Epidemiology and management of *Staphylococcus aureus* Bloodstream Infection

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Overview

- Introduction
- Brief case
- Bloodstream infection (BSI) general aspects and definitions
- The “special” case of *S. aureus* BSI
- Epidemiology
- Diagnosis
- Management
- Case review and conclusion

Conflict of Interest

- No conflicts

Objectives

- Review the definitions for identifying the presence of and classifying bloodstream infections (BSI)
- Recognize the spectrum of clinical disease and complications associated with *Staphylococcus aureus* BSI
- Review the epidemiology of *Staphylococcus aureus* BSI
- Discuss the management of *Staphylococcus aureus* BSI

Case

- 80 year old woman past history of chronic back pain and osteoarthritis
- General weakness, malaise, and fever
- ER found to have fever to 39 degrees C, no focal findings on exam
- WBC 20, and pyuria. CT Abdo/pelvis unremarkable.
- Admitted and treated with piperacillin/tazobactam for suspected pyelonephritis

Case continued

- Blood and urine cultures grow MSSA
- 7 days iv therapy completed feels better but not back to baseline and kept in as inpatient
- Repeat urine culture shows Cipro sensitive *Klebsiella pneumoniae* and started on that drug
- No dysuria. No fever. No focal back tenderness.

Case continued

- ID called and blood cultures ordered
- Echo-cardiogram, bone scan, cefazolin 2g IV q8h
- Development of leg weakness
- Urgent MRI epidural abscess
- Cloxacillin 2g IV q4h and neurosurgical consult
- Declines surgery
- Long complicated hospital stay and eventual death

Bloodstream infection definitions

- A positive blood culture is mandatory for a diagnosis of BSI
- However, not all positive blood cultures are BSI's
  - Contamination
  - Bacteremia
  - Transient bacteremia
  - Bloodstream infection (BSI)

Bloodstream infection definitions

- A degree of subjective assessment is required
  - common contaminants coagulase negative staphylococci, *Bacillus*, *Micrococcus*, *Corynebacterium*, and *Propionibacterium species*
- Blood must be sent and cultured appropriately (before antibiotics)
  - 1 set =1 venipuncture and 2 bottles (aerobic and anaerobic)
  - 2 sets (ie 4 bottles) per patient standard

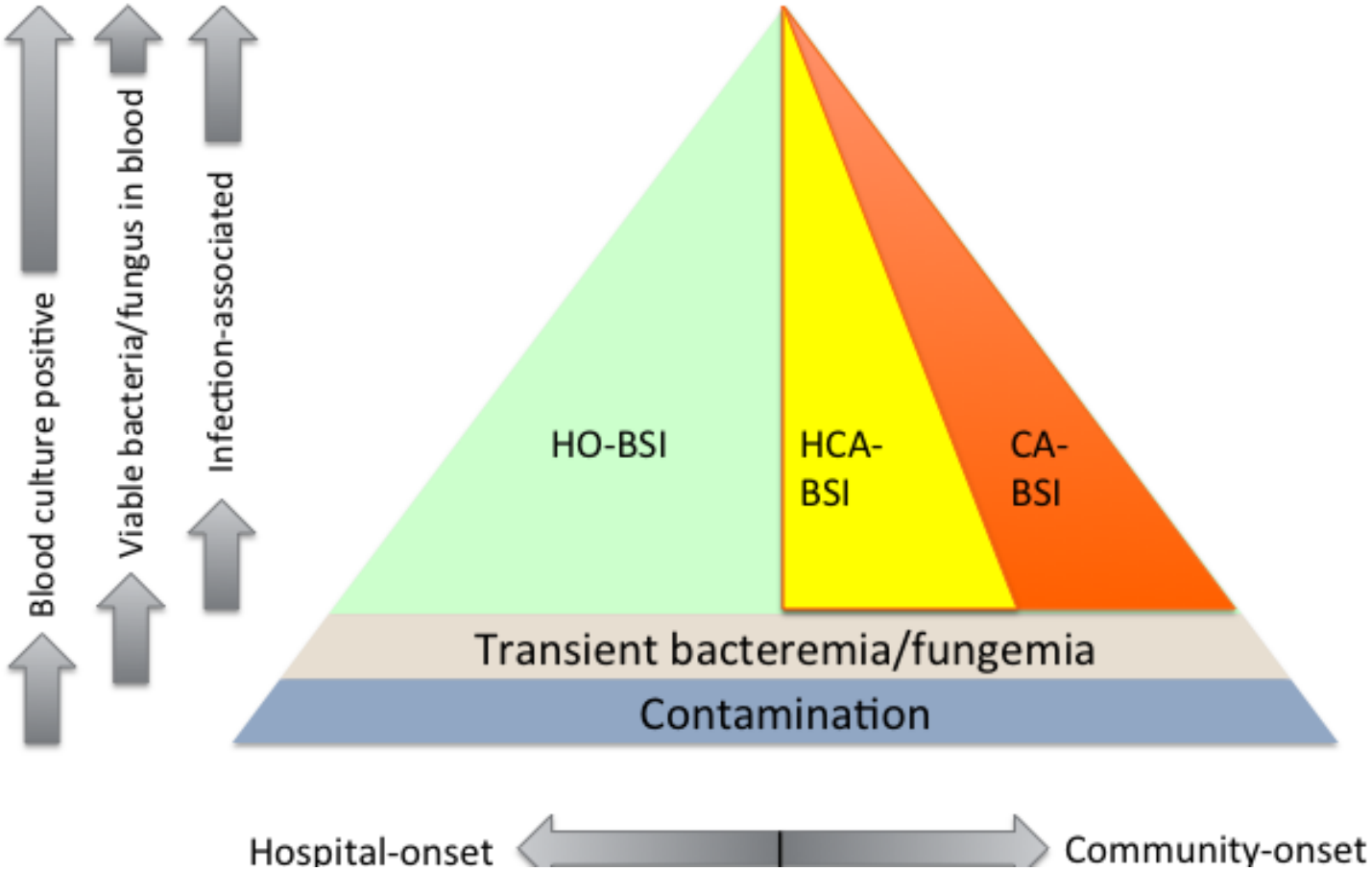
BSI definitions

- Traditional nosocomial versus community-**acquired** BSI
  - Focus on establishing most likely location of acquisition
  - Subjective component and significant inter-observer variation
  - Infection prevention and control
- Hospital-**onset** BSI versus community-**onset** BSI
  - Define by first culture positive after or before 48 hours of admission
  - Objective but lacks detail
  - Clinical management and surveillance

BSI definitions

- Healthcare-associated versus community-associated *community-onset BSI* (Morin *J Infect Dis* 2000)
- Shifts in healthcare provision to community setting
- Healthcare-associated (Friedman *Ann Intern Med* 2002)
  - Recent admission
  - Specialized care
  - Hemodialysis
  - Chemotherapy
  - Nursing home residents
- Older, different organism distribution, more co-morbidities, more resistant, and higher mortality (Lenz *BMC Infect Dis* 2012)

Laupland and Church *Clin Microbiol Rev* 2014



Primary or secondary BSI

- Is BSI an independent entity or just a marker of infection somewhere else?

- **Primary**-vascular catheter-associated only or **no focus** of infection
- **Secondary**-evidence of infection **focus** at a defined body site

- Influences management

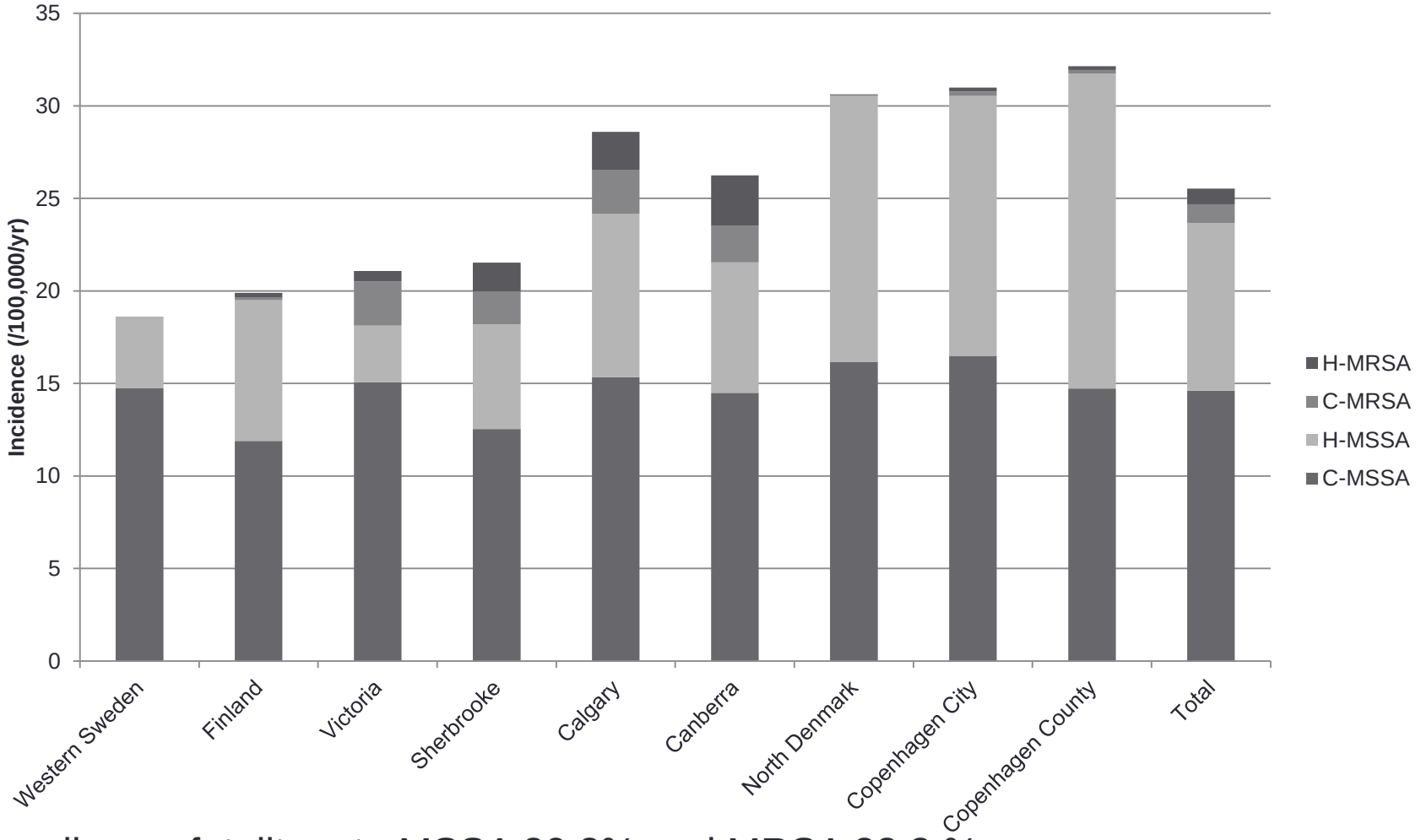
The “special” case of *S. aureus* BSI

- Sticky and “abscessogenic”
- Enterotoxins/superantigens
- BSI will alter management for focal infections
- Propensity to acquire resistance
  - Methicillin-sensitive (MSSA)
  - Methicillin-resistant (MRSA)

Epidemiology

- Second most common cause of BSI overall (Laupland *Clin Microbiol Infect* 2014)
  - *Escherichia coli* 30 per 100,000
  - *Staphylococcus aureus* 21 per 100,000
  - *Streptococcus pneumoniae* 10 per 100,000

International Bacteremia Surveillance Collaborative



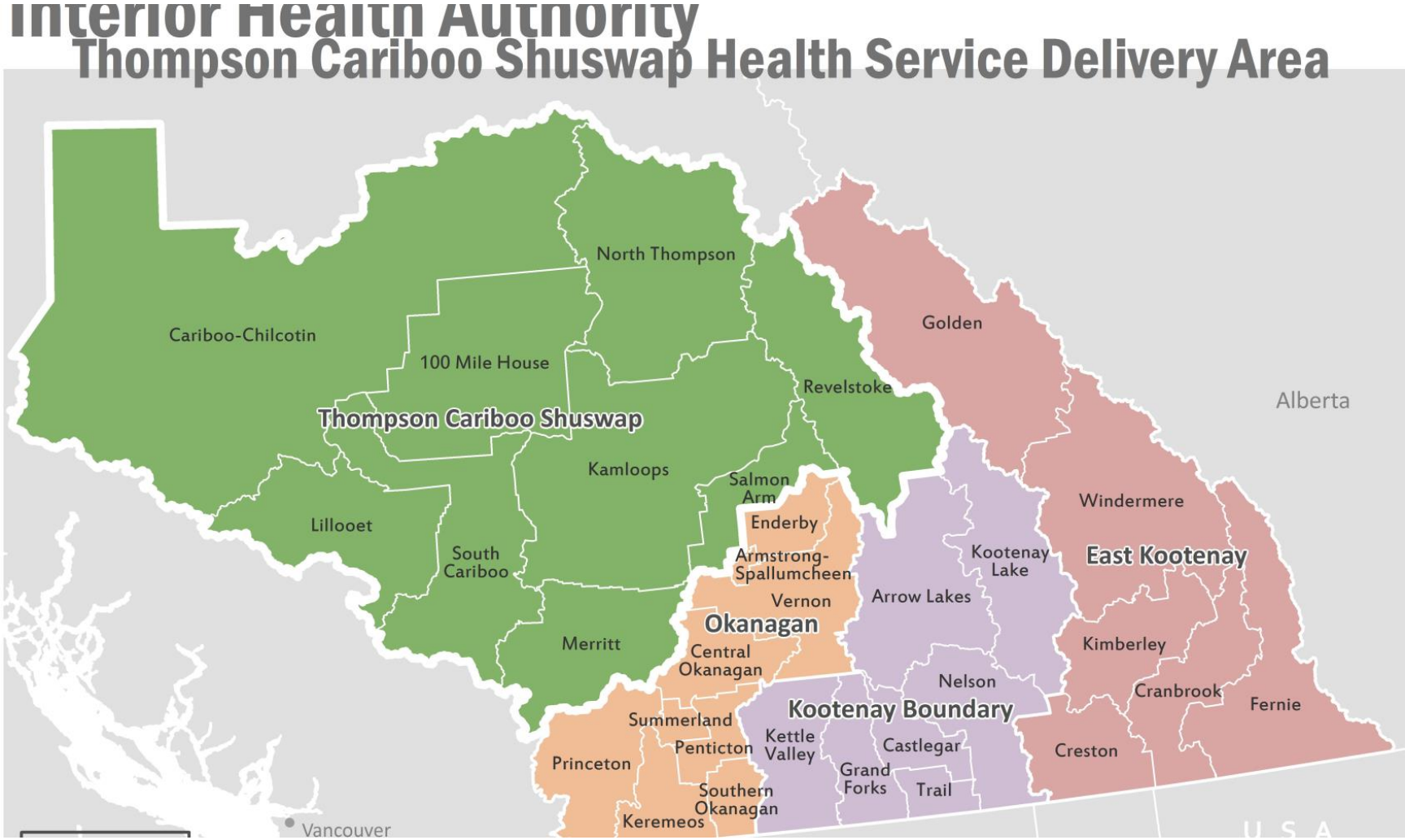
Overall case fatality rate MSSA 20.2% and MRSA 22.3 %
Laupland *CMI* 2013

Underlying condition	No. of patients with ISA infection (n = 226)	Annual incidence, per 100,000	Relative risk (95% confidence interval)	P
Hemodialysis	24	7692	257.2 (161.0–393.6)	<.001
Peritoneal dialysis	3	4918	150.0 (30.5–441.1)	<.001
Human-immunodeficiency-virus infection	4	778	23.7 (6.4–61.4)	<.001
Solid organ transplantation	3	683	20.7 (4.2–61.3)	<.001
Heart disease	114	362	20.6 (15.8–27.0)	<.001
Cancer	47	348	12.9 (9.1–17.8)	<.001
Illicit intravenous drug use	13	321	10.1 (5.3–17.7)	<.001
Alcohol abuse	31	241	8.2 (5.4–12.0)	<.001
Diabetes mellitus	48	192	7.0 (5.0–9.7)	<.001
Stroke	16	200	6.4 (3.6–10.6)	<.001
Chronic obstructive pulmonary disease	26	120	3.9 (2.5–5.9)	<.001
Systemic lupus erythematosus	2	80	2.4 (0.3–8.7)	.3
Rheumatoid arthritis	5	74	2.2 (0.7–5.3)	.1

NOTE. ISA, invasive *Staphylococcus aureus*.

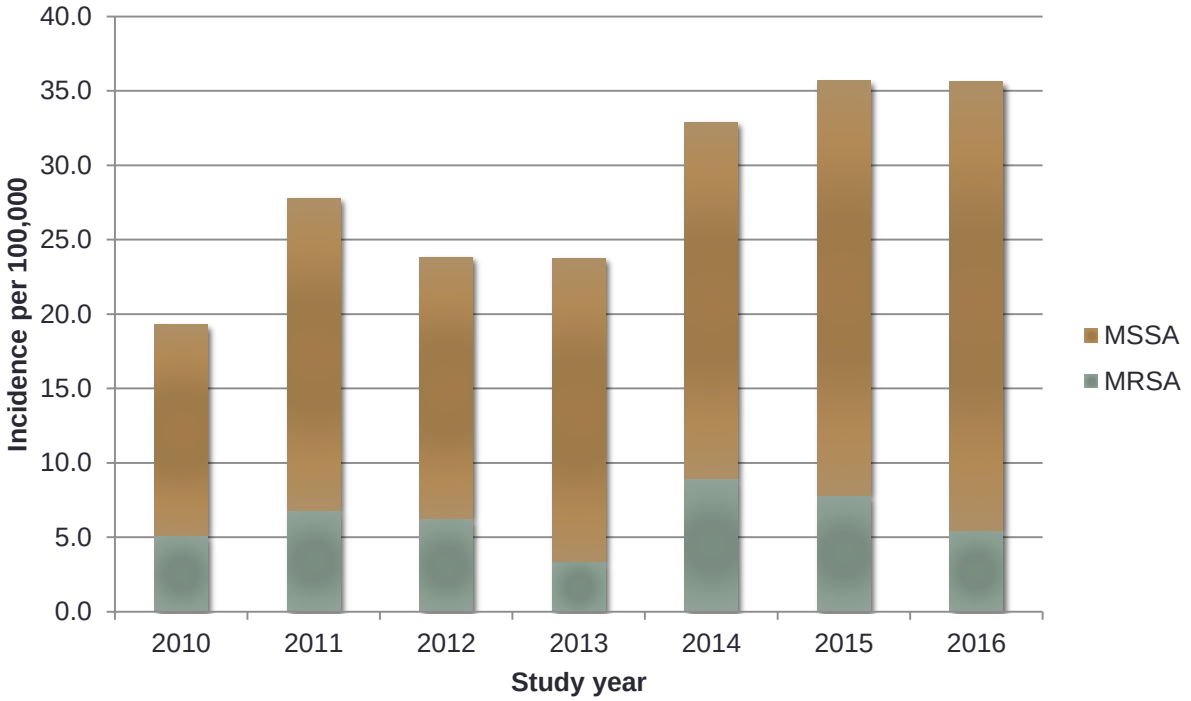
From: Laupland KB et al. Population-Based Study of the Epidemiology of and the Risk Factors for Invasive Staphylococcus aureus Infections
J Infect Dis. 2003;187(9):1452-1459. doi:10.1086/374621

Western Interior of BC



S. aureus BSI western interior

- Overall incidence 2010-2016 (per 100,000)
  - MRSA 6.3
  - MSSA 22.2



S. aureus BSI western interior

- In-hospital case fatality
  - MRSA 23%
  - MSSA 17%
- Focus of infection
  - No focus 28%
  - Bone and joint 24%
  - Endovascular 18%
  - Soft tissue 13%
  - Respiratory 12%
  - Other 3%

Diagnosis-Number of cultures

- Consider any positive blood culture for *S. aureus* a BSI
  - Erroneous use of number of sets positive to classify as BSI not uncommon (ie confused with coag negative staphylococci)
- Persistently positive blood cultures (Kullar *Clin Infect Dis* 2014)
  - Positive blood cultures despite 7 days of therapy
    - More likely endovascular or deep-seated focus
    - Metastatic infection development
    - Risk for post-treatment relapse
    - 2-3 fold higher mortality

Diagnosis-Echocardiography

- Approximately 5-15% of patients will have endocarditis
- Transthoracic approximately 50% sensitive but highly specific
- Transesophageal (TEE) estimated 95%+ sensitive
- TEE on all patients?
- Complicated scoring systems (Palraj *Clin Infect Dis* 2015)

Diagnosis-Clinical

- Clinical and diagnostic imaging search for a focus
  - Respiratory
  - Bone and joint
  - Intra-abdominal/pelvic

Source control

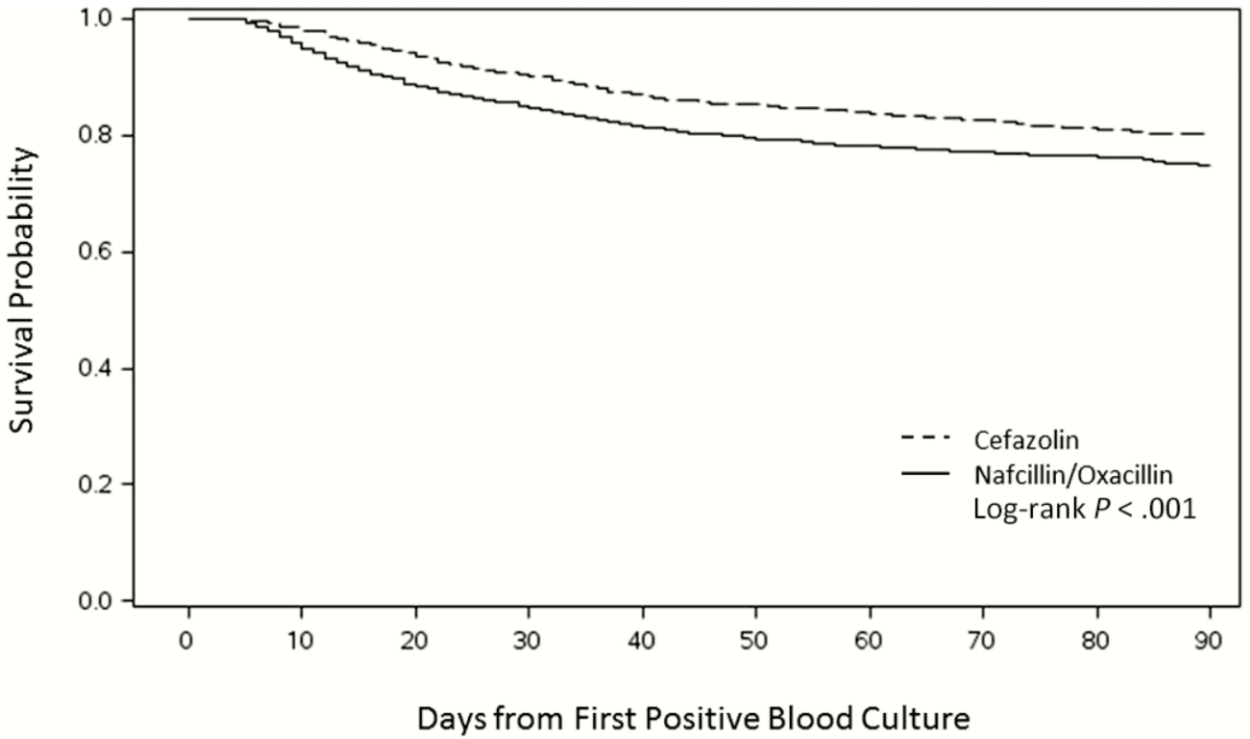
- Abscess=drain the pus
- Remove the line (Fowler *Clin Infect Dis* 1998)
- Evacuate the empyema
- Washout the joint

Antibiotherapy

- MSSA
  - Cloxacillin
  - Cefazolin
- MRSA
  - Vancomycin
  - Daptomycin
  - Linezolid
- Adjuncts and combination therapy

Cefazolin or cloxacillin for MSSA

- No RCT's but increasing observational studies
- Concerns cefazolin
  - high inoculum cefazolin resistance (Nannini *AAC* 2009)
  - broader spectrum
  - lack of CSF penetration
- McDanel *CID* 2017
  - 3,167 patients, 37% cefazolin versus 63% nafcillin/oxacillin
  - 37% reduction in 30-day and 23% reduction in 90-day mortality after adjustment (20% vs. 25% CFR)
  - Odds of recurrence =1.13; 95% CI 0.94-1.36



From: Comparative Effectiveness of Cefazolin Versus Nafcillin or Oxacillin for Treatment of Methicillin-Susceptible Staphylococcus aureus Infections Complicated by Bacteremia: A Nationwide Cohort Study

Clin Infect Dis. 2017;65(1):100-106. doi:10.1093/cid/cix287

Li *Antimicrob Agents Chemother* 2014

- **Comparison of Cefazolin versus Oxacillin for Treatment of Complicated Bacteremia Caused by Methicillin-Susceptible *Staphylococcus aureus***
- TABLE 3
- Adverse drug events with cefazolin or oxacillin for complicated MSSA bacteremia

Outcome or parameter	No. (%) among patients treated with:			P value
	Overall	Oxacillin	Cefazolin	
All adverse drug events	12 (13)	10 (30)	2 (3)	0.0006
Rash	2 (2)	1 (3)	1 (2)	1.0
Elevated transaminases	6 (6)	6 (18)	0 (0)	0.002
Elevated serum creatinine	1 (1)	1 (3)	0 (0)	0.37
Leukopenia	1 (1)	1 (3)	0 (0)	1.0
Diarrhea	1 (1)	0 (0)	1 (2)	0.37
Other	1 (1)	1 (3)	0 (0)	0.37
Discontinued due to adverse event	9 (10)	7 (21)	2 (3)	0.01

Vancomycin and MRSA

- Vancomycin has been the standard drug of choice since MRSA was first identified
- Vancomycin has a number of potential problems
  - Renal dysfunction
  - Penetration
  - Dosing and need for TDM
  - No oral bioavailability
  - Vast anecdotes of dislike

Vancomycin reduced susceptibility

- Vancomycin susceptible ≤2 ug/mL
- Vancomycin intermediate (VISA) 4-8 ug/mL
- Vancomycin resistant (VRSA) ≥16 ug/mL
- Elevated but not resistant MICs ie “MIC creep”

Vancomycin reduced susceptibility

- Jacob *Int JID* 2013
  - Increased mortality (1.4 RR 95% CI, 1.15-1.71) for MIC ≤1ug/mL versus 1.5-2 ug/mL
- Kalil *JAMA* 2014
  - No difference in outcomes with MIC ≤1ug/mL versus 1.5-2 ug/mL in observational studies
- Baxi *AAC* 2016
  - No difference in outcome among 429 episodes with MIC <2ug/mL versus 2 ug/ml

Daptomycin

- Bactericidal
- IV only but once per day (6-12 mg/kg)
- Adjust dosing if cr cl <30 mL/min
- CK elevation/myositis
- Inactivation by pulmonary surfactant

Daptomycin and *S. aureus* BSI

- Fowler *NEJM* 2006
  - Not inferior to standard therapy with low dose gent plus vancomycin (MRSA) or anti-staphylococcal penicillin (MSSA)
- Retrospective observational studies of MRSA BSI patients with vancomycin MIC>1 ug/mL
  - Moore *CID* 2012
    - Clinical failure (31% vs. 17%) and mortality (20% vs.9%) higher with vancomycin as compared to daptomycin
  - Murray *CID* 2013
    - Clinical failure (48% vs. 20%) and mortality (13% vs. 4%) higher with vancomycin as compared to daptomycin
  - Weston *CID* 2014
    - Clinical failure vancomycin versus daptomycin 51% vs. 34%

Linezolid

- Well tolerated (cytopenias, serotonin syndrome)
- Tissue penetration including CNS
- High bioavailability
- Bacteriostatic
- Not inferior to vancomycin but very limited secondary data on BSI (Schorr *JAC* 2005)

Other *in vitro* active drugs?

- Tetracycline/Tigecycline
- TMP-SMX
- Clindamycin
- Quinolones (levofloxacin, moxifloxacin)

Combination therapies

- Combinations of 2 or more active drugs may be either better or worse than one alone
- Rifampin plus vancomycin
  - Observational studies suggest that this combination may be antagonistic (Tremblay *Ann Pharmacother* 2015)
  - MRSA endocarditis RCT (Levine *Ann Intern Med* 1991)
    - No significant difference in duration of bacteremia or cure
    - Small study (42 patients)
- Gentamicin plus cell wall agent
  - May clear bacteremia sooner (1 day) but higher rate of renal dysfunction and no difference in outcome (Cosgrove *CID* 2009)

Combinations with resistant drugs

- A vast array of studies in recent years evaluating combinations of drugs that alone may not be active
  - Daptomycin plus β-lactams (nafcillin, cefotaxime, amoxicillin-clavulanate, and imipenem) reduce cell net positive surface charge increasing that daptomycin binding to the cell surface (Mehta *AAC* 2012)
  - Daptomycin plus TMP-SMX (Claeys *AAC* 2015)
  - Vancomycin plus cephalosporins (Rybak *Exp Opin Pharmacother* 2013)

Evolving treatments

- IV Fosfomycin plus imipenem (del Rio CID 2014)
- Ceftaroline
- Ceftibiprole
- Tedizolid

Duration of therapy

- Endocarditis standard 6 weeks (4 if tricuspid uncomplicated)
- The default duration of therapy for *S. aureus* BSI is 4-6 weeks of IV administered antibiotics (*ie if endocarditis can't be ruled out then treat it)*
- Care with community onset cases
- Difficult to treat foci may need further oral therapy (ie bone and joint)

Duration of therapy

- Short course therapy if all fulfilled
  - Negative TEE
  - Negative repeat blood culture
  - Rapid clinical response
  - Removable focus
  - No clinical signs of metastasis
  - No indwelling device (ie pacemaker)

Case review

- First identification of *S. aureus* in blood cultures should have prompted a clinical search for a focus (urine culture was a red herring)
- TEE
- Repeat blood cultures
- Imaging of spine
- Minimum 4 weeks of IV therapy
- ID consult

Summary

- *Staphylococcus aureus* BSI is a serious condition that is associated with major adverse outcomes
- Second most common but arguably most important etiology of BSI
- Sending blood for culture is necessary to identify *S. aureus* BSIs

Summary

- A clinical and diagnostic imaging search for foci is required in patients who have *S. aureus* BSI
- Core management principles include source control, identification of complicated foci/metastasis, and appropriate anti-biotherapy (drug, dose, duration)
- Infectious diseases consultation is recommended in the management of patients with *S. aureus* BSI

Questions?