Know Your Enemy: *Revisiting Staphylococcus aureus*

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Kansas Association of Osteopathic Medicine Annual Meeting & Convention

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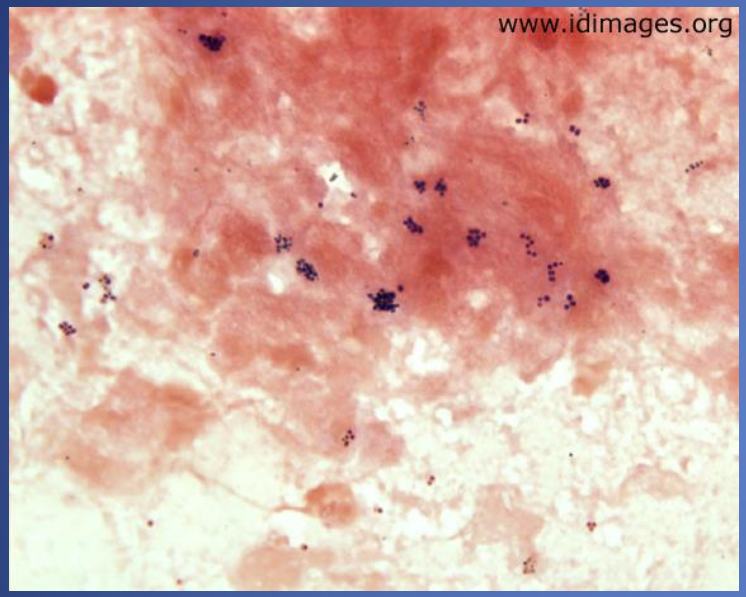


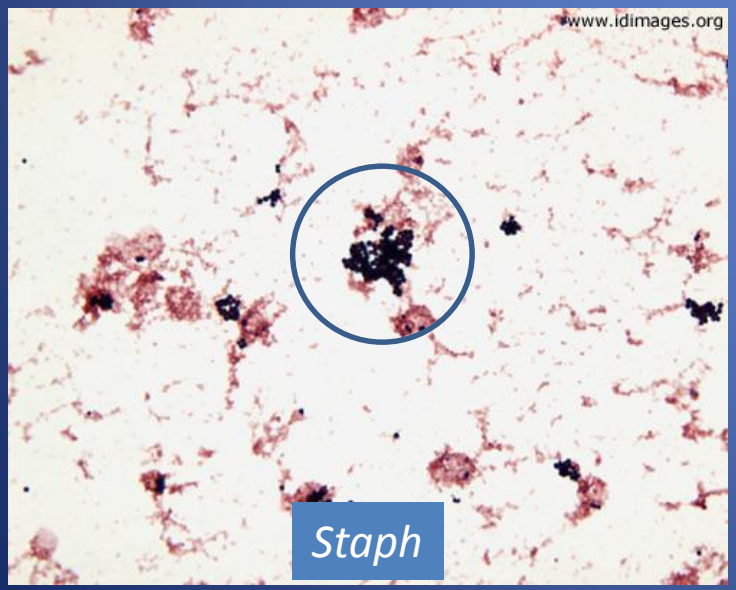
STAPH BASICS (THE MICRO)

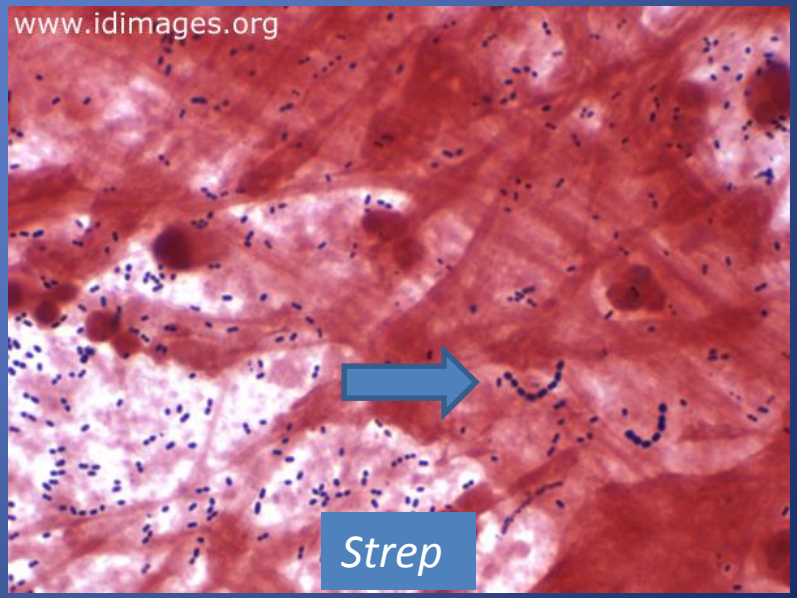
Objectives

- Review microbiology of staphylococci
- Consider virulence factors contributing to morbidity associated with *Staphylococcus aureus* (*S. aureus*) infection
- Apply knowledge to 3 clinical cases related to *S. aureus* infection
- Discuss key concerns in *S. aureus* bacteremia
- Introduce “new” anti-staphylococcal antibiotics

Staphylococci

- Gram positive cocci; 4 major pathogenic species in humans
  - *S. saprophyticus, S. lugdunensis, S. epidermidis, S. aureus*
  - Usually found in “clusters” (strep = chains)
  - Catalase positive (strep = catalase negative)





Coagulase-negative *Staphylococci*

- *S. saprophyticus*
  - Urinary tract infections “sexually active young women”
  - Community-acquired
- *S. lugdunensis*
  - Complicated/destructive endocarditis
  - Propensity to form abscesses
  - Unique amongst coagulase-negative staph as it is often oxacillin-susceptible

Coagulase-negative *Staphylococci*

- *S. epidermidis*
  - Commensal of human skin, commonly isolated from clinical specimens
  - True infections are often hospital-acquired
    - Central venous catheters, dialysis catheters ventriculoperitoneal shunts, prosthetic joints, implanted devices
  - Produces biofilm, contributes to difficulty clearing prosthetic infections

Staphylococcus aureus

- Contains several genes which enhance resistance and govern virulence that can be transferred between other staphylococcal species
- Organized by resistance patterns: MSSA, MRSA, VISA, VRSA
- Also categorized as community-acquired (CA-MRSA) versus hospital-acquired (HA-MRSA) - former did not necessarily evolve from the latter
- Ubiquitous colonizers of skin and mucosa
  - Nasal carriage 20-30% (intermittent)

Virulence factors

- *S. aureus* has a microcapsule surrounding its peptidoglycan cell wall, which in turn surrounds a cell membrane containing penicillin-binding protein (PBP)
- Virulence factors:
  - *mecA* encodes PBP 2a, that establishes resistance to the semisynthetic penicillinase resistant beta-lactams (nafcillin, oxacillin, methicillin) and cephalosporins
    - Lab can test for PBP 2a early allowing you to know if expected MRSA
  - PBP 1-3 will bind to beta-lactams, inactivating enzyme activity, and ultimately contributing to bacterial death
    - Susceptible to the “anti-staphylococcal” b-lactams (nafcillin/cefazolin)

Virulence factors

- Protein A helps protect Staph from opsonization and phagocytosis
- Coagulase can help form fibrin around the bacteria, also protecting it from phagocytosis
- Hemolysins alpha – delta can destroy red blood cells, neutrophils and platelets
- Panton-Valentine Leukocidin (PVL) - associated with more severe infections with CA-MRSA
  - Sepsis, necrotizing PNA, effusions and skin/soft tissue infection
  - WBC destruction

Decolonize?

- Given minimum of 20-30% of people are colonized intermittently and given this association with surgical site infections or recurring soft tissue infection, decolonization is an interest
  - Nasal mupirocin and chlorhexidine wash are most frequently cited in the literature

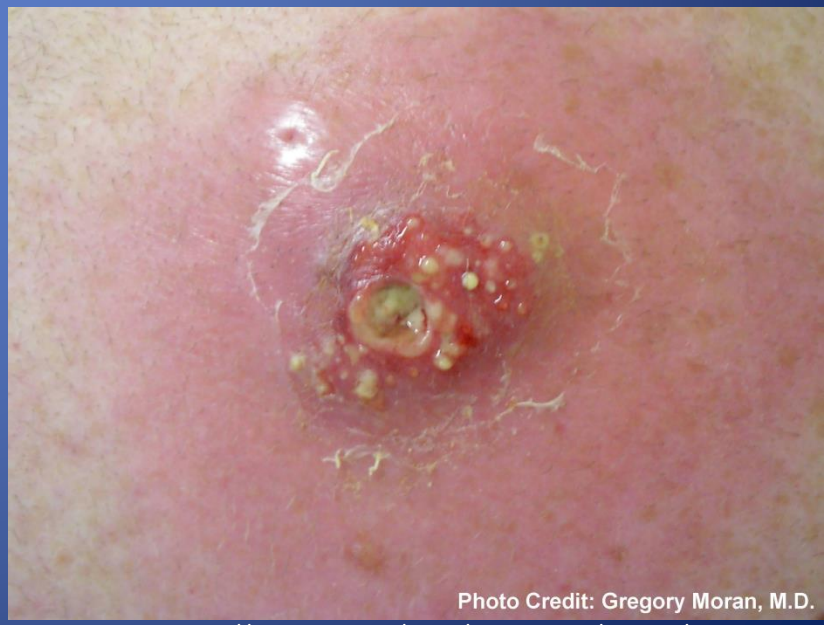
STAPHYLOCOCCUS AUREUS
CLINICAL SYNDROMES

Case 1 “the pimple”

- 36 year-old woman with history of obesity presents to the ER with 1 day history of increased erythema pain and redness around a large “pimple” she had on her upper back
  - Has had prior similar episodes with “boils” in groin

T: 38.2 HR: 95 BP: 125/87 R: 16
Exam: unremarkable aside from photo

WBC: 12.5
Lactate: 1.0
Creat: 0.89
LFTs: normal



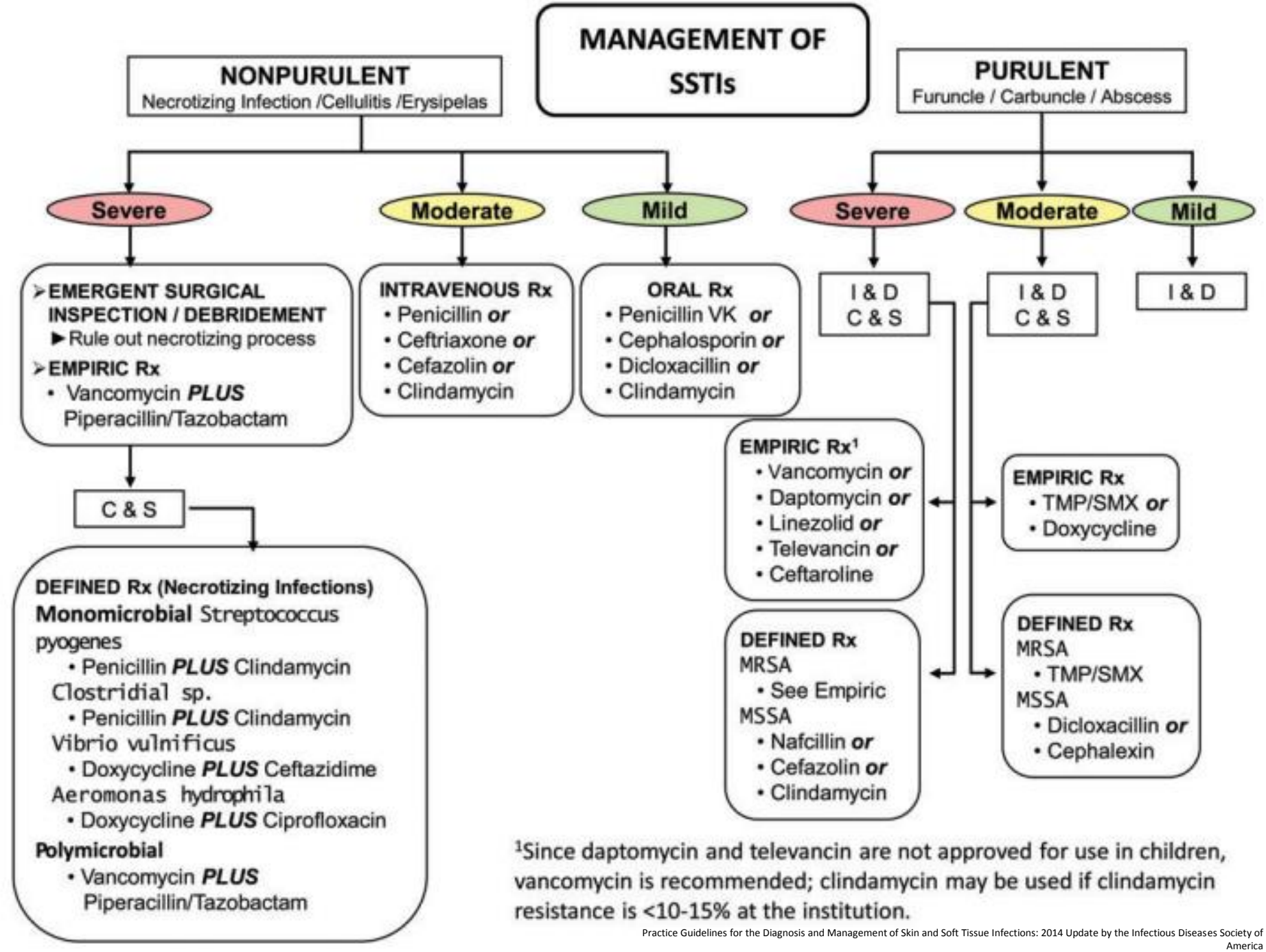
https://www.cdc.gov/mrsa/community/photos/index.html

The patient is admitted for treatment and an I&D is planned. Which of the following is the most appropriate initial antimicrobial therapy?

A. Cefazolin
B. Levofloxacin
C. Vancomycin
D. Piperacillin/tazobactam with Vancomycin

Rationale:
The patient is presenting with purulent cellulitis and sepsis. The most likely pathogen is *Staphylococcus aureus*. Assuming there are no clinical concerns for a necrotizing infection, and taking into account patient allergies, initial treatment options include intravenous Vancomycin, Ceftaroline, Daptomycin, Telavancin or oral/IV linezolid or tedizolid.

Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, Hirschmann JV, Kaplan SL, Montoya JG, Wade JC. Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2014 Jul 15;59(2):e10-52. doi: 10.1093/cid/ciu444. PMID: 24973422

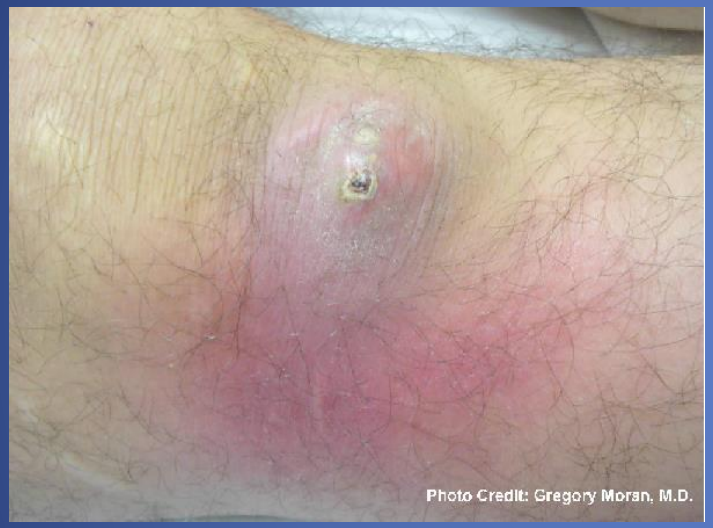


[1]Since daptomycin and televancin are not approved for use in children, vancomycin is recommended; clindamycin may be used if clindamycin resistance is <10-15% at the institution.

Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America

Skin & Soft Tissue

- “Spider bite” phenomenon



- Superficial: impetigo, folliculitis, cellulitis
- Deeper tissue infection: soft tissue abscess, myositis, fasciitis → necrotizing fasciitis

https://www.cdc.gov/mrsa/community/photos/index.html

Case 2 “the disaster boil”

- CC: boil
- HPI: 26 year-old (healthy) man presented to a community hospital with a right arm skin abscess
  - I&D was preformed. Wound culture: MRSA, sensitive to all antibiotics tested except oxacillin and penicillin
  - Prescribed trimethoprim-sulfamethoxazole
- 3 days later he developed low back pain
  - No sig improvement w/approximately 2 weeks of symptomatic treatment
  - MRI of the lumbar spine: L5-S1 disk herniation
  - Epidural corticosteroid injection was administered with only minimal improvement
  - 5 days later he was readmitted for evaluation after a syncopal episode

Objective information

- Vital signs: afebrile, BP: 110/48, P: 97, RR: 21, and O2 sat: 99 % 2 liters NC
- Initial physical examination: unremarkable
- Lab:
  - WBC 17.1; differential 64% segmented neutrophils and 32% bands
  - ESR 53
  - chemistry panel: unremarkable aside from a total bilirubin of 1.6
  - Urinalysis and chest radiograph unremarkable
- What do you think is going on now?

  - Blood cultures: MRSA, sensitive to fluoroquinolones and resistant to oxacillin and erythromycin (VITEK Automated Microbiology System)
  - MRI of the lumbar spine: diskitis at L5-S1 disk space with associated epidural abscess and vertebral osteomyelitis

Case 2 - course

- Paravertebral abscess became complicated by an infected inferior vena cava thrombus leading to bilateral pulmonary septic emboli and respiratory failure requiring mechanical ventilation
- On post-operative day four, physical examination revealed bilaterally injected conjunctiva. Ophthalmologic evaluation revealed bilateral endopthalmitis with vitreal abscesses
  - Intravitreous clindamycin and vancomycin were given
  - After several days he clinically improved and completed a total of nine days of IV antibiotics. At this time, antibiotics were transitioned to oral at equivalent doses and he was discharged home
  - At the time of discharge visual acuity was 20/20 in the right eye and 20/100 in the left

CA-MRSA

- Increasing rates of SSTI
- Mild/limited “boil” to necrotizing fasciitis
- CAP or necrotizing pneumonia
- Concerning is limited soft tissue infection with bacteremia or metastatic sites of infection
- Susceptibility pattern: TMP/SMX, tetracycline, clindamycin (R to methicillin)
  - Erythromycin resistant clones and inducible clindamycin resistance in USA300 CA-MRSA isolates

Chavez TT, Decker CF, 2008

S. aureus bacteremia

- Increased incidence
- High rate of mortality 20-40%
- Treatment failure (death within 30 days following treatment, persistent bacteremia >10 days after initiation of appropriate therapy, or recurrence of bacteremia within 60 days of discontinuing therapy) is common
- Should always be considered “real” and treated with bacterio*cidal* antibiotic which has good bioavailability
  - (cidal = kills microbe, static = haults growth allowing host immune system to kill)

S. aureus bacteremia treatment

- REQUIRES an echo (TEE - up to 25% have SBE)
- Minimum 2 weeks of IV therapy if *uncomplicated case*
  - No endocarditis OR OTHER metastatic site of infection
  - No indwelling prosthetic materials (hardware, graft material)
  - Fever-free within 72 hrs of directed therapy
  - FU BC at 96 hours are negative
- Complicated *patient*? Diabetic, immunosuppressed (systemic steroids or other immunosuppressive drugs, such as those used for transplantation) or neutropenic
  - Consider 4-6 weeks

Eur J Clin Microbiol Infect Dis. 2013 Aug;32(8):1003-8. doi: 10.1007/s10096-013-1838-4. Epub 2013 Feb 17.

Case 3 “the fever”

CC: fatigue and fever

HPI: 37 year-old male, with recent folliculitis and now fatigue, pleuritic chest pain, and fever

- “Facial infection” at beard area (folliculitis) treated with amoxicillin by PCP 2 weeks ago
- A few days later developed right-sided pleuritic CP with fatigue
- Fevers of 102F
- Again saw PCP and started doxycycline; a culture swab was obtained from a small draining wound R face
- Fevers continued so he came to the ED

Questions we might ask?

- Other medical history? ROS?
- Social history?
- Exposures?
  - Alcohol or drug use
  - Occupational risks
  - Ill contacts
  - Animals
  - Travel
- Anything else?

Case 3 history

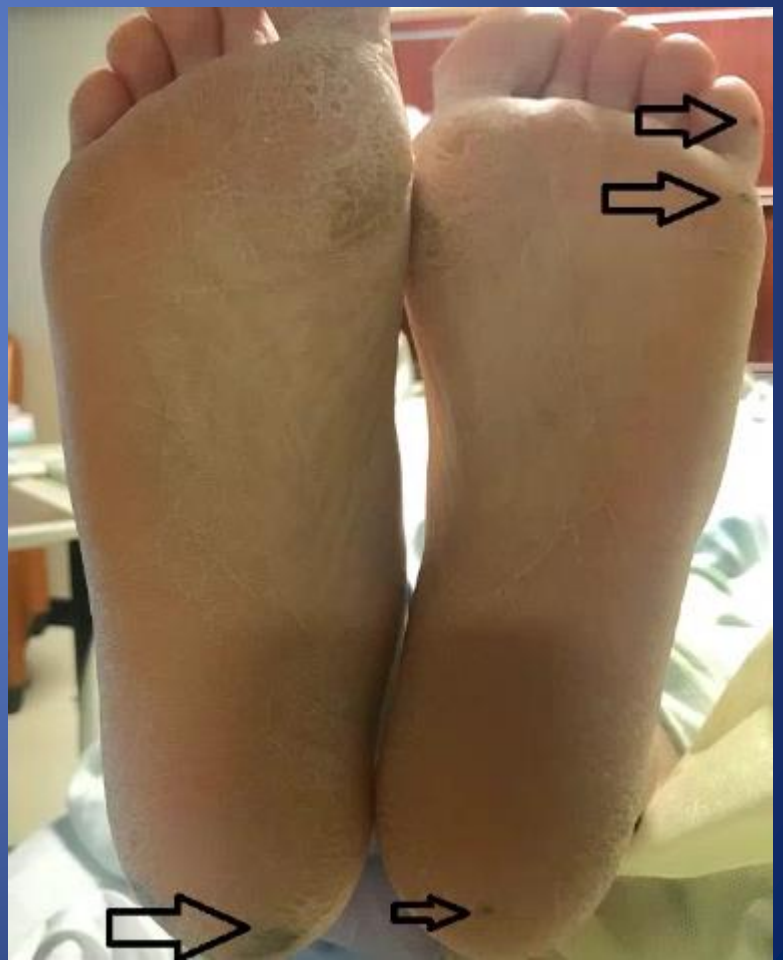
- PMHx: 60% TBSA burn (propane explosion) 2011; hospitalized at KU burn, hospitalization complicated by health-care acquired pneumonia and respiratory failure
- PSHx: multiple skin grafts, prior tracheostomy (now out)
- ROS: otherwise unremarkable
- Social history:
  - Single, living w/his parents in Hutchison; unemployed
  - Denies tob, rarely drinks beer. Remote history of meth use but none for years
  - No recent travel, has a cat, no ill contacts
  - No recent medical procedures or dental work

Objective information

Vitals: Temp 102F P 122 RR 24 sat 96% on RA BP 90/60

Examination:

General: pale, diaphoretic and appears ill
HENT: poor dentition, scarring R face with several pustules (healing) and mild erythema surrounding
Heart: II/VI late systolic murmur at the RLSB
Lungs: clear bilaterally
Skin: multiple healing skin grafts upper legs and lesions on feet and fingers as seen in arrows



Diagnostic tests

- CBC: Hgb 10g, WBC 20.9 w/27% bands, Plt 323
- Chemistry: normal
- CXR: small bilateral effusions and a R mid-lung infiltrate
- UA: 5-10 RBC, no WBC, trace protein

What antibiotic(s) would you start empirically?

A. Vancomycin
B. Nafcillin
C. Vancomycin + metronidazole
D. Nafcillin + gentamicin
E. Cephalexin

Rationale:
The patient is presenting with fever and fatigue, with symptoms and signs of bacterial endocarditis. His prior hospitalizations and initial skin/soft tissue infection make skin flora (primarily staphylococci)high on the differential for pathogens. Initial treatment should cover methicillin-resistant staph as well as streptococci. A gram negative pathogen is less likely based on the provided information and an anaerobic bacterial process is even less likely. Intravenous Vancomycin or Daptomycin would be the most appropriate initial choices.

Baddour L, et al. Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications. Circulation. 2015;132:1435-1486

Additional information

- Blood cultures: just paged from micro, prelim – positive with gram positive cocci in clusters
- Trans-thoracic ECHO: poor visualization of the tricuspid and pulmonic valves but no vegetations seen

Which Echocardiogram technique should I use?

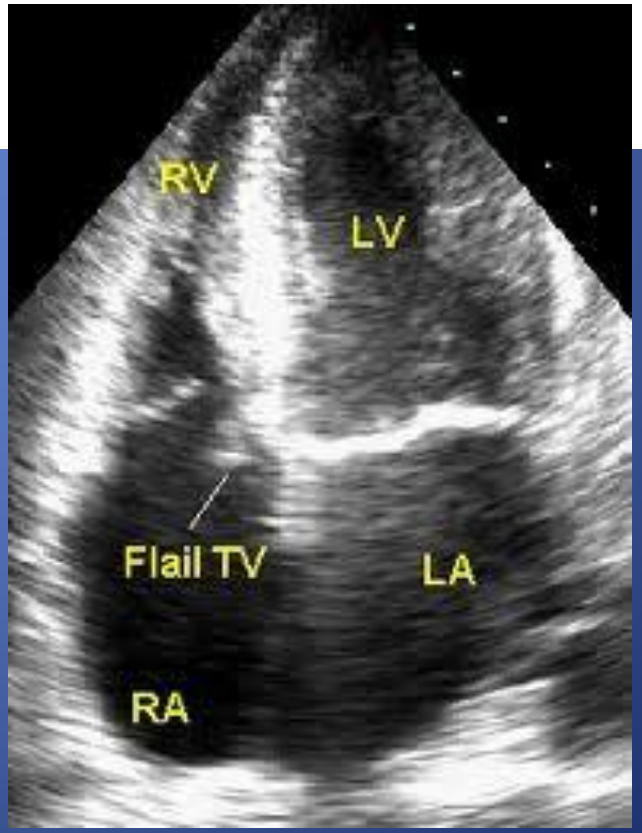
- TEE
  - prosthetic valve
  - congenital heart disease
  - previous endocarditis
  - new murmur
  - heart failure
  - stigmata of endocarditis
  - moderate to high clinical suspicion
  - difficult imaging candidate (morbid obesity, previous cardiac surgery COPD)
- TTE
  - Low initial patient risk
  - Low clinical suspicion

Echocardiogram

- TEE

Interpretation Summary

1. Normal LV systolic function. Estimated LV EF of 60%. No significant wall motion abnormalities.
2. Mobile echodensities visualized on the anterior and septal leaflets of the tricuspid valve suggestive of endocarditis. The anterior echodensity of 2.1cm x 0.8 cm and the septal leaflet measures 2.3cm x 0.9cm. Leaflets are flail and prolapse into the right atrium causing failure of coaptation of the anterior and septal leaflets with associated severe tricuspid regurgitation.
3. Normal RV size and function.
4. No evidence of intracardiac thrombus.
5. No evidence of interatrial septal defects on color flow Doppler.
6. No pericardial effusion.



Blood cultures

- 4/4 bottles with MRSA

Culture & Susceptibility

Antibiotic	Organism		
	METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS POSITIVE FOR PBP2A, INDICATING THAT ISOLATE IS MRSA		
METHOD	MIC (MCG/ML) INTERPRETATION		
CLINDAMYCIN	>2 RESISTANT	R	Final
ERYTHROMYCIN	>4 RESISTANT	R	Final
GENTAMICIN	<=2 SUSCEPTIBLE SS		Final
LEVOFLOXACIN	<=0.5 SUSCEPTIBLE SS		Final
LINEZOLID	1 SUSCEPTIBLE SS		Final
OXACILLIN	>2 RESISTANT	R	Final
RIFAMPIN	<=0.5 SUSCEPTIBLE SS		Final
SYNERCID	<=0.5 SUSCEPTIBLE SS		Final
TETRACYCLINE	>8 RESISTANT	R	Final
TRIMETHSULFA	<=1/19 SUSCEPTIBLE SS		Final
VANCOMYCIN	<=0.5 SUSCEPTIBLE SS		Final

Signs and Symptoms of Endocarditis

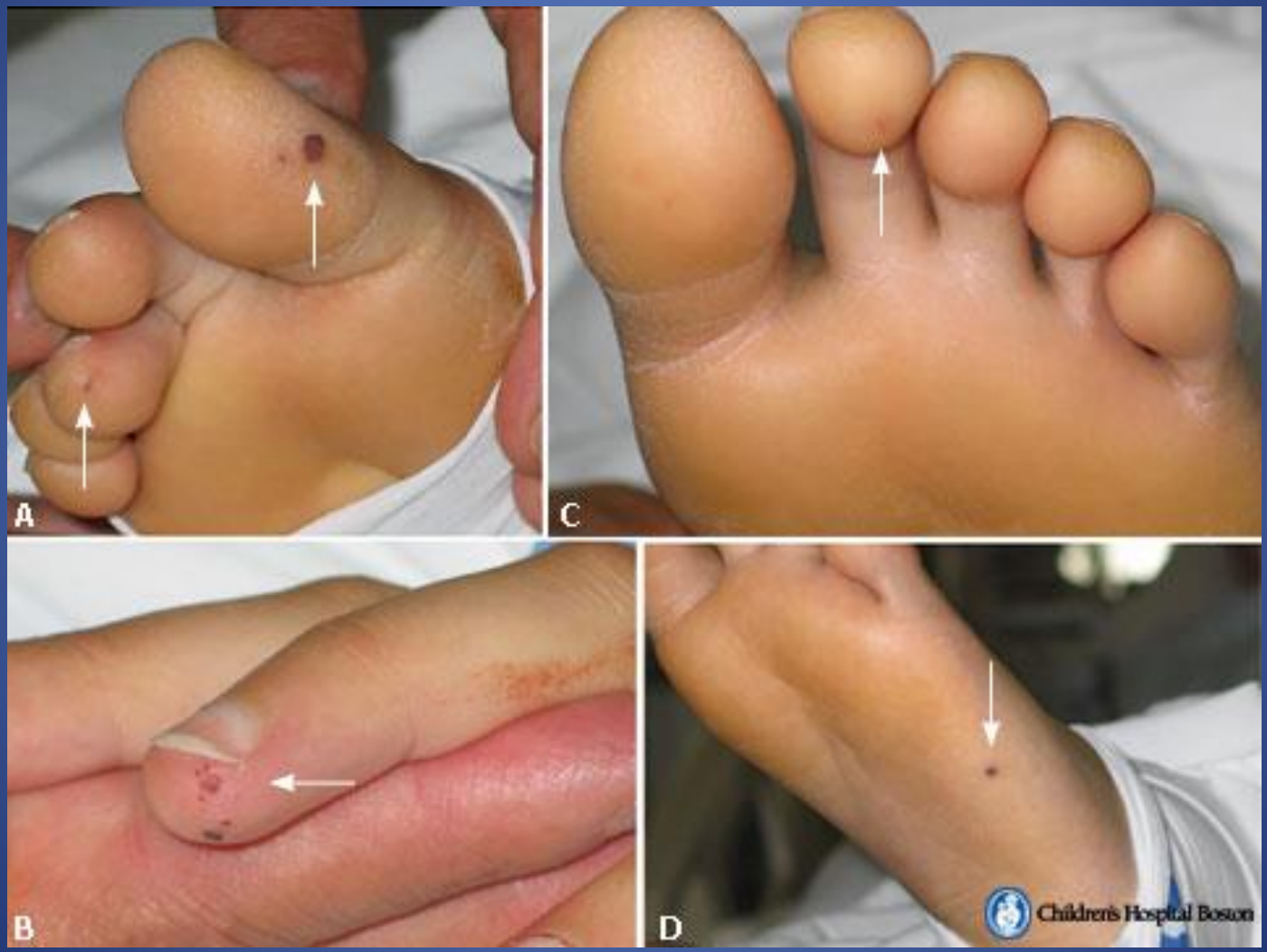
- Non-specific
  - Fever
  - Fatigue
  - Malaise
  - Backache
  - Arthralgias
  - Myalgias
- Cardiac
  - New or changing murmur
  - EKG: PR prolongations, heart block, ST changes
  - ECHO: vegetation

Signs and Symptoms of Endocarditis

- Embolic
  - Splinter hemorrhages
  - Petechiae
  - LUQ pain (spleen)
  - Hematuria (kidney)
  - Focal neurological findings (brain)
  - Pulmonary infiltrates (right sided vegetation)

Eur J Clin Microbiol Infect Dis. 2013 Aug;32(8):1003-8. doi: 10.1007/s10096-013-1838-4. Epub 2013 Feb 17.

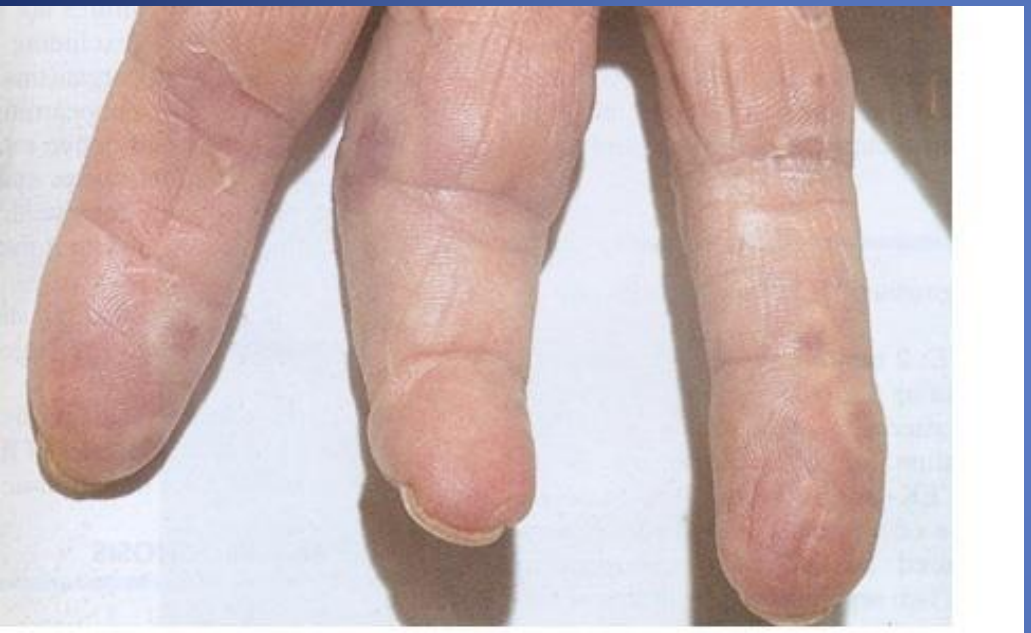
Janeway lesions



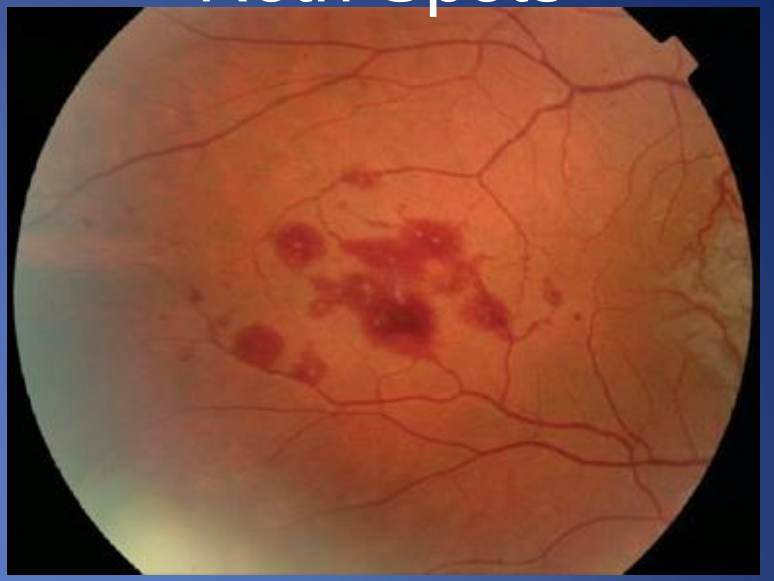
Small, non-tender erythematous macules on the palms and soles

Osler Nodes

Violaceous tender nodules on the distal fingers



Roth Spots



Pale retinal lesions surrounded by hemorrhage

Splinter Hemorrhages

Small hemorrhages in the nail bed

Microbiology

- Staph aureus 31%
- Viridans group streptococci 17%
- Enterococci 11%
- Coagulase-negative staphylococci 11%
- Streptococcus bovis 7%
- Other streptococci 5 %
- Non-HACEK gram-negative bacteria 2%
- Fungi 2%
- HACEK 2%
  - **H**aemophilus aphrophilus (subsequently called Aggregatibacter aphrophilus and Aggregatibacter paraphrophilus); **A**ctinobacillus actinomycetemcomitans (subsequently called Aggregatibacter actinomycetemcomitans); **C**ardiobacterium hominis; **E**ikenella corrodens; and **K**ingella kingae

Arch Intern Med. 2009;169(5):463.

Right-sided Endocarditis in IVDU

- Different pathophysiology
- Shortened duration of treatment if:
  - Uncomplicated
  - MSSA
- 2-weeks Nafcillin (cloxacillin) + Aminoglycoside
- Longer duration if MRSA (glycopeptide)

Prosthetic devices

- Cardiac
  - Infection incidence of 1.9 per 1000 device-years
  - *S. aureus* accounts for 25% of CIED infections
- Orthopedic
  - 1-2% prostheses become infected (first time surgery)
  - 1. CoNS, 2. *S. aureus*
    - <12 weeks = early, acute
    - 12 weeks-24months = late, chronic
      - Treatment: removal, directed (usually IV) antibiotics 4-6 weeks
    - Add rifampin for biofilm treatment/prevention

Kusumoto F, et.al. 2017 HRS expert consensus statement on cardiovascular implantable electronic device lead management and extraction. Heart Rhythm, Vol 14, No 12, December 2017.

Osmon D, et al. **Diagnosis and Management of Prosthetic Joint Infection: Clinical Practice Guidelines by the Infectious Diseases Society of America.** *Clinical Infectious Diseases*, Volume 56, Issue 1, 1 January 2013, Pages e1–e25.

Pneumonia

- <10% CAP, 20-30% HAP
- High mortality
- Complications: necrotizing infection/cavitary disease, empyema, abscess, bronchopleural fistula
  - May require surgical intervention
- Can be primary or hematogenous seeding during bacteremia
- Vancomycin or Linezolid
  - CAP - Ceftaroline
  - Do not use Daptomycin (inactivated by pulmonary surfactant)

Skrupky LP *et al*, 2007
Bhattacharya M *et al*., 2008

Osteomyelitis

- *S. aureus* 50-70% of cases, CoNS ~13%
- Children: hematogenous, long bone metaphyses
- Adults: contiguous (DM foot ulcerations)
- Vertebral osteomyelitis: hematogenous
- Oxygen radicals and cytokines aid in necrosis and abscess formation

Osteomyelitis

- Acute—responds to antibiotics in ~6 weeks
  - Fever, chills, malaise, +blood cultures
- Chronic
  - Can evolve over months-years
  - Chronic ulcers
  - Bone-probe positive

Osteomyelitis

- Diagnosis
  - Physical exam
  - X-ray, MRI, bone scan, CT
  - Blood and tissue cultures indispensible
- Treatment
  - 4-6 weeks
  - Oral treatment generally not recommended
  - +/- surgical intervention depending on location

Clinical Syndromes

- Meningitis
  - Hematogenous seeding (related to overwhelming infection including bloodstream) – evalualte for primary source
  - Postoperative cases– associated with foreign bodies
  - Choose “best” drug that will ALSO penetrate CNS
    - MRSA (Vancomycin, linezolid)
    - MSSA (Nafcillin)

Clinical syndromes

- Septic arthritis
  - Hematogenous seeding, trauma, iatrogenic
  - 3 weeks directed antibiotic therapy starting with IV
- Septic bursitis
  - 80% due to *S. aureus*
  - 2-3 weeks directed antibiotic therapy
- Pyomyositis
  - Rare, children and young adults most common
  - Evolve to muscle destruction, osteomyelitis, septicemia
  - IV antibiotics usually 2 weeks, then PO up to 6 weeks

Quinolone resistance

- MRSA >90% resistance to “older” quinolones
- Delafloxacin - approved by FDA in June 2017 for treatment of bacterial skin & soft tissue infections
  - Delafloxacin has activity against staphylococci, including MRSA and GNs including PSAE

Anti-MRSA Antibiotics	Adult dose	Indication notes
First line		
Vancomycin	15 to 20 mg/kg/dose every 8 - 12 hours	any
Linezolid	600 mg IV (or orally) twice daily	not bacteremia/endocarditis
Daptomycin	4 mg/kg IV once daily	not pneumonia/L sided endocarditis
Alternative antibiotics		
Short-acting alternative antibiotics with IV or oral dosing		
Tedizolid	200 mg IV (or orally) once daily	not bacteremia/endocarditis
Delafloxacin	300 mg IV twice daily or 450 mg orally twice daily	not bacteremia/endocarditis
Short-acting alternative IV antibiotics		
Ceftaroline	600 mg IV every 12 hours	caution in use/dosing in "off-label"
Telavancin	10 mg/kg once daily	not bacteremia/endocarditis
Long-acting alternative IV antibiotics		
Dalbavancin	Single-dose regimen: 1500 mg once	not bacteremia/endocarditis
	Two-dose regimen: Initial dose 1000 mg, followed by 500 mg dose one week later	not bacteremia/endocarditis
Oritavancin	1200 mg IV as a single dose	not bacteremia/endocarditis

Worst of the worst

- VISA (Vancomycin intermediate *S. aureus*)
  - MIC 4 to 8 mcg/mL
  - Most also have intermediate resistance to other glycopeptides (teicoplanin/telavancin) (aka GISAs)
  - Related to cell wall alterations – unusually thick
  - Can co-infect with heteroresistant strains (hVISA) when there are subpopulations that display variable rather than uniform susceptibility to vancomycin
    - *S. aureus* isolates with vanc MICs ≥4 mcg/mL represent < 0.3 %
- VRSA (Vancomycin resistant *S. aureus*)
  - ≥16 mcg/mL
  - Related to plasmid-mediated gene transfer, 14 cases in US (very rare)
- Treatment?
  - Combos such as vanc or dapto + ceftaroline or bactrim + ceftaroline; linezolid or tidezolid, limited info on ortivancin and dalbavancin

Summary

- *S. aureus* infections have the propensity to cause serious morbidity and mortality owing to high rate of colonization and their many virulence factors
- *S. aureus* bacteremia is always 'real' and should be treated with bacteriocidal IV therapy for at least 2 weeks from the time of first negative blood culture
- There are many new (but pricey) antibiotic options in MRSA skin/soft tissue infections and we are hopeful for more date for using these in osteomyelitis and other more complex infections

Thank you!
Comments/Questions?