The Best Duration of Antimicrobial Treatment for Staphylococcal Infections

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Outline

• What does the evidence suggest for treatment duration?
• What do the guidelines propose?
• The role of new agents for shortening the treatment?
Case Discussion-I

• 48 y.o. woman with rupture of a cerebral aneurism
  – Intubated in the ICU w a central line
  – Fever develops at 6th d of hospitalization
  – Pip-tazo and vancomycin empirically started
  – Blood cultures grew Gram (+) cocci
  – Line removed
Case Discussion-II

- De-escalation to vancomycin
- Defervescence and clinical stability (at 48 h)
- MSSA reported
- Tx switched to sulbactam-ampicillin (day 7)
- Repeat cultures negative
- TEE normal
How would you proceed?

- Stop treatment immediately (day 9)
- Continue until day 14
- Continue until day 16
- Treat for 4-6 weeks
Staphylococcal Bacteremia

- The duration of therapy depends on the etiology
- Patients with removable focus
  - 14-day iv therapy after the 1st negative blood culture

Conditions Required for 14-day Therapy

• After iv therapy, patient is afebrile within 48-72 h
  – Focus of infection removed
    • e.g. Soft tissue, catheter
  – Follow-up blood cultures negative
  – No metastatic infection
  – No valvular abnormalities
  – No grafts or prosthetic valves

Other Conditions Required...

- Absence of diabetes mellitus
- Absence of immunosuppression
- No endocarditis and suppurative thrombophlebitis by echo and USG

Management of CRBSI

Complicated

Supp. thromboph., endocarditis, osteomyelitis

Remove catheter and tx w systemic abs, 4-6 weeks

Uncomplicated

Coag. (-) staph.

• Remove catheter and tx systemic abs, for 5-7 days
  • If catheter retained, tx for 10-14 d

S. aureus

• Remove catheter and tx systemic abs, for ≥14 days

Patients with *S. aureus* Bacteremia & Cardiac Valve Abnormalities

- If no vegetation on TEE
  - 14-d therapy sufficient
  - Negative cultures within 72 h
  - No deep staphylococcal infection

Treatment Duration for Uncomplicated *S. aureus* Bacteremia

- Prospective cohort, 2008-2010, Korea
- 12-week observation
- Uncomplicated bacteremia
  - Negative cultures at 2-4 days
  - Defervescence within 72 h therapy
  - No metastatic infection
  - CRBSI and primary bacteremia with no endocarditis in echo

304 patients with SAB: 208 CRBSI + 96 unknown focus

Performance of follow-up blood cultures at 2-4 d after SAB

- (no) 50
- (yes) 254

- (-) 120
  - 22 Endocarditis
  - 24 Primary bac.
  - 74 CRBSI

- (+) 134
  - Negative blood culture results at 2-4 d
  - Defervescence within 72 h
  - No metastatic infection

  11 patients excluded due to death during antibiotic therapy

- (-) 12
  - Primary bac.
  - 29 CRBSI

- (+) 28
  - Primary bac.
  - 54 CRBSI

111 patients 12 weeks follow-up
Results

• 47.7% with MRSA bacteremia
• Short-course (<14 d) vs intermediate (≥14 d) therapy
  – No difference in
    • Treatment failure (26% vs 22%)
    • Crude mortality (18% vs 22%)
  – More relaps with short-course
    • 7.9% vs 0 (p=.0036)
  – Primary bacteremia, more likely to have treatment failure (p=.06)

**S. aureus as a Virulent Pathogen**

- In patients with *S. aureus* bacteremia, the rate of:
  - Metastatic infection (34%)
    - In patients with CRBSI, this rate is 14%
  - When aggressively sought in CRBSI patients
    - Endocarditis >12%
    - Septic thrombophelbitis >70%

Predicting Focal Sites of Infection in *S. aureus* Bacteremia

- Community acquisition
- Clinical signs
- Persistence of fever and bacteremia at 48 to 96 h after antibiotic therapy

Evidence for Duration of Treatment for S. aureus Bacteremia

• Only one RCT examining the duration of iv therapy
  – 11 adults, 2-week vs 4-week of iv therapy
  – One patient in 2-weeks group developed infective endocarditis compared none in 4-week group

• The remaining evidence comes from observational studies

Coagulase-negative Staphylococci

- Considered to have lower virulence
- But in a series with native valve endocarditis
  - 8% of patients caused by CNS
  - 39% had heart failure, 60% required surgery
  - Mortality was similar to S. aureus native-valve endocarditis (25% vs 27%)

Approach to Blood Culture (+) for CNS

• Exclude contamination
  – 93% with single culture
  – 39% with 2 cultures
  – 0% with 3 cultures

• Determine complicated or focal infection
  – Community-acquired
  – Positive blood culture during follow-up
  – IV or other foreign material not removed early
  – Septic thrombophlebitis, endocarditis, immunosuppression

Treatment for CNS BSI

• Identification to species level is not necessary for duration of tx

• With a beta-lactam antibiotic
  – 3-5 d for non-complicated infection
  – 5-7 d for CRBSI

• Questions
  – 3 d therapy w daptomycin
  – 5-7 d therapy with vanco or linezolid

New and Alternative Therapies

• Linezolid
  - No comparative trials for *S. aureus* bacteremia (SAB)
  - Two meta-analysis with subsets of SAB
    • 99 patients in 5 trials
      - Linezolid vs vanco for severe infections
      - No difference
    • 6093 patients in 12 controlled trials
      - 255 SAB
      - Tx success higher w linezolid vs beta-lactam or vancomycin
      - No survival advantage

Tedizolid

- An oxazolidinone w po and iv formulation
  - Once daily dosing
  - Shown to be non-inferior to linezolid in skin infections
- Compared in two RCT
  - po vs po
  - initial iv followed by po
  - No duration advantage

Daptomycin

- Non-inferior to vanco plus low-dose gentamicin for SAB w or w/o right-sided endocarditis
- No tx duration advantage

Other Drugs

• Ceftaroline
  – Approved only for cSSTI and CAP
  – No duration advantage

• Ceftobiprole
  – Non-US approved for skin infections
  – Comparable efficacy w vanco + ceftazidime

• Telavancin
  – As effective as vanco in cSSTI
  – No duration advantage

Corey GR; et al. Clin Infect Dis 2010;51:641
Dalbavancin

• Semisynthetic lipoglycopeptide
• Half-life 6-12 days, once weekly dosing
  – 1000 mg followed by 500 mg one w later
• Approved for acute bacterial skin infections
  – Tested in >1200 patients
    • 2 dose dalbavancin vs vanco for 72 h followed by po linezolid for 10-14 days
    • Similar success

Dalbavancin for CR-BSIs

• Phase II, open label trial
  – 75 adult patients w CR-BSIs
  – 2 dose dalbavancin vs 14 d vancomycin

• Success rate favors dalbavancin
  – 87% vs 50%

Oritavancin

- Semisynthetic glycopeptide
- Half life 100 hours
- Approved for acute bacterial skin infections
- Two RCTs showed non-inferiority to vancomycin in skin infections
  - 1200 mg single dose oritavancin vs 7-10 d vancomycin

Conclusions

• 14 d iv tx following the 1st negative blood culture is standard for uncomplicated S. aureus bacteremia
• Complicated cases require treatment 4-6 weeks
• Empiric therapy should cover MRSA
  – Beta-lactam tx for MSSA
• New agents promising shorter duration of tx
Thank you...