremia . Clinical Therapeutics 36;10,2014 1317-33

Nadrah et al. Antibiotic combinations with Daptomycin for the treatment of Staphylococcus aureus infections Chemotherapy Research and Practice. Vol 2011,Article ID 619321

Patient

- MSSA bacteremia x 5 days, septic emboli brain, spleen, kidney, coronary artery, endocarditis (2 valves involved). R elbow bursa. Shoulder painful.

QUESTION

Management

- Appropriate ATB agent, dose, duration (CNS penetration)
- Does cefazolin have good CNS penetration? What other anti staph antibiotics have good cns penetration?

Staph aureus antibiotics with CNS penetration

- Cefazolin- should NOT be used for MSSA meningitis/ CNS lesions because it does not adequatley penetrate CNS

- Other ATB include

-vancomycin + rifampin

-nafcillin

-linezolid

-daptomycin (with rifampin)

-TMP/SMX

Case presentation

- At day 15 hospitalization, afebrile for 4-5 days on ceftriaxone (CNS doses) and daptomycin . Started having fever again 38.2. Complained of worsening R hip pain, R UE swelling/pain persistent.
- Palliative care consulted

Interesting data

Role of ID consult in Staphylococcus Aureus bacteremia (SAB)

- Higher rates of various quality of care metrics
- Obtaining follow up blood cultures
- Obtaining an echocardiograph
- Removing infecting foci
- Providing a longer duration of treatment for complicated SAB
- Administering beta lactams for MSSA infections
- Reduced patient mortality rates
- Collectively ,results suggest that ID consultation should be regarded as the standard of care in institutions where this subspecialty service is available

Pastagia et al .2012. 18:1072-1080. Isobe et al. 2012 J Infect Chemother 18: 842-847 Nagao et al .2010 Clin Microbiol Infect 16:1783-88 Choi ey al 2011. J Infect 16: 1783-1788 Robinson et al. 2012. Eur J Clin Microbiol Infect Dis 31:2421-2428

Costs of Antimicrobials

Drug	Dose	Daily Cost
Nafcillin	2 gm Iv q 4h	$45
Cefazolin	2 m IV q 8h	$ 6- 25
Ceftriaxone	2 gm IV q 24h	$ 2.5
Vancomycin	1000 mg IV Q12h	$57
Ceftaroline	600 mg IV Q12h	$387
Linezolid	600 mg PO Q12	$8
	600 mg IV Q12h	$87
Tedizolid	200 mg PO Q24h	$386
	200 mg IV Q24h	$307
Quinupristin/Dalfopristin	7.5 mg/kg IV Q8-12	$1,460-$974 a
Daptomycin	4-6 mg/kg IV Q24h	$487
Telavancin	10 mg/kg IV Q24h	$472 a
Dalbavancin	1500 mg IV once	$5634 b
Oritavancin	1200 mg IV once	$3480 b

a based on 70 kg person b cost of full couse

Average Whole Price February 2017

2018 Top 10 BUMCP Anti-infectives Overall (IV + PO)

9 of the 10 antibiotics same as 2017, but a few switched places on the list (rank 5-10)

Good to see ciprofloxacin drop from the top 10!

Rank	2017	2018
1	Vancomycin	Vancomycin
2	Pip/tazo	Pip/tazo
3	Ceftriaxone	Ceftriaxone
4	Cefazolin	Fluconazole
5	Fluconazole	Cefazolin
6	Metronidazole	Cefepime
7	Ampicillin/sulbactam	Metronidazole
8	Cefepime	Ampicillin/Sulbactam
9	Levofloxacin	Sulfa/TMP
10	Ciprofloxacin	levofloxacin

IN THE JOURNALS PLUS

Monitoring vancomycin AUCs may prevent kidney injury

SHOW CITATION

February 12, 2019

ADD TOPIC TO EMAIL ALERTS

Marc H. Scheetz

The risk for acute kidney injury may be reduced if vancomycin area under the curve dosing measured within the first or second 24 hours is lower than approximately 650 mg*h/L, according findings from a systematic review and meta-analysis.

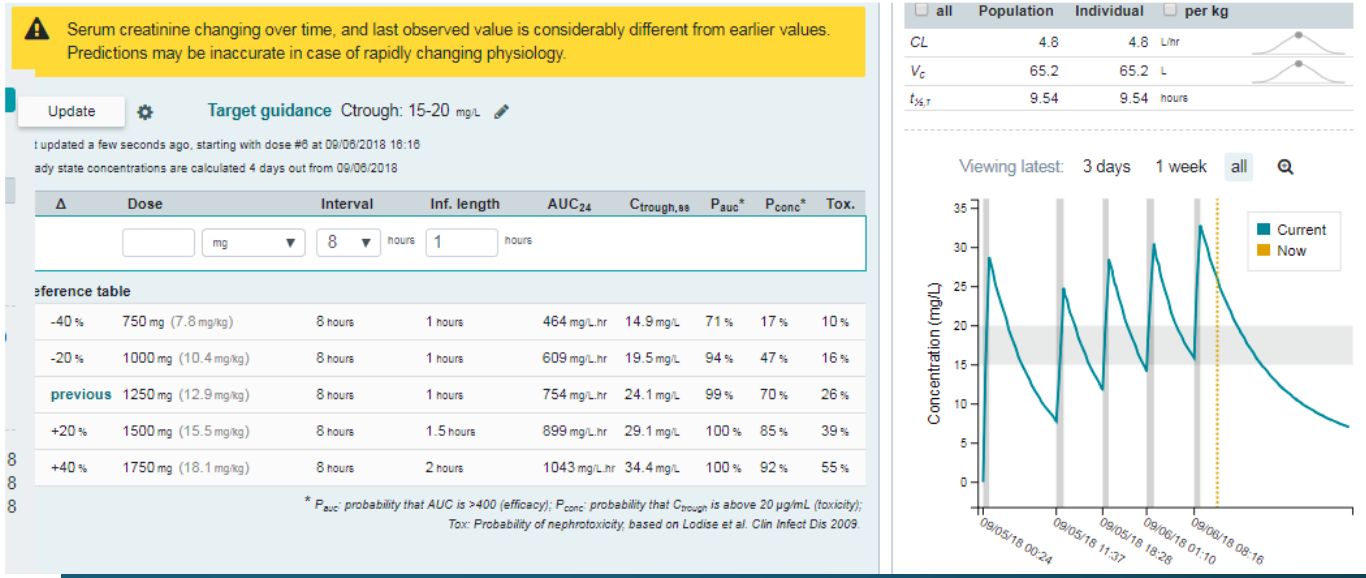
Vancomycin — a "drug of choice" for infections caused by MRSA, according to the study — is known to damage the kidney, explained **Marc H. Scheetz, PharmD, MSc**, professor of pharmacy practice and director of the Pharmacometric Center of Excellence at Midwestern University Chicago College of Pharmacy and infectious disease pharmacist at Northwestern Medicine.

"Vancomycin therapeutic drug monitoring was previously suggested as a means to ensure efficacy and safety of therapy," Scheetz told *Infectious Disease News*. "Specifically, the old vancomycin guidelines suggested monitoring trough concentrations to ensure appropriate vancomycin exposures — ie, area under the curve (AUC). Recent research suggests that vancomycin trough concentrations are imprecise for estimating AUCs, and it is anticipated that the new guidelines will recommend monitoring vancomycin AUCs. However, it is not clear at what value the vancomycin AUCs are unsafe for the patient's kidney."

For their review, Scheetz and colleagues included randomized, cohort and case-control studies that reported vancomycin AUCs and risk for acute kidney injury (AKI). The included studies were compiled from Medline, PubMed and Scopus and conducted from Jan. 1, 1990, to Jan. 31, 2018. The primary outcome was AKI defined as an increase of 0.5 mg/L or more in serum creatinine or a 50% increase from baseline on two or more consecutive measurements, Scheetz and colleagues explained.

1 **Therapeutic monitoring of vancomycin: A revised consensus guideline and review of**
2 **the American Society of Health-System Pharmacists, the Infectious Diseases Society of**
3 **America, the Pediatric Infectious Diseases Society and the Society of Infectious Diseases**
4 **Pharmacists**

5 Rybak, MJ,[1-3] Le J,[4] Lodise, TP,[5,6] Levine DP,[2,3] Bradley, JS,[7,8] Liu, C,[9,10] Mueller, BA,[11] Pai,
6 MP,[11] Wong-Beringer, A,[12] Rotschafer, JC,[13] Rodvold, KA,[14] Maples, HD,[15] Lomaestro, B.[16]



CID ciz 051 https://doi.org/10.1093/cid/ciz051
CID ciz460 https://doi.org/10.1093/cid/ciz460

Why Order a MRSA Nares PCR?

1. To facilitate early de-escalation of vancomycin in the treatment of patients on empiric, broad-spectrum antibiotic therapy for the treatment of pneumonia.

2. Numerous studies have shown that MRSA pneumonia is highly unlikely in the absence of detectable MRSA in the nares.
   a) Negative predictive value between 90 – 98% for all types of pneumonia utilizing the PCR. NOT APPLICABLE FOR ICU PTS

Parente. CID.2018;67:1-7.

Biomarkers for staphylococcus aureus?

- Significant knowledge gap in the identification of relevant biomarkers that predict clinical outcomes to differentiate patients prone to severe disease, therby facilitating either implementation of more aggressive therapies
- Heterogeneity in the host response to invasive S.aureus infections suggests that specific biomarker signatures could be utilized.

Study identified 13 candidate proteins that were correlated with mortality and persistent bacteremia. IL 8 and CCL2 as the strongest individual predictors of mortality. Baseline IL 17 A levels elevated in patients with persistent bacteremia

A Complicated Staphylococcus prognostic Model of Persistent Bacteremia in Complicated Staphylococcus aureus Bloodstream Infection CID 2019:68(9):1502-11

Teaching points

- Staphylococcus aureus has a diverse arsenal of components and products that contribute to pathogenesis of infections
- Source control is important
- Perform echocardiography in all patients with Staphylococcus aureus bacteremia
- Always advise patients of chances of recurrence of staphylococcus aureus bacteremia
- ID is available to assist

Reading material

- Tong SY, Davis JS, Eichenberger E. etal. Staphylococcus aureus infections: epidemiology, patophysiology, clinical manifestations and management. Clin Microbiol Rev 2015; 28:603-61
- Lowy F. Staphylococcus aureus Infections. N Engl J med 1998 Aug 20, 339(8) 520-32