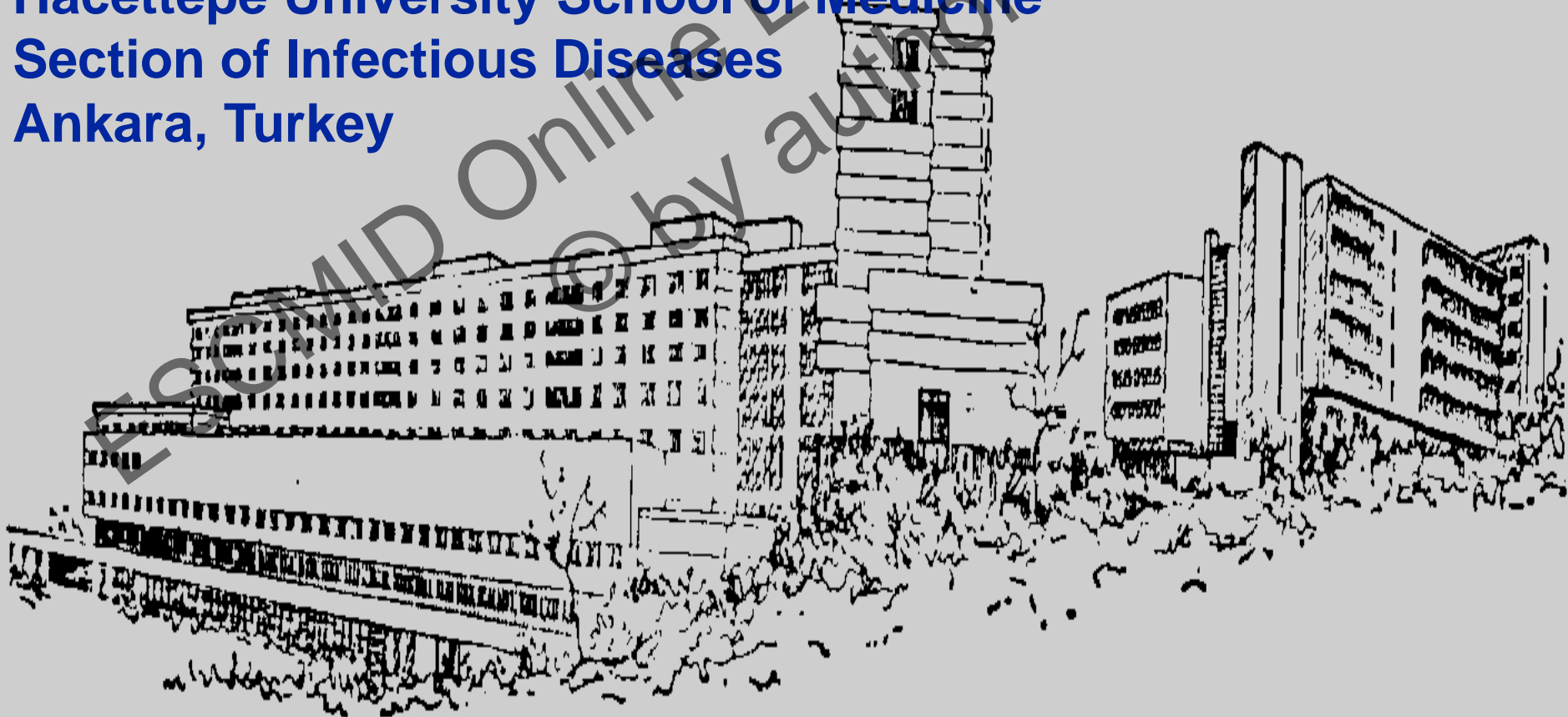


The Best Duration of Antimicrobial Treatment for Staphylococcal Infections

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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

Liu C, et al. Clin Infect Dis. 2011;52:e18

Mermel LA, et al. Clin Infect Dis. 2009;49:1

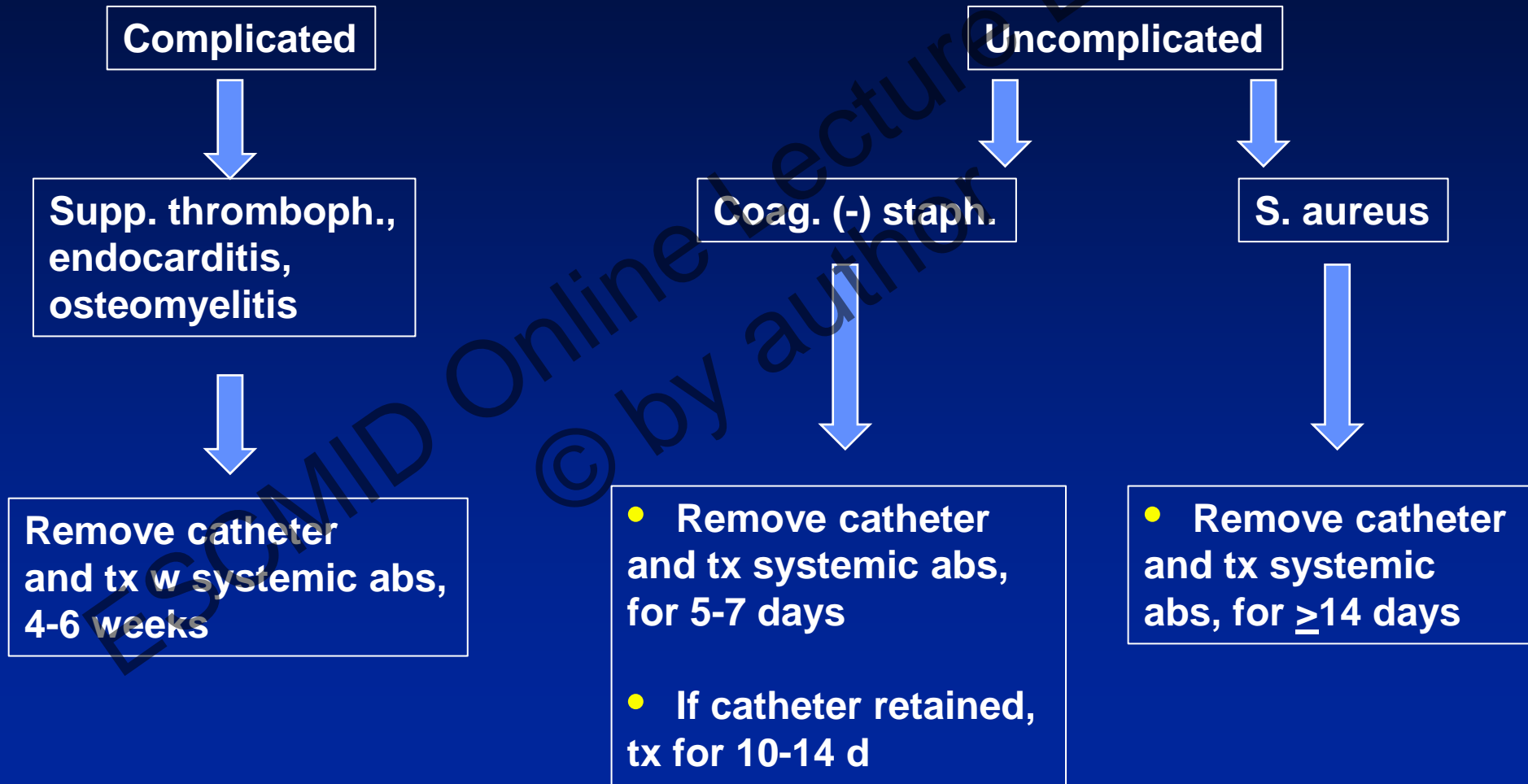
Conditions Required for 14-day Therapy

- 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



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

Liu C, et al. Clin Infect Dis. 2011;52:e18

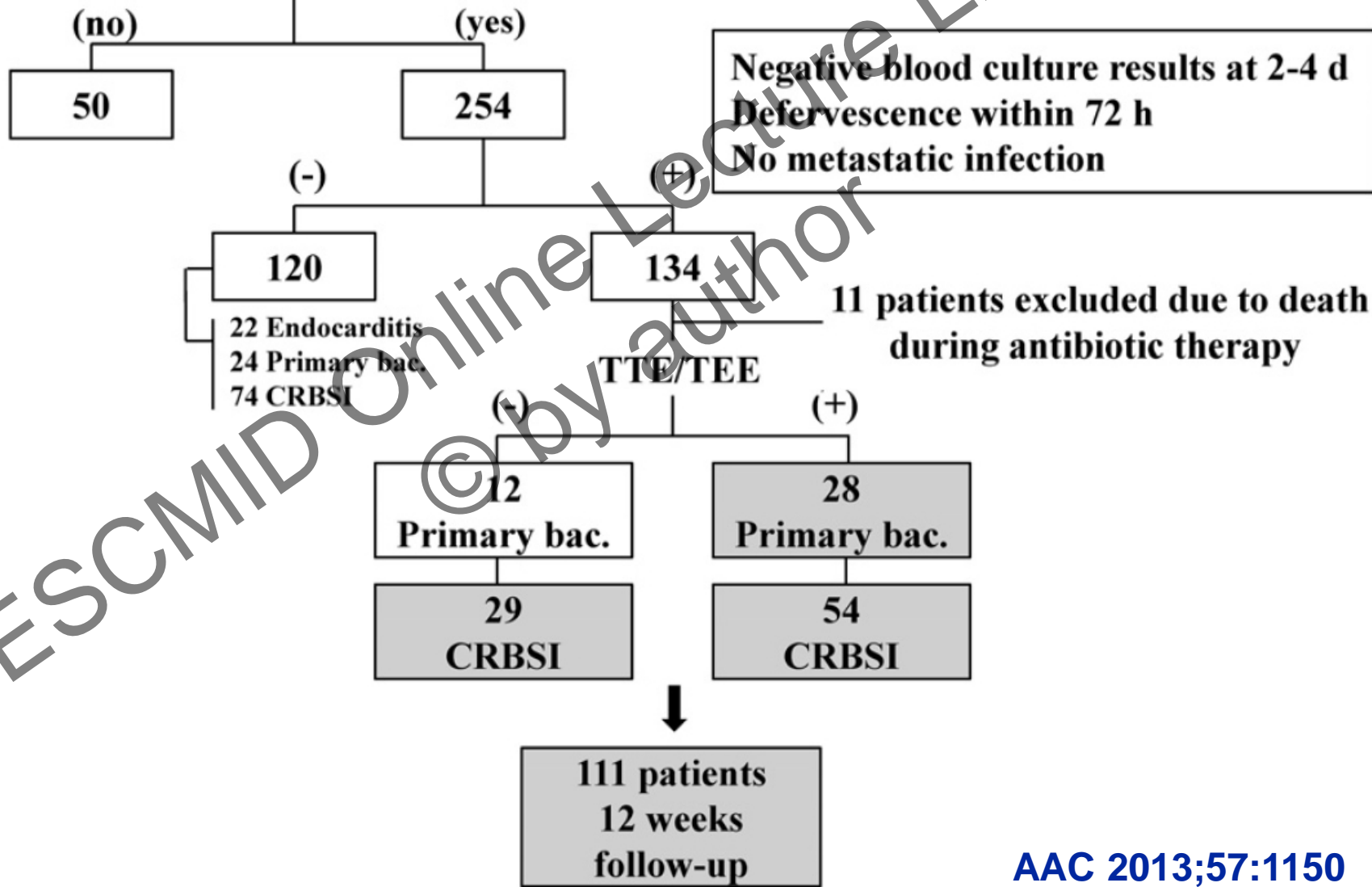
Mermel LA, et al. Clin Infect Dis. 2009;49:1

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



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%

Crowley AL, et al. Crit Care Med 2008;36:385

Fowler VG, et al. Arch Intern Med 2003;163:2066

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

Fowler VG, et al. Arch Intern Med 2003;163:2066

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 thrombophelbitis, endocarditis, immunosuppression

Everts RJ, et al. ASM General Meeting, 1999. Abst. 142

Corey GR, et al. Int J Antimicrob Agents 2009;34S:S47

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

Corey GR, et al. Int J Antimicrob Agents 2009;34S:S47
Mermel LA, et al. Clin Infect Dis. 2009;49:1

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

Shorr AF, et al. J Antimicrob Chemother 2005; 56: 923
Falagas ME, et al. Clin Microbiol Infect 2008;14:101

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**

Prockimer P, et al. JAMA 2013;309:559
Moran GJ, et al. Lancet 2014;14:696

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 \pm ceftazidime

- **Telavancin**

- As effective as vanco in cSSTI
- No duration advantage

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

Noel GJ, et al. Clin Infect Dis 2008;46:647

Stryjevski ME, et al. Clin Infect Dis 2008;46:1683

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

Corey GR, et al. N Engl J Med 2014;370:2180

Corey Gr, et al. Clin Infect Dis 2015;60:254

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....

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