Staphylococcus aureus Endocarditis:

New Data 2007

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S. aureus Endocarditis: New Data

- Epidemiology
- Risk factors
- Clinical spectrum
- Pathogenesis
- Therapy
- Outcome

Infective Endocarditis: Microbiology (1970-2000)

- Causative microorganisms
  - Streptococci 54 %
    - Viridans 44 %
    - Other 10 %
  - Staphylococci 33 %
    - S. aureus 26 %
    - CoNS 7 %
  - Enterococci 6 %
  - Other 8 %
  - Culture-negative 1 %
- No temporal trend for either pathogen group

Tleyjeh IM, et al. JAMA 2005; 293: 3022-3028.

Infective Endocarditis: Microbiology

	Native-valve IE (n=280)	IE in intravenous drug users (n=87)	Prosthetic-valve IE	
			Early (n=15)	Late (n=72)
Pathogen				
Staphylococci	124 (44%)	60 (69%)	10 (67%)	33 (46%)
Staph aureus	106 (38%)	60 (69%)	3 (20%)	15 (21%)
Coagulase negative	18 (6%)	0	7 (47%)	18 (25%)
Streptococci	86 (31%)	7 (8%)	0 (0%)	25 (35%)
Oral streptococci	59 (21%)	3 (3%)	0	19 (26%)
Others (non-enterococcal)	27 (10%)*	4 (5%)	0	6 (8%)
Enterococcus spp†	21 (8%)	2 (2%)	1 (7%)	5 (7%)
HACEK group	12 (4%)‡	0	0	1 (1%)
Polymicrobial	6 (2%)	8 (9%)	0	1 (1%)
Other bacteria	12 (4%)§	4 (5%)	0	2 (3%)
Fungi	3 (1%)	2 (2%)	0	0
Negative blood culture	16 (6%)	4 (5%)	4 (27%)	5 (7%)

*Including nine *Streptococcus agalactiae*, six *Strep bovis*, three *Streptococcus pneumoniae*, two *Streptococcus pyogenes*, one group *G streptococcus*, and one *Abiotrophia* spp. †>80% *Enterococcus faecalis*. ‡ Includes *Haemophilus* spp, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *E corrodens*, and *K kingae*. §Includes four *Escherichia coli*, two *Corynebacterium* spp, two *Proteus mirabilis*, one *Mycobacterium tuberculosis*, and one *Bacteroides fragilis*. Data from studies providing comparable microbiological details[4,5,10]

Lancet 2004; 363: 139-149.

Infective Endocarditis: Microbiology

	Community-acquired (n=136)	Hospital-acquired (n=67)	Native valve (n=124)	Prosthetic valve (n=70)
S. aureus	27 %	37 %	30 %	29 %
CoNS	12 %	15 %	8 %	21 %
Streptococci	31 %	15 %	33 %	16 %
Enterococci	18 %	15 %	15 %	20 %
Other	4 %	3 %	2 %	4 %
Culture-neg	10 %	15 %	12 %	10 %

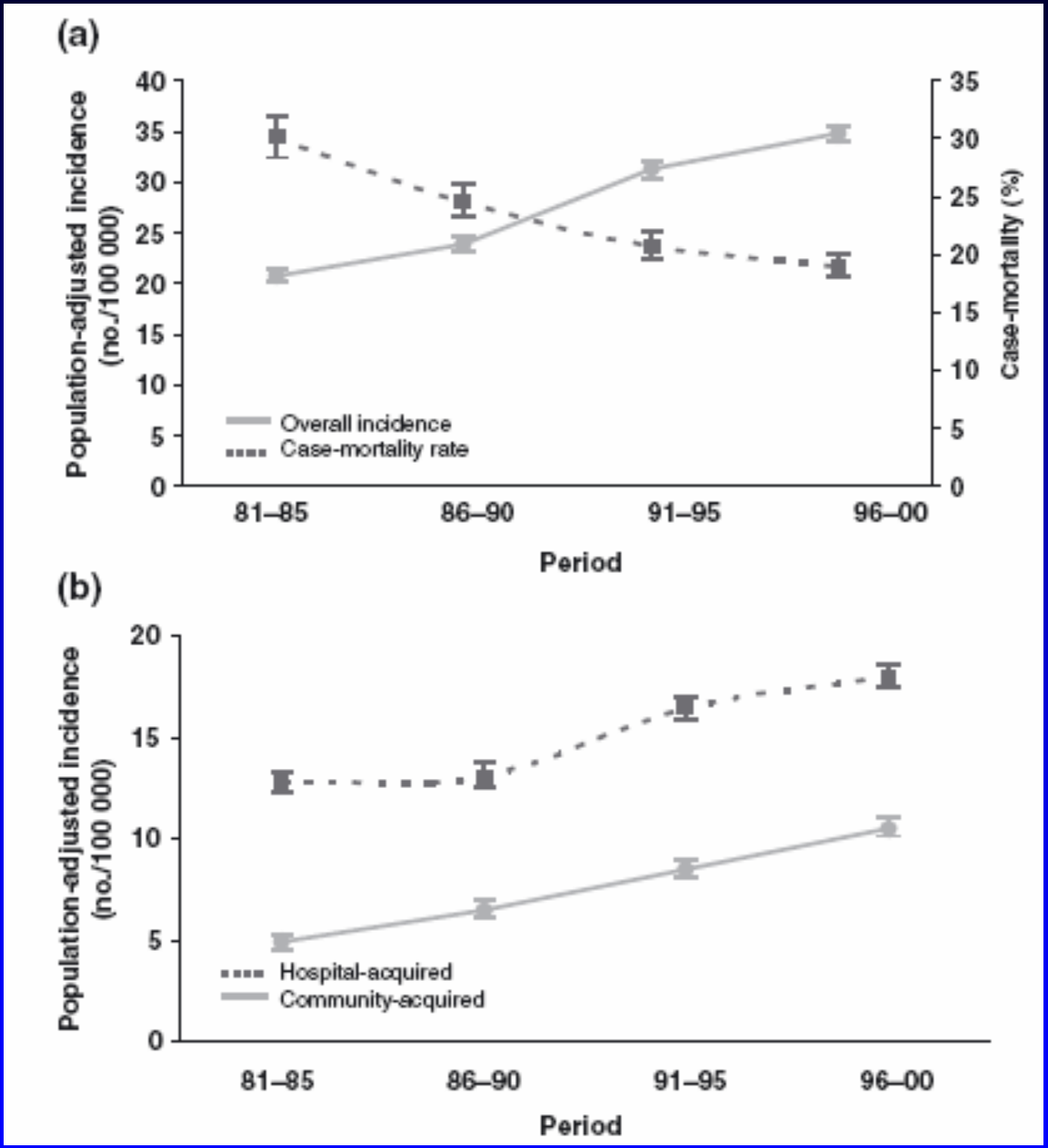
Hill EE, et al. Eur Heart J 2007; 28: 196-203.

S. aureus bacteremia

- 18702 adult cases between 1981 and 2000 in Denmark
- 57% hospital-acquired and 28% community-acquired
- Incidence increased from 18.2 to 30.5 cases per 100.000 population
- Annual increase: - by 6.4% for C.A. cases
  - by 2.2% for H.A. cases
- Case mortality decreased: - C.A: from 34.5% to 26.5%
  - H.A. from 36.2% to 20.7%

Benfield T, et al. Clin Microbiol Infect 2007; 13: 257-263.

S. aureus bacteremia



Benfield T, et al. Clin Microbiol Infect 2007; 13: 257-263.

S. aureus endocarditis following S. aureus bacteremia

	SAIE (n=64)	SAB (n=441)	p value
Heart disease			
Native valve	36 %	8 %	0.002
Prosthetic valve	12 %	1 %	0.001
Prior IE	13 %	1 %	0.005
IV drug use	27 %	7 %	0.02
Unknown portal	50 %	27 %	0.008
Community-acquired	67 %	37 %	0.004
Persistent bacteremia (3 days)	27 %	9 %	0.001
Mortality (30 days)	31 %	21 %	NS

Chang FY, et al. Medicine 2003; 82: 322-332.

S. aureus endocarditis following S. aureus bacteremia

- Persistent bacteremia was independent risk factor for both endocarditis and mortality
- Blood cultures must be repeated 3 days following initiation of antistaphylococcal antibiotics in all patients with SAB
- Echocardiography to screen for IE if SAB with community origin, underlying valvular heart disease, IV DU, unknown portal of entry and history of prior IE

Chang FY, et al. Medicine 2003; 82: 322-332.

Risk factors for SAIE in patients with SAB

- Nested case-control study (June 2000-Dec 2005)
  - 39 CA-SAIE versus 78 CA-SAB
  - 27 nosocomial SAIE versus 54 nosocomial SAB
- Independent predictors of SAIE (multivariate analysis)
  - unknown origin of SAB: OR 4.2
  - valvular prosthesis: OR 9.2
  - persistent fever (> 48 hours): OR 3.1
  - persistent bacteremia (> 48 hours): OR 6.8
- 6-month mortality 35% for SAIE versus 8% for SAB ($p < 0.001$)

Hill EE, et al. Submitted.

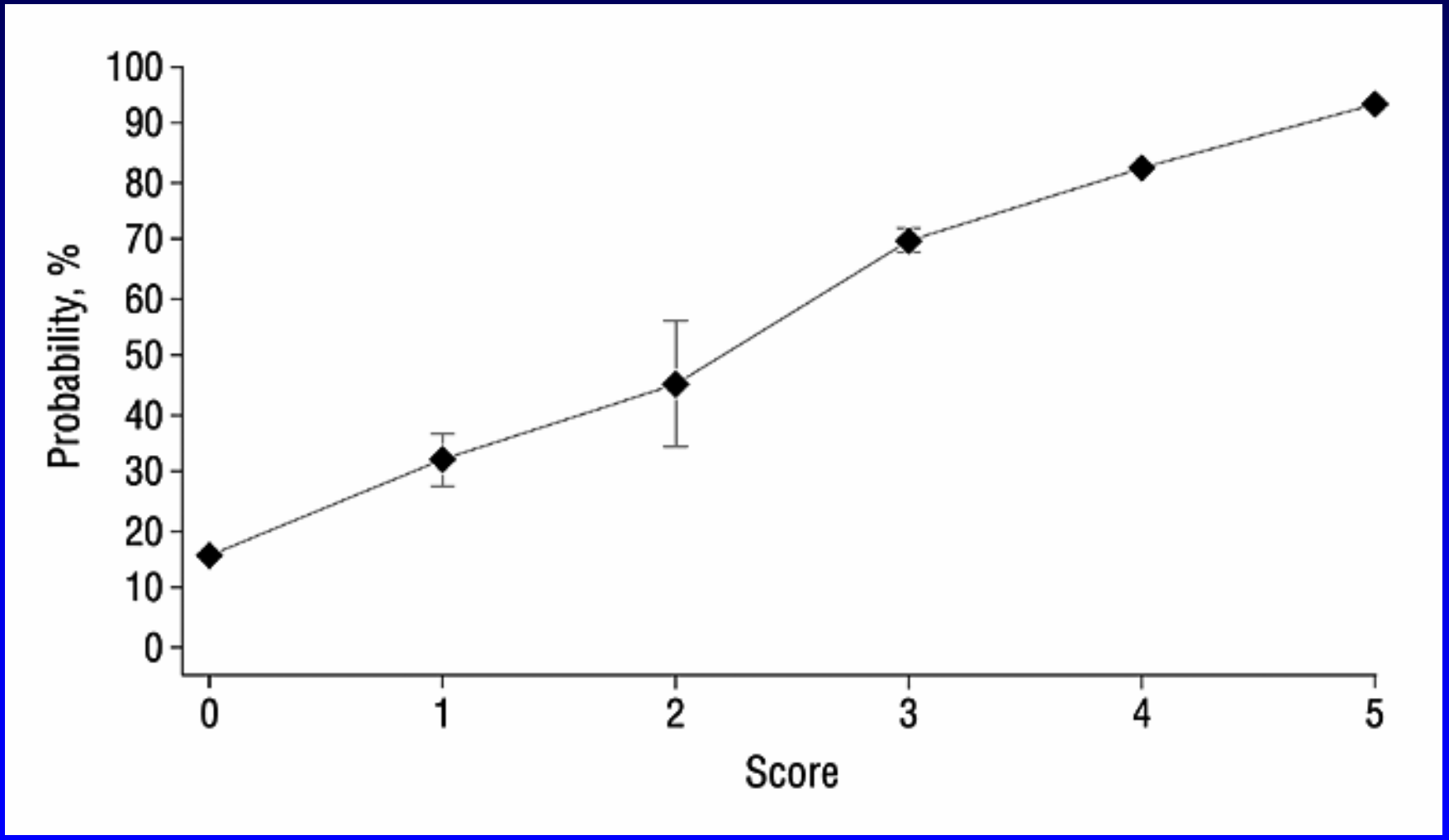
Clinical identifiers of complicated SAB

- Complicated SAB due to attributable mortality, complicated infection (IE, arthritis, abscess, osteomyelitis), embolic stroke or recurrence during 12 weeks.
- Risk factors

Risk factors	OR	Risk points
Community-acquired	3.10	1
Skin examination findings for systemic infection	2.04	1
Positive follow-up blood culture at 48 – 96 hrs	5.58	2
Persistent fever at 72 hrs	2.23	1

Fowler VG, et al. Arch Intern Med 2003; 163: 2066-2072.

Clinical identifiers of complicated SAB



Fowler VG, et al. Arch Intern Med 2003; 163: 2066-2072.

Risk factors for hematogenous complications of IV catheter-associated SAB

- Hematogenous complications in 13% of 324 patients
- Patient characteristics at diagnosis (R.R.)

Community onset:	2.25
Increased symptom duration:	1.14 / day
Long term catheter or IV device:	4.02
Hemodialysis:	3.84

- Subsequent failure to remove the catheter: RR 2.28
- Methicillin resistance : RR 2.09

Fowler VG, et al. Clin Infect Dis 2005; 40: 695-703.

SAIE among patients with SAB and prosthetic valves

- Rate of definite PVE: 51 %
- Risk similar in patients with late (≥ 12 months) and early SAB
- Risk similar in patients with mitral versus aortic prostheses and mechanical versus bioprosthetic valves

El-Ahdab F, et al. Am J Med 2005; 118: 225-229.

Time to positivity in SAB

- Metastatic infection 8% and mortality rate 25.6%
- Median duration of SAB 1 day (70th percentile: 3 days)
- Median TTP 15.5 hrs (4.2 – 98.2 hrs)
- TTP shorter if
  - endovascular source 14.9 vs 19.5
  - duration of SAB ≥ 3 days 14.1 vs 18.6
  - metastatic infection 12.9 vs 18.0

Khatib R, et al. Clin Infect Dis 2005; 41: 594-598.

Time to positivity in SAB

- TTP ≤ 14 hrs was independent predictor in multivariate analysis of
  - endovascular source (sens 67.2%)
  - extended bacteremia (sens 67.3%)
  - metastatic infection (sens 92.0%)
  - attributable mortality (sens 89.1%)

Khatib R, et al. Clin Infect Dis 2005; 41: 594-598.

Time to positivity in SAB

- In hospital mortality was independently associated with
  - Charlson score ≥ 3 (OR 14.4)
  - MRSA (OR 9.3)
  - TTP ≤ 12 hrs (OR 6.9)

Marrra AR, et al. J Clin Microbiol 2006; 44: 1342-1346.

S. aureus Endocarditis (ICE – data)

- S. aureus most common pathogen (31.4 %)
- Healthcare-associated infection most common form of SAIE (39.1 %), mostly acquired outside the hospital (60.1 %)

Fowler VG, et al. JAMA 2005; 293: 3012-3021.

S. aureus Endocarditis (ICE – data)

	non S. aureus (n=1221)	S. aureus (n=558)	p value	O.R.
Male sex	71.1 %	61.1 %	0.001	-
Age (median)	59.3	56.6	0.007	-
PVE	22.6 %	15.4 %	0.001	-
First symptoms <1 month	67.8 %	92.7 %	0.001	5.1
Hemodialysis	6.0 %	14.2 %	0.001	-
Diabetes mellitus	14.8 %	19.7 %	0.009	1.3
Other chronic illness	44.6 %	57.2 %	0.001	-

Fowler VG, et al. JAMA 2005; 293: 3012-3021.

S. aureus Endocarditis (ICE – data)

	non S. aureus (n=1221)	S. aureus (n=558)	p value	O.R.
Dental procedure	10.4 %	3.2 %	0.001	-
Other invasive procedure	16.4 %	23.8 %	0.001	-
IV device source	9.1 %	28.4 %	0.001	1.7
Healthcare-associated	17.3%	39.1 %	0.001	2.9
Community-acquired				
IVDU-associated	4.1 %	21.0 %	0.001	9.3
non IVDU	72.7 %	37.5 %	0.001	-

Fowler VG, et al. JAMA 2005; 293: 3012-3021.

S. aureus Endocarditis (ICE – data)

Complications	non S. aureus (n = 1221)	S. aureus (n = 558)	p value	O.R.
Stroke	14.3 %	21.3 %	0.001	1.6
Other embolization	18.7 %	27.1 %	0.001	-
Congestive heart failure	31.9 %	28.9 %	NS	-
Intracardiac abscess	16.0 %	12.7 %	NS	-
Persistent bacteremia	5.2 %	17.0 %	0.001	2.3
In-hospital death	14.6 %	22.4 %	0.001	-

Fowler VG, et al. JAMA 2005; 293: 3012-3021.

S. aureus endocarditis (ICE – data)

	MSSA (n = 283)	MRSA (n = 141)	p value	O.R.
Hemodialysis	13.8 %	22.7 %	0.02	-
Diabetes mellitus	18.0 %	34.0 %	0.001	2.0
Immunosuppression	3.5 %	17.7 %	0.001	4.1
Cancer	8.5 %	14.9 %	0.04	-
Recent invasive procedure	24.4 %	37.6 %	0.002	-
IV device source	30.7 %	60.3 %	0.001	2.1
Community-acquired	60.8 %	19.9 %	0.001	-
Healthcare-associated	37.1 %	75.9 %	0.001	3.4
nosocomial	21.9 %	46.1 %	0.001	-
non-nosocomial	15.2 %	29.8 %	0.001	-
In-hospital death	23.3 %	29.8 %	NS	-

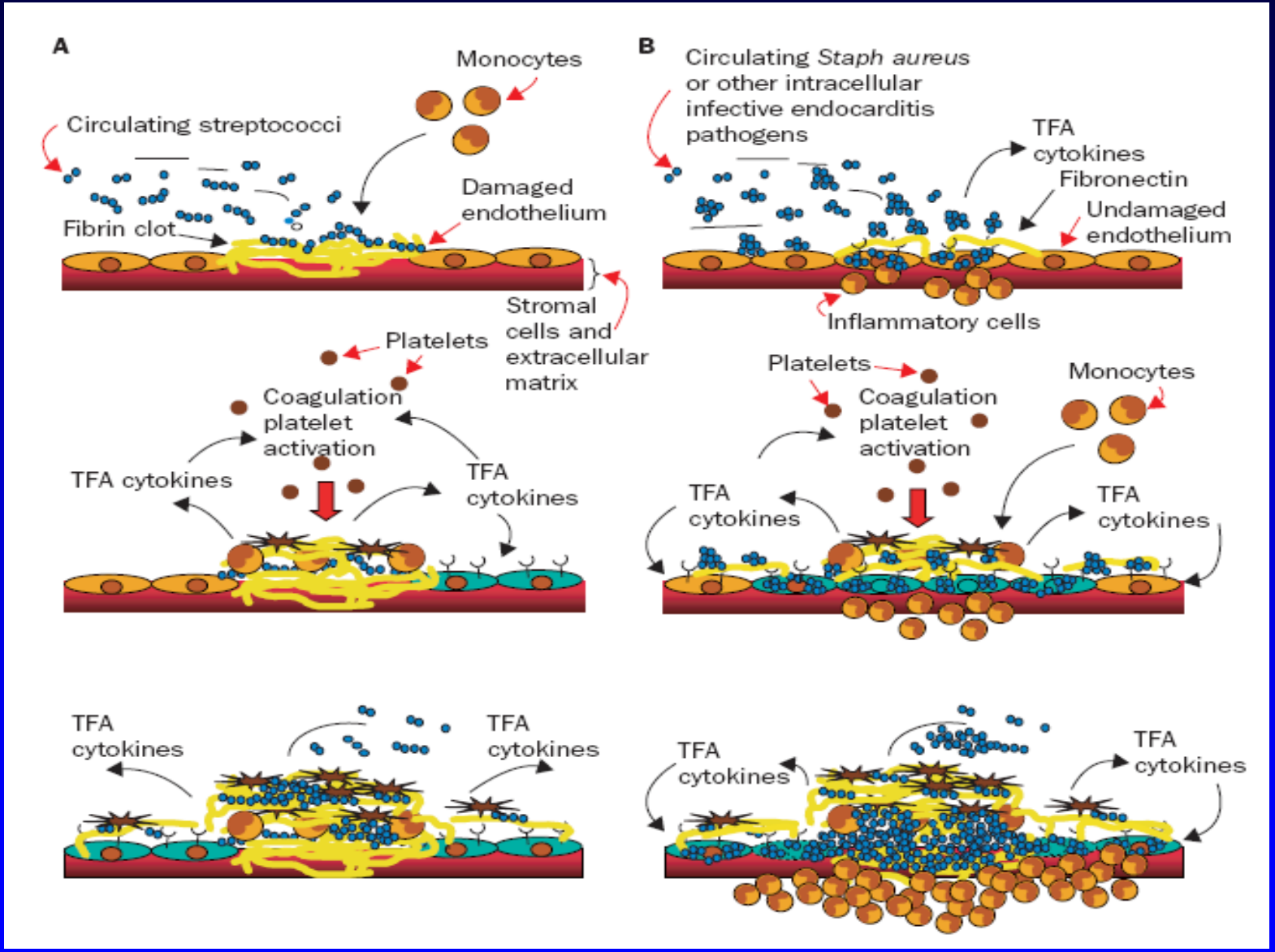
Fowler VG, et al. JAMA 2005; 293: 3012-3021.

MRSA versus MSSA Infective Endocarditis

- Prospective observational cohort study (n=68; June 2000-June 2006)
- Predictors of MRSA:
  - Surgery in previous 6 months
  - Surgical site infection
  - Nosocomial origin
  - Presence of a catheter
- Mortality was 57% in MRSA vs 30% in MSSA (p 0.055)

Hill EE, et al. Submitted.

S. aureus endocarditis: pathogenesis



Lancet 2004; 363: 139-149.

S. aureus endocarditis: pathogenesis

Adherence

- β_1 integrins on endothelial cells bind fibronectin to the endothelial surface. S. aureus strains carry fibronectin-binding proteins on their surface.
- MSCRAMMs (microbial surface component reacting with adhesive matrix molecules) are surface adhesins that mediate attachment to the vegetation. For S. aureus fibrinogen-binding proteins (called clumping factor) and fibronectin-binding proteins are involved in valve infection

Lancet 2004; 363: 139-149.

S. aureus endocarditis: pathogenesis

Internalisation by host cells

S. aureus can trigger active internalisation by host cells

Lancet 2004; 363: 139-149.

S. aureus endocarditis: pathogenesis

Persistence and maturation of the vegetation

- Staphylococci trigger tissue-factor production from local monocytes and induce platelet aggregation
- Microorganisms recovered from IE are consistently resistant to platelet-microbicidal proteins

Invasion and dissemination

- Wealth of exoenzymes of S. aureus convert local host tissues into nutrients for bacterial growth and extoxines are detrimental to host

Lancet 2004; 363: 139-149.

S. aureus endocarditis: pathogenesis

- Vaccines or artificial peptides directed against bacterial adhesins could interfere with valve colonization.
- Interaction with global regulators of S. aureus internalisation, invasion and dissemination could interfere with tissue inflammation and destruction

Lancet 2004; 363: 139-149.

S. aureus endocarditis: antibiotic treatment

- Guidelines of European Society of Cardiology and American Heart Association: NVE

oxacillin	8-12 g/d IV for 4-6 weeks
	w/wo
gentamicin	3 mg/kg/d IV for the first 3-5 days

if allergy: vancomycin 30 mg/kg/d or cefazolin 6 g IV/d

if MRSA: vancomycin

Eur Heart J 2004; 25: 267-276.
Circulation 2005; 111: 3167-3184.

S. aureus endocarditis: antibiotic treatment

- Guidelines of European Society of Cardiology and American Heart Association: PVE

  oxacillin (6 weeks) + gentamicin (2 weeks)
  + rifampin 900 mg/d for at least 6 weeks
  or
  vancomycin (6 weeks) + gentamicin (2 weeks)
  + rifampin 900 mg/d for at least 6 weeks

Eur Heart J 2004; 25: 267-276.
Circulation 2005; 111: 3167-3184.

Role of aminoglycosides in combination with beta-lactams for staphylococcal IE

- Meta-analysis of 4 studies
- No difference versus monotherapy in terms of
  - mortality
  - treatment success
  - relapse
- Nephrotoxicity more common in combination therapy

Falagas ME, et al. J Antimicrob Chemother 2006; 57: 639-647.

Impact of antibiotic treatment on relapse of SAB

- Prospective observational study (n=505) with 6 month follow-up (SAB) and 3 year follow-up (SAIE)
- Nafcillin superior to vancomycin in preventing bacteriologic failure (persistent bacteremia > 7 days or relapse) for MSSA
- Relapse independently associated with endocarditis (OR 7.6) and vancomycin treatment (OR 6.5)

Chang FY, et al. Medicine 2003; 82: 333-339.

Comparative activity of cloxacillin and vancomycin against methicillin-susceptible SAIE

- after 24 hours:
  - both equally effective in preventing mortality
  - cloxacillin greater decrease in number of staphylococci: 3.5 log $_{10}$ CFU/g vegetation versus 6.25 log $_{10}$ CFU/g vegetation ($p<0.05$)
  - cloxacillin 41% of rabbits with sterile vegetations versus none for vancomycin
- after 48 and 72 hours: equivalent activity

Fernandez-Guerrero ML, et al. J Antimicrob Chemother 2006; 58: 1066-1069.

S. aureus endocarditis: Linezolid

- Successes and failures reported (publication bias !)
  - for MRSA / GISA / CoNS / VRE
  - for NVE and PVE

but

- Better bactericidal activity in experimental (MRSA) IE in combination with gentamicin
- No synergy or antagonism in combination with rifampin
- Vancomycin more effective in experimental (MRSA) IE

Hill EE, et al. Eur J Clin Microbiol Infect Dis 2006; 25: 202-204.
Falagas ME, et al. J Antimicrob Chemother 2006; 58: 273-280.

S. aureus endocarditis: Daptomycin

- Non-inferiority of daptomycin versus standard therapy for SAB, including SAIE
- Similar success rates in patients with complicated bacteremia, MRSA and right-sided IE

but

- Higher rate of microbiological failure with daptomycin due to emerging resistance
- Only 19 patients with right sided IE treated with daptomycin: 8 successes (42%)
- Only 9 patients with left sided IE treated with daptomycin: 1 success (11%)

Fowler VG, et al. N Engl J Med 2006; 355: 653-665..

S. aureus endocarditis: new agents

- Quinupristin-dalfopristin:
  - effective in animal model of MRSA-IE when combined with vanco or oxa
  - 11 patients with MRSA-IE: 6 success
- Tigecycline:
  - effective in animal model
  - no data in humans

Drees M, et al. Curr Op Infect Dis 2006; 19: 544-550.

S. aureus endocarditis: new agents

- Fluoroquinolones:
  - levofloxacin and moxifloxacin effective in animal model
  - clinafloxacin 94% success rate in MSSA-NVE (n=33) and 100% in MRSA-NVE (n=5)
- Dalbavancin, telavancin, oritavancin:
  - telavancin and oritavancin effective in animal model of MRSA-IE
- Ceftobiprole:
  - effective in animal model of MRSA-IE and VISA-IE

Drees M, et al. Curr Op Infect Dis 2006; 19: 544-550.

S. aureus endocarditis: new data

- Experimental vancomycin-resistant SAIE effectively treated by combination of vancomycin and nafcillin

  Antimicrob Ag Chemother 2006; 50: 2951-2956.

- Daptomycin and moxifloxacin activity against intracellular MSSA and MRSA

  ECCMID 2007: P703 and P829.

Medical versus surgical management of SAIE

- Surgical treatment seems to be the best way to improve the results of SAIE
  - mortality rate 41% vs 35% (NS)
  - 24 month survival curve: 43% versus 74% (p 0.001)

Remadi JP, et al. Int J Cardiol 2005; 99: 195-199.

- Early surgery independently associated with reduced mortality
  - in-hospital mortality 34% vs 16% (p 0.03)
  - 36 month survival curve: 39% vs 77% (p 0.001)

Remadi JP, et al. Ann Thorac Surg 2007; 83: 1295-1302.

Medical versus surgical management of SAIE

- Surgical intervention may improve survival in patients with SAIE (PVE and NVE)

  Roder BL, et al. Scand Cardiovasc J 1997; 31: 305-309.

- Performing valve replacement surgery during antimicrobial therapy will reduce mortality among patients with S. aureus PVE

  John, et al. Clin Infect Dis 1998; 26: 1302-1309.

Medical versus surgical management of SA-PVE

- S. aureus was suggested an indication for surgery, independent of other risk factors
- Studies suggesting better outcomes in surgically treated patients may reflect biases inherent in patient selection for surgery
- Subsets of medically treated patients characterized by age less than 50 years, ASA score III, without cardiac, CNS or systemic complications were cured without surgery.

Sohail MR, et al. Am J Med 2006; 119: 147-154.

Medical versus surgical management of SA-PVE

	Surgery	Deliberate conservative	Perforce conservative
Treatment modality	12/23 (52)	5/23 (22)	6/23 (26)
Mortality	5/12 (42)	0/5 (0)	6/6 (100)

Hill EE, et al. Submitted.

Infective Endocarditis: Outcome

- 6-month mortality rate was 22 %
  - PVE 31 % versus NVE 18 % (p 0.09)
  - nosocomial 27 % versus CA 19 % (p 0.23)
- 6-month mortality was associated with causative microorganisms (p 0.01)
  - S. aureus 32 %
  - CoNS 35 %
  - streptococci 8 %
  - enterococci 24 %

Hill EE, et al. Eur Heart J 2007; 28: 196-203.

MRSA versus MSSA Infective Endocarditis

Mortality (%)	Surgery		Deliberate conservative		Perforce conservative	
MSSA	10/36	(28)	0/11	(0)	6/7	(86)
MRSA	1/5	(20)	1/3	(33)	6/6	(100)

Hill EE, et al. Submitted.

S. aureus Endocarditis (ICE – data)

Multivariate analysis In-hospital death	Unadjusted OR	95 % C.I.
Age (10 year increment)	1.40	1.16 - 1.69
Male sex	2.23	1.17 - 4.26
Persistent bacteremia	2.88	1.89 - 4.47
Stroke	2.69	1.43 - 5.07
Congestive heart failure	2.19	1.20 - 4.00
Intracardiac abscess	2.89	1.57 - 5.23
Surgery this episode	0.53	0.31 - 0.92

Fowler VG, et al. JAMA 2005; 293: 3012-3021.

Native Valve SAIE: outcome (ICE-MD)

- NV-SAIE patients were:

  more likely to - die (20% vs 12%),

  - experience an embolic event (60% vs 31%)

  - a CNS event (20% vs 13%)

  less likely to undergo surgery (26% vs 39%)

- Mortality of NV-SAIE associated with age (OR 1.4), periannular abscess (OR 2.4), heart failure (OR 3.9), absence of surgery (OR 2.3) and geographical region (11.4 up to 31.9 %)

Miro JM, et al. Clin Infect Dis 2005; 41: 507-241

Prosthetic Valve SAIE: outcome (ICE-MD)

- PV – SAIE (n=61) had overall mortality of 47.5 % (7.7 % up to 71.4 % according to geographical region)
- Mortality not significantly associated with potential prognostic characteristic or early valve replacement

Chirouze C, et al. Clin Infect Dis 2004; 38: 1323 – 1327.

S. aureus endocarditis: Conclusions (1)

- Most common etiology of IE in recent series from referral hospitals:
  - more nosocomial origin
  - more co-morbidities
  - (IVDU)
- Risk factors in patients with SAB
  - unknown origin of SAB
  - persistent bacteremia
  - persistent fever

  ↳ perform follow-up blood cultures

  ↳ perform TEE in (selected ? all ?) patients with SAB

S. aureus endocarditis: Conclusions (2)

- SAIE is associated with high rates of mortality and complications
- Oxacillin derivatives are superior to vancomycin if MSSA-IE
- Combination with rifampin improves outcome in S. aureus PVE
- New drugs do not offer real break-through

S. aureus endocarditis: Conclusions (3)

- Many but not all patients require surgery, even for S. aureus PVE
- Perforce conservative treatment has a disastrous prognosis
- Shared expertise of cardiologist, cardiac surgeon and infectiologist is required for optimal management.