Staphylococcus aureus

Leonor Echevarria, M.D.,FACP
Infectious Disease Attending
BUMC-P

A 36 year-old man who was admitted to the intensive care unit for treatment of multiple traumatic injuries sustained in a motor vehicle accident is diagnosed with ventilator-associated pneumonia.

On physical examination, temperature is 38.3 °C (101.0 °F), blood pressure is 130/88 mm Hg. pulse rate is 108/min, and respiration rate is 22/min. Breath sounds reveal bilateral basilar crackles. The remainder of the physical examination, consistent with his history of multiple trauma-related injuries, is otherwise noncontributory.

A chest radiograph reveals bilateral lower lobe infiltrates. A quantitative bronchoalveolar lavage culture grows methicillin-resistant Staphylococcus aureus with susceptibilities to vancomycin, daptomycin, linezolid, rifampin, and Tigecycline. Two sets of blood cultures are negative. Vancomycin is initiated, and on hospital day 3, the patient develops an urticarial rash. The patient's clinical status has remained unchanged.

In addition to discontinuining vancomycin, which of the following is the most appropriate treatment?

- ☐ A Daptomycin
- ☐ B Linezolid
- ☐ C Rifampin
- ☐ D Tigecycline

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A 42 year-old woman undergoes evaluation after admitted to the hospital 2 days ago with fever; chills; and redness, pain, and swelling over the left mid-anterior shin to just below the knee. She reports falling 5 days before admission and abrading her shin.

Empiric vancomycin was started on admission. Medical history is notable for type 2 diabetes mellitus controlled by diet. She takes no other medications.

On physical examination, temperature is 38.7 °C (101.7 °F), blood pressure is 112/74, pulse rate is 110/min, and respiration rate is 20/min. On cardiopulmonary examination, the lungs are clear, and no murmur is heard. A large area of erythema, tense edema, and diffuse tenderness is observed over the left anterior shin without signs of lymphangitic spread.

Laboratory studies show a leukocyte count of 14,500 µL (14.5 x 109/L) and serum vancomycin trough level of 17 µL/mL. Blood cultures obtained at admission grow methicillin-resistant Staphylococcus aureus with a vancomycin minimum inhibitory concentration of 4 µL/mL.

Which of the following is the most appropriate management of this patient's antimicrobial regimen?

☐ A Add rifampin

☐ B Continue current vancomycin dose

☐ C Increase vancomycin dose

☐ D Switch vancomycin to daptomycin

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Blood Culture - Accession: 000012017156002763
Result Status - Modified

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

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4	Tetracycline	<=1	S
5	Levofloxacin	>=8	R
6	Daptomycin	0.25	S
7	Erythromycin	>=8	R
8	Clindamycin	>=4	R
9	Linezolid	2	S
10	Trimethoprim/Sulfa	<=10	S
11	Vancomycin	1	S

Micrococcus , which, when limited in its extent and activity causes acute suppurative inflammation (phlegmon), produces, when more extensive and intense in its action on the human system, the most virulent forms of septicemia and pyemia”

Ogston A. Micrococccus poisoning. J Anat 1882;17: 24-58

Lowy F. Staphylococcus aureus Infections. N Engl J med 1998 Aug 20, 339(8) 520-32

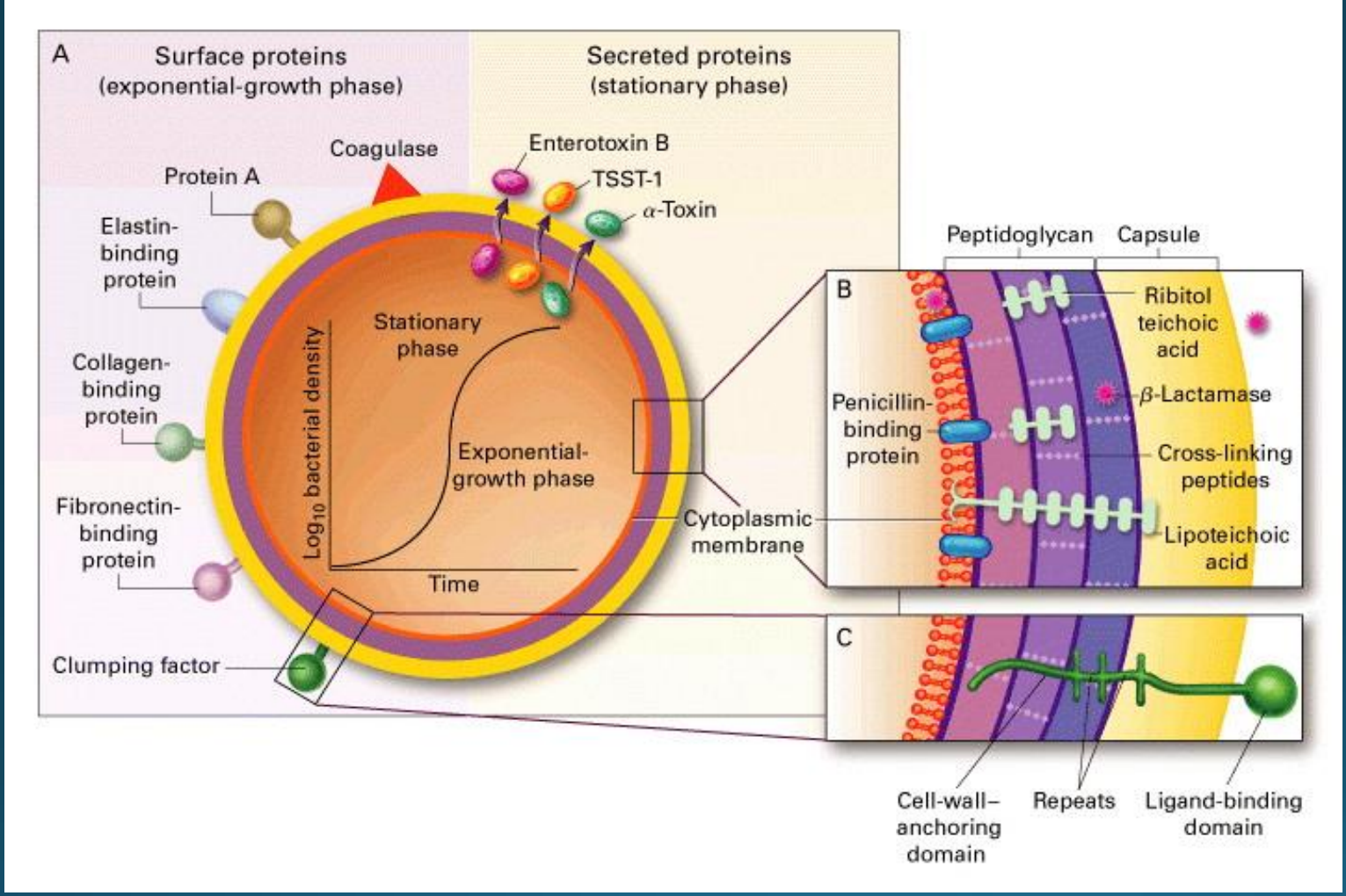
Staphylococcus aureus

- Microbiology /pathogenesis
- Case presentation
- Teaching points

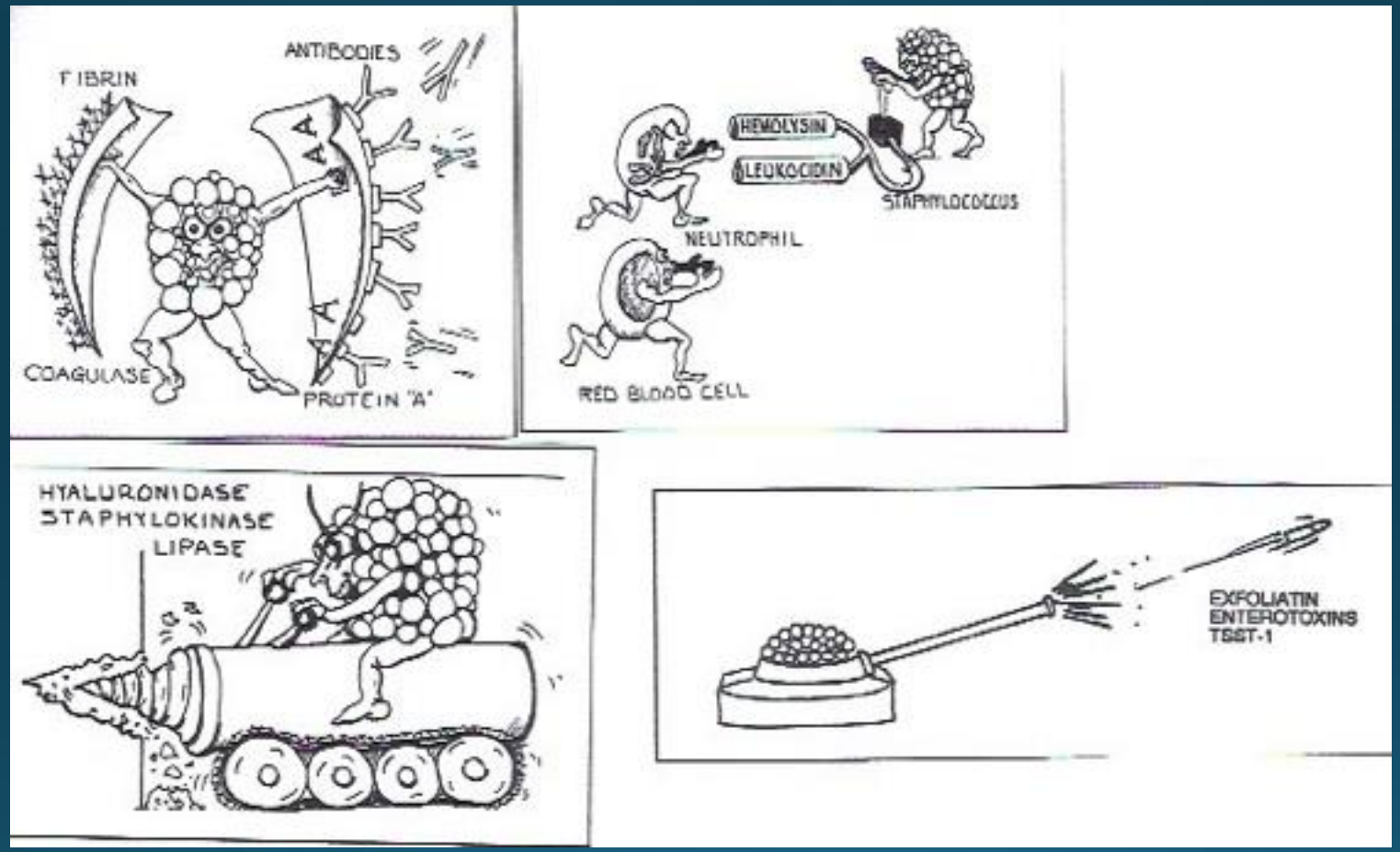
Staphylococcus aureus

- 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*.

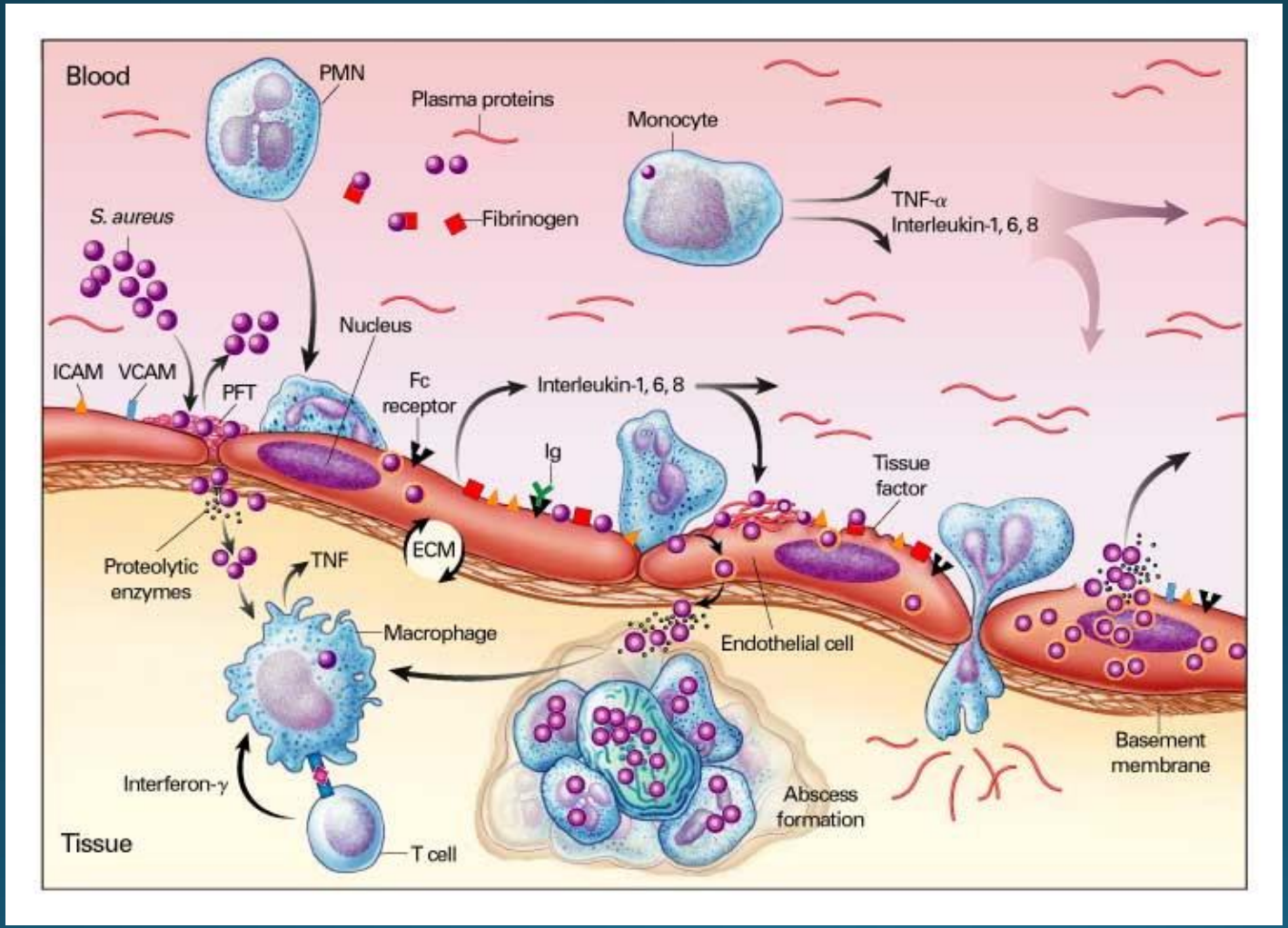


Lowy FD. N Engl J Med 1998;339:520-532.



Clinical Microbiology made ridiculously simple Edition 6

Pathogenesis of Staphylococcal Invasion of Tissue.



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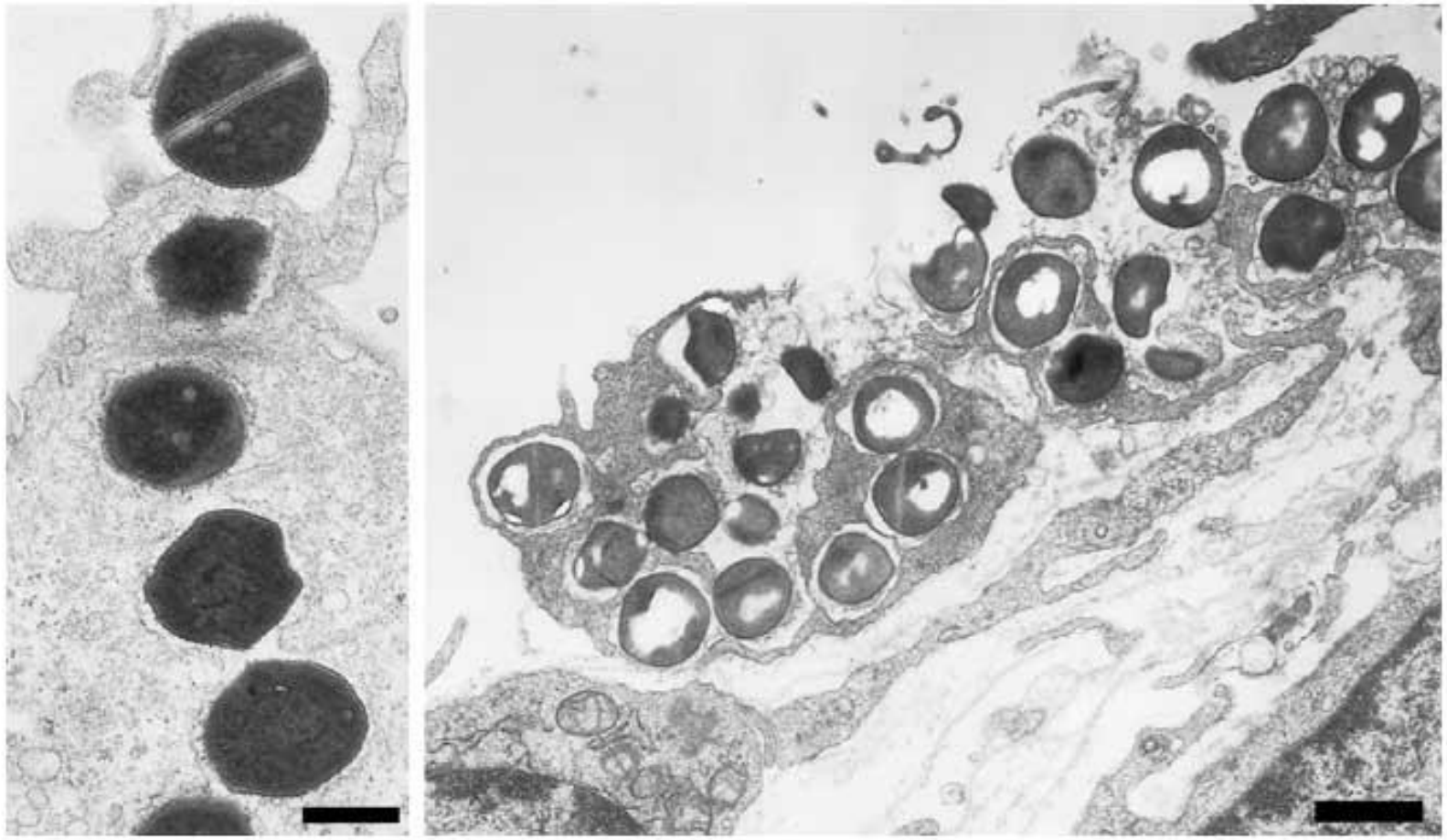
The NEW ENGLAND JOURNAL of MEDICINE

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



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The NEW ENGLAND JOURNAL of MEDICINE

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

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

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 recommended reimaging valve once patient has recovered from CVA to assess size of vegetation

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

Patient

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

Management

-Defining patient having a complicated vs uncomplicated bacteremia

- Source control?
- Appropriate ATB agent, dose, duration (CNS penetration)

-When do we consult surgery?

Physical Exam

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 MRSA 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

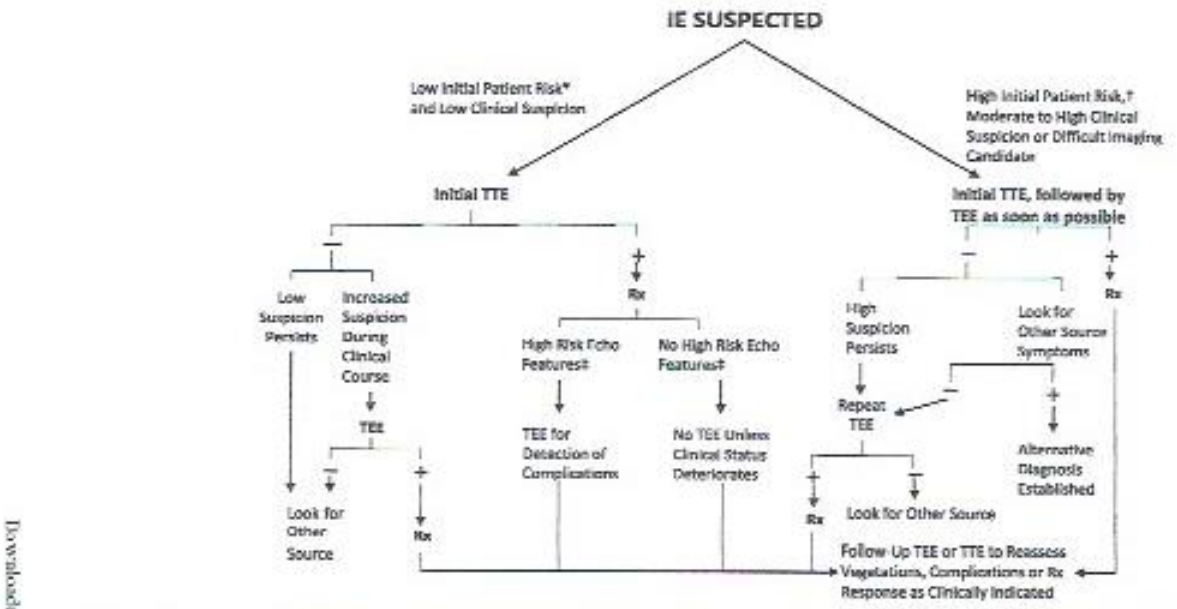

Figure. An approach to the diagnostic use of echocardiography (echo). Rx indicates prescription; TEE, transesophageal echocardiography; and TTE, transthoracic echocardiography. *For example, a patient with fever and a previously known heart murmur and no other stigmata of infective endocarditis (IE). †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

Low risk subset of patients

- Negative TTE results
- Nosocomial acquisition of bacteremia
- Negative fu blood cultures
- Abscence of an intracardiac device
- Absence of hemodyalisis dependance
- No clinical signs of endocarditis or metastatic foci

ABOVE RECOMMENDATIONS WOULD CLEARLY BE STRENGTHENED BY A PROPSPECTIVE TRIAL

Van Hal SJ et al.The role of TTE in excluding left sided endocarditis in Staphylococus aureus bacteremia J Infect 51:218-221. 2005
Khatib et al. Echocardiography is dispensable in uncomplicated Staphylococus aureus bacteremia . Medicine 92:182-188. 2013
Joseph JP et al. Prioritiazing echocardiography in Staphylococcus aureus bacteremia. J Antimicrob Chemother 88:444-449. 2013

Which ATB is right MSSA

- Nafcillin
- Monitoring?
- Persistent bacteremia

Persistent bacteremia

- Add rifampin?
- Add gentamicin?
- D #5 add daptomycin

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

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

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.

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5	Clindamycin		R
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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

- 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

MSSA vs MRSA

- Retrospective studies . Small number of cases (No difference).
- Metanalysis. MRSA had increase mortality compared with MSSA
- Thought to be associated : ? Virulence, vancomycin may be inferior SA ATB, inappropriate initial treatment

Laupland KB et al. Staphylcoccus aureus bloodstream infections: risk factors, outcomes, and the influence of methicillin resistance in Calgary, Canada. J Infect Dis 198:336-43
Crosgrove SE et al. Compariison of mortality associated with methicillin resistant and methicillin susceptible Staphylococcus aureus bacteremai: a meta analysis. Clin Infect Dis 2003;36:53-9
Whitby et al. MJA 2001; 175: 175: 264-267. Risk of death from methicillin-resistant Staphylococcsu aureus bacteremia: A meta-analysis

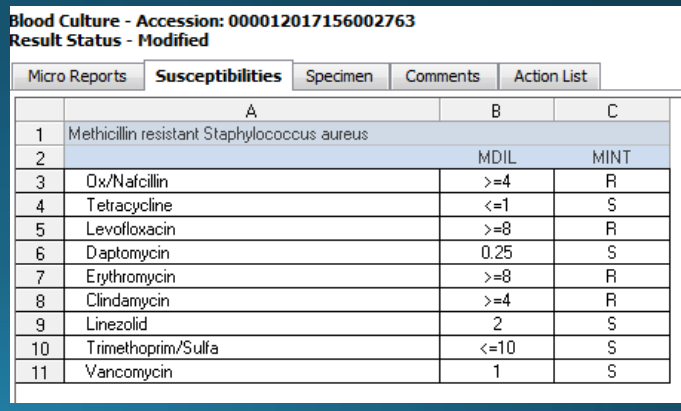
Role of ID consult in Staphylococcus Aureus bacteremia (SAB)

- 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

Agents with Activity Againt MRSA in Addition to Vancomycin

- β-Lactams
  - -Ceftaroline
- Lipoglycopeptides
  - -Telavancin
  - -Dalbavancin
  - -Oritavancin
- Cyclic lipopeptide
  - -Daptomycin
- Oxazolidinones
  - -Linezolid
  - -Tedizolid



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10	Trimethoprim/Sulfa	<=10	S
11	Vancomycin	1	S

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	$367
	600 mg IV Q12h	$192
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

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