

# Staphylococcus aureus bacteremia of unknown source

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# Outline

- Definition
- Impact
- Epidemiology : trends
- MRSA: hospital-acquired (HA),  
community-acquired (CA)
- Metastatic infection: endocarditis;  
prostheses; others
- Therapy

# Definitions

- Bacteremia of unknown source, or primary bacteremia, is a bacteremia the source of which is not certain after history, physical examination and initial evaluation, typically including chest X-ray.
- Secondary bacteremia: an illness associated with one or more positive blood cultures from a known primary source, such as skin or bone

# Staphylococcus bacteremia: scope of the problem

- Staphylococcus aureus remains a major human pathogen. As a cause of healthcare associated infection, it is estimated to kill 12,000 patients per year in the US and cost \$9.5 billion. It is responsible for 20% of monomicrobial nosocomial bloodstream infections . It remains a major cause of community acquired infection, particularly skin and soft tissue, and is increasingly antimicrobial resistant.
- (Noskin et al, Arch Intern Med 2005;165:1756-61;Wisplinghoff et al, Clin Infect Dis 2004;39:309-17)

# Staphylococcus aureus bacteremia: case fatality

- Pre-antibiotic era: over 80%
- Now: generally in the 20-30% range

# SAB rates increasing: UK

- Wyllie et al (BMJ 2006;333:281-4)
  - 2 Oxfordshire hospitals 1997-2004
  - Rates of nosocomial SAB rising
  - Attributable to increase in MRSA
  - 29% mortality (MRSA 34%, MSSA 27%)
- Johnson, Pearson & Duckworth ( J Antimicrob Chemother 2005;56:455-62)
  - National survey
  - Rising rates of SAB
  - Increase in proportion of MRSA

# SAB Rates rising:

- Kaech et al, Switzerland (Clin Microbiol Infect 2006;12:345-52):
  - 23% increase in SAB over 2 decades from 1980s to 2000s (2.2 to 2.7 episodes/1000 admissions)
  - 140% increase in community-acquired (attributed to ivdu), mostly of unknown primary source (52%)
  - 60% increase in catheter-related SAB
  - Diminished mortality (20%, down from 34%):community – 26%, hospital 13%.

# SAB : USA

- SCOPE project- prospective surveillance
- 20% of nosocomial bacteremia was due to *S. aureus*
- 57% MRSA (was 22% in 1995)
- Strikingly similar to proportion of MRSA in pyogenic skin infections in Moran study (59%)
- (Wisplinghoff et al, Clin Infect Dis 2004;39:309-17;Moran et al NEJM 2006;355:666-74)

# MRSA: why it matters

- Has been shown to be associated with increased mortality of SAB in 2 meta-analyses
- Increased mortality in endocarditis ,50 vs 23% (Chang et al, Medicine (Baltimore) 2003;82:322-32).
- Increased mortality controlling for severity of underlying illness (Shurland et al, Infect Control Hosp Epidemiol 2007;28:273-9 )

# Why increased mortality in SAB due to MRSA?

## ■ Therapy

- Delay in effective therapy
- No effective therapy
- Vancomycin intrinsically less cidal –slower killer- than beta lactams

# Why increased mortality in SAB due to MRSA?

- Virulence of organism
- CA-MRSA associated with Panton Valentine leukocidin
- Increased rates of invasive cutaneous infection and severe necrotizing pneumonia; less endocarditis, mycotic aneurysms (Wang et al, Clin Infect Dis 2008;46:799-806).

# Blurring of distinctions in MRSA: CA vs HA

- Increasing proportion of hospital-acquired MRSA were phenotypically like community-acquired strains in terms of antimicrobial susceptibility (Popovich et al, Clin Infect Dis 2008;46:787-94)
- Not surprising, in view of burden of chronic disease and interventions in community, traffic of people between community and hospital, virulence of CA-organism

# Metastatic spread from SAB

- Not clear how hard to look for it
- Metastatic spread happens to all parts of body, critically heart and CNS
- How to predict

# Bacteriologic associations of metastatic SAB

- Rapid onset of positivity of blood cultures <12 hours
- Associated with endocarditis and other hematogenous spread
- (Khatib et al, Clin Infect Dis 2005;41:594-8)

# Bacteriologic associations of metastatic SAB

- Duration of positivity of blood cultures: persistence > 3 days associated with indwelling devices, endocarditis, multiple sites of infection (Khatib et al, Scand J Infect Dis 2006;38:7-14)
- Not clear how rise of CA-MRSA plays out: will it turn out to predispose to metastatic infection?

# Endocarditis

- Common (one recent estimate of 13% of SAB (21% of CA, 5% of HA)
- Increased mortality (31% vs 21% mortality)
- (Chang et al, Medicine (Baltimore) 2003;82:322-32 )
- Increasingly easy to diagnose

# Endocarditis: echocardiography

- TEE more sensitive than TTE (25% vs 7%) (Fowler et al, J Am Coll Cardiol 1997; 30:1072-8).
- TEE useful guide to duration of therapy (4 weeks if +, 2 weeks if negative)
  - Rare failures
  - More effective compared with short-course and cost-effective compared with long (<\$5000/QALY)
  - (Rosen et al, Ann Intern Med 1999;130:810-820)

# Endocarditis: alternative echo strategy (Van Hal)

- Delayed TTE if no embolic phenomena
- 2% false negative
- Needs confirmation
- (J Infection 2005;51:218-21)

# Prostheses

- Increasing prevalence
- Insertion figures easier to come by: in US, >700,000 joint replacements/year, 384,000 pacer procedures, 60,000 valves (Defrances et al, 2005 National Hospital Discharge Survey: advance data from Vital and Health Statistics, no 385, July 12, 2007; Vongpatanasin et al, NEJM 1996;335:407-16).
- Joints and valves at high risk, >40%, of getting seeded by SAB (Chu et al, Am J Med 2005; 118:19-24).
- Joints at higher risks than other orthopedic devices
- Higher mortality of SAB complicated by prosthetic valve endocarditis

# Therapy

- Secondary: drain, debride, remove device
- Antimicrobials
- Vancomycin: plodder. Slow kill, worsened outcomes compared with beta lactams

# Therapy: MRSA

- A raft of new agents out targetting MRSA
- Daptomycin, tigecycline, linezolid
- Ceftibiprole, telavancin

# Therapy: MRSA

- Daptomycin: equivalent to alternative therapy (inactivated in lung)
- Linezolid: perhaps advantageous in pneumonia but equivalent in bacteremia
- Cetibiprole: equivalent to vancomycin plus ceftazidime in skin and soft tissue infections

# Therapeutic quandry

- Presumptive therapy of SAB
- Vancomycin more active than beta lactams vs. MRSA
- Vancomycin less active than beta lactams against MSSA
- Role of other agents uncertain
- Local epidemiology a key element in presumptive therapy

# Investigations

- Echocardiography: indicated in all patients with SAB; TEE preferred
- Other: unclear
  - Special populations: prostheses
  - Rapid onset of positivity; persistent bacteremia
  - CA-MRSA

# Summary

- SAB increasing in incidence worldwide
- Particular rise in community acquired SAB of unknown primary source
- Rise in MRSA
- SAB capable of metastatic spread; frequent in presence of prosthetic devices

# Summary, cont.

- Therapy of SAB requires antibiotics
- Use of presumptive vancomycin compromises efficacy of therapy of MSSA
- Role of newer agents not yet fully worked out
- Endocarditis should be ruled out
- Other investigation for metastatic infection: not clear when it should be sought , perhaps if bacteremia of rapid onset or when it is persistent