Data Supplement 42. Infective Endocarditis

Methodology and Evidence Review

The recommendations listed in the guideline are, whenever possible, evidence based. An extensive review was conducted through March 1, 2020. Key search words included, but were not limited to, the following: valvular heart disease, aortic stenosis, aortic regurgitation, bicuspid aortic valve, mitral stenosis, mitral regurgitation, tricuspid stenosis, tricuspid regurgitation, pulmonic stenosis, pulmonic regurgitation, prosthetic valves, anticoagulation therapy, infective endocarditis, cardiac surgery, transcatheter aortic valve replacement or implantation, and percutaneous mitra-clip.

Studies related to Diagnosis, Medical Therapy and Intervention of Infective Endocarditis

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Scholtens, AM; 2018 (1)	Aim: Comparison of Standard and late FDG PET/CT images in detecting PVE	Inclusion criteria: Pts referred for FDG PET/CT with suspected PVE in the University Medical Center	Intervention: Standard (60 min post injection) and late (150 min post injection) time points were scored based on visual interpretation and semi-quantitatively with SUVmax and target-to-background ratio (TBR, defined as [SUVmax valve/SUVmean blood pool]).	1° endpoint: Late images had significantly higher TBR values compared to the standard images, due mostly to a decrease in measured activity in the blood pool (SUVmax PHV standard 3.77 ± 1.06 vs. late 4.30 ± 1.64, P = 0.02; TBR standard 2.55 ± 0.93 vs. late 4.27 ± 1.89, (P = 0.0001)..	• Late images were more prone to false positive interpretation for both visual and semi-quantitative analyses. • Early imaging after surgery or in patients with historical findings that would be more prone to having increased inflammation considerably influences the interpretation of findings.
	Study type: Prospective Observational Size:13 patients	Exclusion criteria: N/A	Comparator: Final diagnosis was based on surgical findings in all cases of infection (n= 6) and unremarkable follow-up in all others (n = 8).	Safety endpoint (if relevant): N/A	
Wei, X 2017 (2)	Aim: Determine the prognostic ability of NT-proBNP in patients with IE.	Inclusion criteria: All pts diagnosed with IE between January 2009 and July 1215	Intervention: Registration of in-hospital outcome and one year mortality after discharge as well as demographic and clinical characteristics including imaging findings and baseline NT-proBNP levels at admission. Pts were divided into 4 groups according to quartile of admission NT-proBNP	1° endpoint: The in-hospital mortality was increased from the lowest to the highest NT-proBNP quartiles (1.1%, 3.4%, 9.1% and 22.3%, P<0.001, respectively). During the one-year follow-up period, 29 patients died: 0 in Q1, 7 (4.6%) in Q2, 8 (5.7%) in Q3 and 14 (12.0%) in Q4 (P<0.001). Multivariate analysis showed log transformed	• Log-transformed (lg) NT-proBNP had a linear correlation with lg C-reactive protein (r=0.308, P<0.001). • NT-proBNP had a higher

				NT-proBNP was an independent predictor for both in-hospital (odds ratio 4.59, 95% confidence interval (CI) 2.45–8.61, P<0.001) and one-year mortality (hazard ratio 3.11, 95% CI 1.65–5.87, P<0.001).	predictive power for in-hospital death than C-reactive protein (area under the curve 0.797 vs. 0.670, P¼0.005). • NTproBNP>2260 pg/mL had 76.2% sensitivity and 69.1% specificity for predicting in-hospital death. Kaplan–Meier analysis showed that patients with NT-proBNP>2260 pg/ml had a worse prognosis than those without (log-rank test 18.84, P<0.001).
	Study type: Prospective Observational Size: 703	Exclusion criteria: <18 years of age, cardiogenic shock at admission, multiple hospital admissions, diagnosed with IE after major cardiac surgery during hospitalization, missing admission NT-proBNP test, serious liver disease, or End-stage renal disease.	Comparator: N/A	Safety endpoint: N/A	
Miranda, W. 2018 (3)	Aim: Assess the diagnostic yield of echocardiography in PVE after TAVR	Inclusion criteria: Definite or suspected PVE after TAVR	Intervention: Registration of demographics, TTE/TEE findings, bacterial organisms, and outcomes	1° endpoint: TEE was diagnostic for PVE in 47% of cases and TTE in 18%. TEE was diagnostic in 62% of patients if only definite PVE cases are included.	• Enterococcus faecalis was the most commonly encountered organism (29%) • All patients had TEE performed at the time of PVE; TTE was performed in 11 patients. • Two patients showed prosthetic obstruction at the time of PVE; obstruction improved with antibiotic therapy in the surviving patient.
	Study type: Retrospective Observational Size: 17 patients	Exclusion criteria: N/A	Comparator: N/A	Safety endpoint: NA	
Al-Omari: 2014 (4)	Aim: Systemic Review of Oral Antibiotic Therapy for the Treatment of IE	Inclusion criteria: systematic search strategy was developed to capture all articles of IE in which oral antibiotic therapy was used - y included studies of IE in which the duration of antibiotic treatment was >2 weeks and oral antibiotics where the only antibiotics given after 2 weeks of treatment initiation. To be	Intervention: N/A -registration of Data	1° endpoint: Clinical Cure Rates	• Reported cure rates for IE caused by susceptible organisms and treated with appropriate oral antibiotic regimens range between 77-100% • Limited evidence from one small clinical trial suggests that the combination of oral ciprofloxacin and rifampin for the treatment of uncomplicated

		eligible, studies had to a) report mortality and clinical cure as their outcomes of interest; b) report the microbiology of their IE cases; and c) present their data in a way that it allowed for the calculation of outcome rates as a function of the entire study cohort. Studies with focus on culture negative endocarditis were excluded.			right-sided IE caused by susceptible strains of S. aureus in IVDUs could be as effective as, and produce less adverse events than conventional IV antibiotic regimens.
	Study type: Meta-analysis of Observational and Randomized Controlled Studies Size: 11 studies; 284 pts	Exclusion criteria: excluded case series (defined as studies with <10 participants) and articles without original data	Comparator: N/A	Safety endpoint: N/A	
Solamaki:2017 (5)	Aim: Use of 18F-FDG positron emission tomography/computed tomography (PET/CT) in IE	Inclusion criteria: consecutive patients admitted to Turku University Hospital, Turku, Finland between September 2011 and September 2014 due to suspected NVE or PVE	Intervention Visual evaluation of 18F-FDG-PET/CT. 18F-FDG uptake was measured also semiquantitatively as maximum standardized uptake value (SUVmax) and target-to-background ratio (TBR).	1° endpoint: 18F-FDG-PET/CT is a sensitive method for the detection of paravalvular infection associated with PVE. Instead, the sensitivity of PET/CT is limited in NVE.	
	Study type: Prospective Observational Size:23	Exclusion criteria: Patients with hemodynamic instability or need for urgent surgery were excluded	Comparator: The modified Duke criteria were used as a reference.	Safety endpoint: N/A	
	Aim: Assessment of the value of additional	Inclusion criteria: all adult patients presenting with a	Intervention: Patients receiving FDG-PET/CT, MDCTA, transthoracic (TTE), and	1° endpoint: 69% of patients (121/176) adhered to the flowchart. Sensitivity of	• N/A

Gomes: 2018 (6)	imaging to echocardiography in patients selected by a proposed flowchart	suspicion of endocarditis/device infection according to "the British Society for Antimicrobial Chemotherapy criteria"were consecutively enrolled	transoesophageal (TEE) echocardiography were included in a head-to-head comparison of imaging accuracy for infective endocarditis and/or infection of any component of intracardiac prosthetic material. Patients were treated according to current guidelines and expert opinion.	echocardiography, MDCTA, FDG-PET/CT in patients without prosthesis was 71%, 57%, 29% (86% when combined), while specificity was 100%, 75%, 100%, respectively. Sensitivity in patients with prosthesis was 75%, 75%, 83%, respectively (100% when combined), while specificity was 86% for all three modalities. Echocardiography performed best in the assessment of vegetations, morphological valve abnormalities/dehiscence, septum defects, and fistula formation. MDCTA performed best in the assessment of abscesses and ventricular assist device infection. FDG-PET/CT performed best in the assessment of cardiac device infection, extracardiac infectious foci, and alternative diagnoses.	
	Study type: prospective observational Size: 176	Exclusion criteria: N/A	Comparator: N/A	Safety endpoint: N/A	
De Camargo; 2019 (7)	Aim: Deetermine accuracy of 18F-FDG-PET/CT for the Diagnosis of NVE	Inclusion criteria: Left-sided IE was suspected in the presence of 1 of the following criteria: (1) patients with risk factors for IE (rheumatic valve disease, chronic degenerative valve disease, prosthetic valve, previous episodes of IE, or cyanotic congenital heart disease) and at least 1 of the following: (a) inflammatory syndrome, defined as an unexplained fever >37.8°C or an unexplained increase in C-reactive protein (>20 mg/L) or white blood cell count >12 000 mm3 ; (b) new embolic event; or (c) acute heart failure due to valve regurgitation; and (2) fever of unknown origin with new heart murmur or embolic	Intervention: Registration of clinical variables to determine sensitivity, specificity, accuracy, and positive and negative predictive values of 18F-FDG-PET/CT for IE diagnosis	1° endpoint: Among 188 patients with PVE/AAPI, the sensitivity, specificity, and positive and negative predictive values of 18F-FDGPET/CT focal uptake were 93%, 90%, 89%, and 94%, respectively, while among 115 patients with NVE, the corresponding values were 22%, 100%, 100%, and 66%.	The inclusion of abnormal 18F-FDG cardiac uptake as a major criterion at admission enabled a recategorization of 76% (47/62) of PVE/AAPI cases initially classified as "possible" to "definite" IE.

		event			
	Study type: Prospective observational Size: 303	Exclusion criteria: Early Death (<5days); urgent surgery (<5days); Hemodynamic instability/respiratory distress; increased physiologic uptake of F-FDG in the myocardium	Comparator: N/A	Safety endpoint (if relevant): N/A	Study type: Prospective observational
POET; Iversen: 2019 (8)	Aim: To determine the feasibility of a shift from intravenous to oral anti-biotics would result in efficacy and safety similar to those with continued IV antibiotics	Inclusion criteria: adults in stable condition who had endocarditis on the left side of the heart caused by streptococcus, Enterococcus faecalis, Staphylococcus aureus, or coagulase-negative staphylococci and who were being treated with intravenous antibiotics; fulfilled the modified Duke criteria; transesophageal echocardiography performed before randomization had to show no signs of abscess formation or valve abnormalities that would require surgery; At the time of randomization, at least 10 days of scheduled antibiotic treatment had to remain. Patients assigned to receive intravenous treatment remained in the hospital until antibiotic treatment was completed. If feasible, patients assigned to receive oral treatment were treated in the outpatient clinics and were seen two to three times per week.	Intervention: Randomized to receive roal treatment versus continued inpatient IV antibiotics; All patients had repeat TEE's done within 1-3 days before completion of the assigned therapy	1° endpoint: The primary outcome was a composite of all-cause mortality, unplanned cardiac surgery, clinically evident embolic events, or relapse of bacteremia with the primary pathogen (detected in blood cultures obtained during follow-up or for clinical reasons) from randomization through 6 months after antibiotic treatment was completed. The primary composite outcome occurred in 24 patients (12.1%) in the intravenously treated group and in 18 (9.0%) in the orally treated group (between-group difference, 3.1 percentage points; 95% confidence interval, −3.4 to 9.6; P=0.40), which met noninferiority criteria. The between-group difference was 3.1 percentage points (95% CI, –3.4 to 9.6; P=0.40) in favor of oral treatment, and the criterion for noninferiority was therefore met. In the per-protocol analysis, the primary composite outcome occurred in 24 of 199 patients (12.1%) in the intravenously treated group and in 18 of 197 (9.1%) in the orally treated group (between-group difference, 3.0 percentage points; 95% CI, –3.2 to 9.2).	• In a sensitivity analysis in which the 4 patients who were switched from oral to intravenous therapy were considered to have had treatment failure, the criterion for noninferiority was still met. In this analysis, the primary outcome occurred in 24 of 199 patients in the intravenously treated group and in 22 of 201 patients in the orally treated group (between-group difference, 1.2 percentage points; 95% CI, –5.6 to 7.5). The incidences of embolic episodes, unplanned cardiac surgery, and relapse of bacteremia with the primary pathogen were similar in the two groups. There were fewer deaths in the orally treated group than in the intravenously treated group. Adverse effects from antibiotics were reported in 22 patients (6%) after randomization — in 12 patients (6%) in the intravenously treated group and in 10 (5%) in the orally treated group (P=0.66). The most frequently reported adverse effects were allergy (50%), bone marrow suppression (27%), and gastrointestinal effects (14%), with no significant differences between groups

	Study type: Randomized, Non-inferiority,, multi-center trial Size: 400	Exclusion criteria: Other pathogens not listed above, clinically unstable, pts who did not have satisfactory clinical responses to initial IV clinical treatment; Abscess or valve abnormalities requiring surgery; other indications for prolonged IV antibiotics, suspected reduced GI uptake or BMI>40; Bacterial susceptibility examinations that showed less than 2 different classes of orally administered antibiotics effective	Comparator: Prolonged IV versus oral antibiotics	Safety endpoint: In 7 patients in the orally treated group, the plasma concentration of one of the two administered antibiotics was not at the most effective level, as assessed by peak levels and time above the MIC. In all seven patients, the plasma concentration of the other simultaneously administered antibiotic was appropriate. The primary outcome did not occur in any of these patients. No antibiotic regimens were changed on the basis of pharmacokinetic findings.	
Schranz; 2019 (9)	Aim: To examine hospitalization trends for Drug use-associated infective endocarditis (DUA-IE), the proportion of hospitalizations with surgery, patient characteristics, length of stay, and charges.	Inclusion criteria: All patients aged 18 years or older admitted to North Carolina Hospitals from 2017-2017	Intervention: examined annual trends in the aggregate and stratified by drug use for all IE hospitalizations	1° endpoint: Of 22 825 IE hospitalizations, 2602 (11%) were for DUA-IE. Valve surgery was performed in 1655 IE hospitalizations (7%), including 285 (17%) for DUA-IE. Annual DUA-IE hospitalizations increased from 0.92 to 10.95 and DUA-IE hospitalizations with surgery from 0.10 to 1.38 per 100 000 persons. In the final year, 42% of IE valve surgeries were performed in patients with DUA-IE. Compared with other surgical patients with IE, those with DUA-IE were younger (median age, 33 vs. 56 years), were more commonly female (47% vs. 33%) and white (89% vs. 63%), and were primarily insured by Medicaid (38%) or uninsured (35%). Hospital stays for DUA-IE were longer (median, 27 vs. 17 days), with higher median charges ($250 994 vs. $198 764). Charges for 282 DUA-IE hospitalizations exceeded $78 million.	Schranz; 2019
	Study type: Retrospective	Exclusion criteria: N/A	Comparator: N/A	Safety endpoint: N/A	

	Size: 22 825 IE hospitalizations				
Englander; 2017 (10)	Aim: Point of care improvements for inpatients with substance abuse disorders	Inclusion criteria: Hospiitalized Medicaid patients ≥18 years in age who screened positive for alcohol or drugs	Intervention: Surveys assessed social and demographic factors, healthcare utilization, substance use severity, and treatment experience. Participants who reported high-risk illicit drug or alcohol use19 were asked to indicate their readiness to change on a 3-point scale developed for this study. Response range included: no interest, interest in cutting back, or interest in quitting. A subset of participants completed in-depth qualitative interviews exploring patient perceptions of substance use treatment needs.20 Hospital administrative data was obtained from hospital financial services.	1° endpoint: Identifying barriers to care and creating a comprehensive needs assessment	Development and assessment of specific techniques and operational changes to address the identified needs. Limitations: • Single academic center in a Medicaid expansion state • Limited racial/ethnic diversity • Virtually all patients were insured
	Study type: Needs assessment	Exclusion criteria: Non-English speaking; incarcerated adults; people who only were using marijuana or tobacco; psychiatry inpatients; people unable to consent	Comparator:N/A	Safety endpoint:	
	Size:185				
Liebschutz; 2014 (11)	Aim: To determine whether buprenorphine administration during medical hospitalization and linkage to office-based buprenorphine opioid agonist treatment (OAT) after discharge increase entry into office-based OAT, increase sustained	Inclusion criteria: Hospitalized, opioid dependent patients were recruited from the inpatient medical service of a safety-net, academic hospital	Intervention: Five-day buprenorphine detoxification protocol or buprenorphine induction, intrahospital dose stabilization, and postdischarge transition to maintenance buprenorphine OAT affiliated with the hospital's primary care clinic (linkage).	1° endpoint: Compared with those in the detoxification group, participants randomized to the linkage group reported less illicit opioid use in the 30 days before the 6-month interview (incidence rate ratio, 0.60; 95% CI, 0.46-0.73; P < .01) in an intent-to-treat analysis.	• During follow-up, linkage participants were more likely to enter buprenorphine OAT than those in the detoxification group (52 [72.2%] vs 8 [11.9%], P < .001). • At 6 months, 12 linkage participants (16.7%) and 2 detoxification participants (3.0%) were receiving buprenorphine OAT (P = .007).

	engagement in OAT, and decrease illicit opioid use at 6 months after hospitalization.				

A. Nonrandomized Trials, Observational Studies, and/or Registries of IE

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (p values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Mackie AS, et al., 2016 (12)	Study type: Retrospective Size: n=9,431 pts with IE hospitalizations	Inclusion criteria: IE Hospitalizations Exclusion criteria: N/A	1 endpoint: Incidence of IE of hospitalizations per 10 million Results: There was no difference in the rates of hospitalization for IE before and after publication of the revised recommendations	• This retrospective study examined the incidence of IE hospitalizations before and after the 2007 AHA prophylaxis guidelines publication • The rate of IE hospitalizations increased before/after implementation • 2007 AHA recommendations had no impact on incidence rates of hospitalization for IE
Dayer MJ, et al., 2015 (13)	Study type: Retrospective secular trend study: relationship AP vs. none on IE incidence Size: Cases reported per 10 million people per mo	Inclusion criteria: Single dose IE prophylaxis all pts w/IE dx Exclusion criteria: N/A	1 endpoint: IE dx at discharge/death and number of Rxs of IE prophylaxis Results: • Decrease IE Prophylaxis; • Increase IE incidence	• AP has fallen and incidence of IE has increased since 2008 NICE guidelines
Glenny AM, et al., 2013 (14)	Study type: Meta-analysis Size: Only 1 study met criteria for inclusion	Inclusion criteria: RCT, cohort, case control Exclusion criteria: Guidelines, editorial discussion	1 endpoint: Development of IE, mortality Results: Only 1 study met criteria	• There remains no evidence to determine whether AP is effective or ineffective
Sherman-Weber S, et al., 2004 (15)	Study type: Retrospective literature review Size: n=659 pts	Inclusion criteria: Single-center heart transplant hospitalization with IE Exclusion criteria: N/A	1 endpoint: N/A Results: Between 1993-Feb. 2004, 10 pts had endocarditis	• Endocarditis is substantially more common in heart transplant recipients than in general populations. Central venous catheter access and multiple endomyocardial biopsies appear to predispose to infection
Gillinov AM, et al., 2002 (16)	Study type: Retrospective review Size: n=22 pts	Inclusion criteria: 22 pts with endocarditis of a previously repaired MV Exclusion criteria: N/A	1 endpoint: N/A Results: 15 had repeat MV operations; 7 were treated with antibiotics	N/A

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (p values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Karavas AN, et al., 2002 (17)	Study type: Retrospective review of MV repairs Size: n=1,275 pts	Inclusion criteria: MV repairs at a single institution Exclusion criteria: N/A	1 endpoint: Endocarditis (non-recurrent) of previously repaired MV Results: 9 of 1,275 pts developed endocarditis after MV repair: all required excision of the annuloplasty ring	N/A
Duval X, et al., 2006 (18)	Study type: Survey	Inclusion criteria: Pts 25–85 y of age; French	1 endpoint:	• A large no. of pts would need prophylaxis to
	Size: n=2,805 pts	adults with predisposing cardiac conditions, antibiotics prophylaxis eligible Exclusion criteria: N/A	N/A Results: • The results were extrapolated to general French population. • Risk of developing IE in unprotected procedure: • 1 in 10,700 for prosthetic valve predisposing cardiac conditions and 1 in 54,300 for native valve predisposing cardiac conditions • Risk of developing IE in protected procedures: 1 in 150,000	avoid 1 case of IE • The results cannot be generalized to general population
Strom BL, et al., 1998 (19)	Study type: Observational case control Size: n=273 cases (238 native valve infections, 35 prosthetic valve infections)	Inclusion criteria: Subjects with community acquired IE discharged within 3 mo and matched community residents Exclusion criteria: IE due to IV drug abuse, <18 y of age, hospital acquired IE	1 endpoint: N/A Results: • Dental treatment not more common in cases compared to controls (adjusted OR: 0.8, 95% CI: 0.4–1-5) • Cases with Hx of MV prolapse OR: 19.4; congenital heart disease OR: 6.7, valvular surgery OR: 74.6, rheumatic fever OR: 13.4; heart murmur OR: 4.2 Prophylaxis dental therapy was significantly low (p=0.03) in cases with cardiac lesions as compared to controls.	• Cardiac valvular abnormalities associated with IE more than the dental treatment

B. RCTs for IE

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, p values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Mouget FK, et al., 2015 (20)	Aim: To assess the impact of AP on bacteremia Study type: Double-blind, randomized, placebo-controlled Size: n=290 pts	Inclusion criteria: 2008 cohort urgent care presentation for tooth extraction. Exclusion criteria: <10 teeth antibiotic use within 2 wk. Need for AP based on practice guidelines active viral disease. Immunocompromised, poorly-controlled systemic disease penicillin allergy, fever, cellulitis, chewing/tooth brushing within 1 h.	Intervention: • Tooth brushing (n=98 pts) • Single tooth extraction with AP (n=96 pts) Comparator: Single tooth extraction with placebo	1° endpoint: Bacteremia 32% brushing 33% amoxicillin 60% placebo	• Given frequency of IE causing bacteremia during a tooth brushing; recommend RCT to determine efficacy of prophylaxis for dental procedure; recommend good dental hygiene.
Lockhart PB, et al., 2008 (21)	Aim: To compare the incidence, duration, type and extent of endocarditis related bacteremia and to determine the impact of AP on single tooth extraction. Study type: RCT Size: n=290 pts	Inclusion criteria: Subjects in need for tooth extraction Exclusion criteria: Use of systematic antibiotics within previous 2 wk; on AP; active viral disease; immunocompromised; systemic disease with bad prognosis; Hx of penicillin allergy; 100.5°F temp; facial cellulitis; and handling of the gingival tissues within 1 h before the study.	Intervention: • Tooth brushing group (98) • Extraction with amoxiillin group (96) • Extraction with Placebo group (96)	1° endpoint: • 32/98 bacterial species identified cause IE. Cumulative incidence from 6 blood draws tooth brushing: 23%, extraction-amoxicillin: 33% and extraction-placebo: 60%; p<0.0001} • Amoxicillin resulted in decrease of positive cultures (p<0.05) • 1° Safety endpoint (if relevant): N/A	• The results cannot be generalized to general public • Tooth brushing and single tooth-extractions seem to be similar in terms of at risk individuals for IE

C: Surgical Outcome in IE

Author/ Year	Aim of Study	Study Type	Study Size (N)	Patient Population	Study Intervention	Primary Endpoint	Predictors of Outcome
Jault, 1997 (22)	Identify significant predictors of operative mortality, reoperation, and recurrent IEs	Retrospective single-center surgical cohort study	247	NVE alone; surgery 100%	Registration of epidemiological and microbiological features, echocardiography data, treatment strategy	Operative mortality was 7.6% (n=19). Overall survival rate (operative mortality excluded) was 71.3% at 9 y. The probability of freedom from reoperation (operative mortality included) was 73.3±4.2% at 8y. The rate of IE of the implanted prosthetic valve was 7%.	Increased age, cardiogenic shock at the time of operation, insidious illness, and greater thoracic ratio (>0.5) were the predominant risk factors for operative mortality; the length of antibiotic therapy appeared to have no influence. Increased age, preoperative neurologic complications, cardiogenic shock at the time of operation, shorter duration of the illness, insidious illness beforethe operation, and MV endocarditis werethe predominant risk factors for latemortality.
Castillo 2000 (23)	To determine the clinical features and long-term prognosis of IE in pts who were not drug users.	Prospective single-center case series	138	NVE 69%, PVE 31%; surgery 51%	Registration of epidemiological and microbiological features, echocardiography data, treatment strategy	Severe complications (HF, embolic phenomenon, severe valve dysfunction, abscesses, renal failure,and immunologic phenomenon) occurred in 83% ofpts. 51% of pts underwent surgery during the active phase (22% was emergency surgery) Inpt mortality was 21%. Overall 10 y survival was 71%	There were no significant differences in survival depending on the type of treatment received during the hospital stay (medical vs. combined medical-surgical) in this observational study.
Alexiou 2000 (24)	Single-center experience in the surgical treatment of active culture-positive IE and identify determinants of early and late	Retrospective single-center surgical cohort study	118	NVE 70%, PVE 30%; 100% of pts underwent surgery	Registration of epidemiological and microbiological features, echocardiography data, treatment strategy	Operative mortality was 7.6% (9 pts). Endocarditis recurred in 8 (6.7%). A reoperation was required in 12 (10.2%). There were 24 late deaths, 17 of them cardiac. Actuarial freedom from recurrent endocarditis, reoperation, late cardiac death, and long-termsurvival at 10 y were 85.9%, 87.2%, 85.2%, and 73.1%, respectively.	Predictors of operative mortality: HF, impaired LV function. Predictors of recurrence: PVE. Predictors of late mortality: myocardial invasion, reoperation. Predictors of poor long-term survival: coagulase- negative staphylococcus, annular abscess, long ICU stay.
Wallace, 2002 (25)	To identify clinical markers available within the first 48 h of admission that are associated with poor outcome in IE	Retrospective single-center cohort study	208	NVE 68%, PVE 32%; surgery 52%	Registration of epidemiological, clinical, microbiological and other laboratory features, echocardiography data, and treatment strategy	Mortality at discharge was 18% and at 6 mo 27%. Surgery was performed in 107 (51%) pts. In-hospital mortality was not influenced by surgery (23% vs. 15% in the nonsurgical group); p=0.3 At 6 mo there was a trend towards increased mortality in the surgical group (33% vs. 20%)	Duration of illness, age, gender, site of infection, organism, and LV function did not predict outcome. Abnormal white cell count, raised creatinine, ≥2 major Duke criteria, or visible vegetation conferred poor prognosis.

Author/ Year	Aim of Study	Study Type	Study Size (N)	Patient Population	Study Intervention	Primary Endpoint	Predictors of Outcome
Hasbun, 2003 (26)	To derive and externally validate a prognostic classification system for pts with complicated left-sided native valve IE	Retrospective multicenter cohort study	513	Pts with left-sided NVE with current indication of surgery in 45%`	Registration of clinical information, sociodemographic data, comorbid conditions, previous heart disease, symptoms, physical findings, blood cultures, electrocardiogram, echocardiography, type of surgery performed, and operative findings	In the derivation and validation cohorts, the 6-mo mortality rates were 25% and 26%, respectively. In the derivation cohort, pts were classified into 4 groups with increasing risk for 6-mo mortality: 5%, 15%, 31%, and 59% (p<0.001). In the validation cohort, a similar risk among the 4 groups was observed: 7%, 19%, 32%, and 69% (p<0.001).	5 baseline features were independently associatedwith 6 mo mortality (comorbidity [p=0.03], abnormal mental status [p=0.02], moderate-to-severe congestive HF [p=0.01], bacterial etiology other than viridans streptococci [p<0.001 except *S. aureus*, p=0.004], and medical therapy without valve surgery [p=0.002])
Vikram, 2003 (27)	To determine whether valve surgery is associated with reduced mortality in pts with complicated, left-sided native valve IE	Retrospective multicenter cohort study; Propensity analysis	513	Pts with left sided NVE with current surgical intervention in 45%	Registration of clinical information, sociodemographic data, comorbid conditions, previous heart disease, symptoms, physical findings, blood cultures, ECG, echocardiography, type of surgery performed, and operative findings	After adjustment for baseline variables associatedwith mortality (including hospital site, comorbidity, HF, microbial etiology, immunocompromised state, abnormal mental status, and refractory infection),valve surgery remained associated with reduced mortality (adjusted HR: 0.35; 95% CI: 0.23–0.54; p<0.02). In further analyses of 218 pts matched bypropensity scores, valve surgery remained associated with reduced mortality (15% vs. 28%; HR: 0.45; 95% CI: 0.23–0.86; p=0.01). After additional adjustment for variables thatcontribute to heterogeneity and confounding within the propensity-matched group, surgical therapy remained significantly associated with a lower mortality (HR: 0.40; 95% CI: 0.18-0.91; p=0.03). In this propensity-matched group, pts with moderate- to-severe congestive HF showed the greatest reduction in mortality with valve surgery (14% vs. 51%; HR: 0.22; 95% CI: 0.09–0.53; p=0.001).	Pts with moderate-to-severe HF showed the greatest reduction in mortality with valve surgery. Stratifying the data by congestive HF among propensity- matched pts undergoing surgery revealed that among pts with none to mild HF, valve surgery was not associated with reduced mortality compared with medical therapy (HR: 1.04; 95% CI: 0.43–2.48; p=0.93). Among propensity-matched pts with moderate-to-severe HF, valve surgery was associated with a significant reduction in mortality compared with medical therapy (HR: 0.22; 95% CI: 0.08–0.53; p=0.01).
Habib, 2005 (28)	To identify prognostic markers in 104 pts with PVE and the effects of a medical vs.surgical strategy outcome in PVE	Retrospective multicenter cohort study	104	100% PVE pts; surgery 49%	Registration of epidemiological, clinical, microbiological and other laboratory features, echocardiography data, and treatment strategy	Overall, 22 (21%) died in hospital. By multivariate analysis, severe HF (OR: 5.5) and *S. aureus* infection (OR: 6.1) were the only independent predictors of in-hospital death. Among 82 in-hospital survivors, 21 (26%) died duringa 32 mo follow-up. Mortality was not significantly different between surgical and nonsurgical pts (17% vs. 25%, respectively, not significant). Both in-hospital and long-term mortality were reduced by a surgical approach in high-risk subgroups of pts with staphylococcal PVE and complicated PVE.	Factors associated with in-hospital death were severe comorbidity (6% of survivors vs. 41% of those whodied; p=0.05), renal failure (28% vs.45%, p=0.05), moderate- to-severe regurgitation (22% vs. 54%; p=0.006), staphylococcal infection (16% vs. 54%; p=0.001), severe HF (22% vs. 64%; p=0.001), and occurrence of any complication (60% vs. 90%; p=0.05).

Author/ Year	Aim of Study	Study Type	Study Size (N)	Patient Population	Study Intervention	Primary Endpoint	Predictors of Outcome
Revilla, 2007 (29)	Describe the profile of pts with left-sided IE who underwent urgent surgery and to identify predictors of mortality	Prospective multicenter cohort study	508	NVE 66%,PVE 34%; surgery studied for the present report	Brucella, Q fever, Legionella, and Mycoplasma. Persistent infection despite appropriate antibiotic treatment (31%).	Of these 508 episodes, 132 (34%) wereelectively operated on, and 89 pts required urgent surgery (defined as prior to completion of antibiotic course). 1° reasons for urgent surgery in these 89 pts were HF that did not respond to medication (72%) and persistent infection despite appropriate antibiotic treatment (31%). 32 pts (36%) died during their hospital stay. 32% of NVE died vs. 45% of pts with PVE. Late PVE was associated with a higher mortality than early PVE (53% vs. 36%)	Univariate analysis identified renal failure, septic shock, Gram-negative bacteria, persistent infection, and surgery for persistent infection as factorsassociated with mortality. Multivariate analysis confirmed only persistent infection and renal insufficiency as factors independently associated with a poorprognosis.
Hill, 2007 (30)	Analyze epidemiology, optimal treatment, and predictors of 6- mo mortality in IE	Prospective single-center cohort study	193	NVE 66%, PVE 34%; surgery 63%	Registration of epidemiological, clinical, microbiological and other laboratory features, echocardiography data, and treatment strategy	43% included staphylococci, 26% streptococci,and 17% enterococci. At least 1 complication occurred in 79% of the episodes and 63% had surgical intervention. 6-mo mortality was 22%: 33% for staphylococci, 24% for enterococci, and 8% for streptococci. 74% of pts with a contraindication to surgery diedwhen compared with 7% with medical treatment without a contraindication and 16% with surgical treatment.	*S. aureus*, contraindication to surgery (present in 50% of deaths).
Remadi, 2007 (31)	To evaluate the predictors of outcome and to establish whether early surgery is associated with reduced mortality	Prospective multicenter cohort study	116	*S. aureus* IE alone; NVE 83%, PVE 17%; surgery 47%	Registration of epidemiological, clinical, microbiological and other laboratory features, echocardiography data, and treatment strategy. Antibiotic treatment.	In-hospital mortality rate was 26%, and the 36-mo survival rate was 57% Surgical group mortality was 16% vs. 34% in the medically treated group ($p<0.05$) In unadjusted analyses, early surgery performed in 47% of pts was associated with lower in-hospital mortality (16% vs. 34%; $p=0.034$) and with better 36-mo survival (77% vs. 39%; $p<0.001$).	Multivariate analyses identified comorbidity index, HF, severe sepsis, prosthetic valve IE, and majorneurologic events as predictors of in-hospitalmortality Severe sepsis and comorbidity index were predictorsof overall mortality After adjustment of baseline variables related to mortality, early surgery
Akso, 2007 (32)	To better understand the impact of surgery on the long-term survival of pts with IE	Prospective single-center cohort study with propensity score matching	426	NVE 69%, PVE 19%, “other” 12%; surgery in 29%	Registration of epidemiological, clinical, microbiological and other laboratory features, echocardiography data, and treatment strategy. Pts’ propensities for surgery	The fit of the propensity model to the data was assessed using the concordance index with pts who underwent surgery matched to those who did not undergo surgery, using individual propensity scores. The following factors were statistically associated with surgical therapy: age, transfer from an outsidehospital, evidence of IE on physical examination, the presence of infection with staphylococci, HF, intracardiac abscess, and hemodialysis without a chroniccatheter.	Revealed that surgery was associated with decreased mortality (HR: 0.27; 95% CI: 0.13–0.55). A HX of DM (HR: 4.81; 95% CI: 2.41– 9.62), the presence of chronic IV catheters at the beginning of the episode (HR: 2.65; 95% CI: 1.31– 5.33), and with increased mortality.

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Tleyjeh, 2007 (33)	To examined the association between valve surgery and all-cause 6 mo mortality among pts with left- sided IE	Matched propensity analysis	546	NVE alone; surgery 24%	Propensity score to undergo valve surgery was used to match pts in the surgical and nonsurgical groups. To adjust for survivor bias, the follow-up time was matched so that each pt in the nonsurgical group survived at least as long as the time to surgery in the respective surgically-treated pt.	Death occurred in 99 of the 417 pts (23.7%) in the nonsurgical group vs. 35 deaths among the 129 pts (27.1%) in the surgical group. 18 of 35 (51%) pts in the surgical group died within 7 d of valvesurgery.	After adjustment for early (operative) mortality, surgery was not associated with a survival benefit (adjustedHR: 0.92; 95% CI: 0.48–1.76).
Tleyjeh, 2008 (34)	To examine the association between the timing of valve surgery after IE dx and 6-mo mortality among pts with left-sided IE	Retrospective single-center cohort propensity analysis	546	NVE alone; surgery 24%	The association between time from IE dx to surgery and all-cause 6 mo mortality was assessed using Cox proportional hazards modeling after adjusting for the propensity score (to undergo surgery 0–11 d vs. 11 d, median time, after IE dx).	The median time between IE dx and surgery was 11 d (range 1–30). Using Cox proportional hazards modeling, propensity score and longer timeto surgery (in d) were associated with unadjusted HRs of (1.15, 95% CI: 1.04–1.28, per 0.10 unit change; p=0.009) and (0.93; 95% CI: 0.88–0.99, per d; p=0.03), respectively. In multivariate analysis, a longer time to surgery was associated with an adjusted HR: (0.97; 95% CI: 0.90– 1.03). The propensity score and time from dxto surgery had a correlation coefficient of r=20.63, making multicollinearity an issue in the multivariable model.	On univariate analysis, a longer time to surgery showed a significant protective effect for the outcome of mortality. After adjusting for the propensity to undergo surgery early vs. late, a longer time to surgery was nolonger significant, but remained in the protective direction.
Thuny, 2009 (35)	To determine whether the timing of surgery could influence mortality and morbidity in pts with complicated IE	Retrospective single-center cohort propensity analysis	291	NVE 82%, PVE 18%; surgery 100%	The time between the beginning of the appropriate antimicrobial therapy and surgery was used as a continuous variable and as a categorical variable with a cut-off of 7 d to assess the impact of timing ofsurgery. 2 groups of pts were formed according to the timing of surgery: the "≤1st wk surgery group" and the ">1st wk surgery group". The impact of the timing of surgery on 6 mo mortality, relapses, and PVD was analyzed using PS	1st wk surgery was associated with a trend of decrease in 6-mo mortality in the quintile of pts with the most likelihood of undergoing this early surgical management (quintile 5: 11% vs. 33%, OR: 0.18, 95% CI: 0.04 –0.83; p=0.03). Pts of this subgroup were younger, were more likelyto have *S. aureus* infections, congestive HF, and larger vegetations. ≤1st wk surgery was associated with an increased number of relapses or PVD (16% vs. 4%, adjusted OR: 2.9, 95% CI: 0.99–8.40; p=0.05).	Very early surgery (<7 d) associated with improved survival (especially in highest risk pts), but greater likelihood of relapse or post-operative valve dysfunction.

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Manne, 2012 (36)	Describe the morbidity and mortality associated with surgery for IE and compare differences in characteristics, pathogens, and outcomes for pts with NVE and PVE from a large surgery-minded tertiary referral center	Retrospective single-center surgical cohort study	428	NVE 58%, PVE 42%; surgery 100%	Registration of epidemiological, clinical, microbiological and other laboratory features, echocardiography data, and treatment strategy	Overall 90% of pts survived to hospital discharge. When compared with pts with NVE, pts with PVE had significantly higher 30-d mortality (13% vs. 5.6%; p<0.01), but long-term survival was not significantly different (35% vs. 29%; p=0.19).	Pts with IE caused by *S. aureus* had significantly higher hospital mortality (15% vs. 8.4%; p<0.05), 6 mo mortality (23% vs. 15%; p=0.05), and 1 y mortality (28% vs. 18%; p=0.02) compared with non–*S. aureus* IE.
Kang, 2012 (37)	To compare clinical outcomes of early surgery and conventional treatment in pts with IE	Prospective randomized trial at 2 centers with intention to treat analysis	76	Left-side NVE and high risk of embolism to early surgery (49%) vs. conventional treatment (51%)	Pts were randomly assigned in a 1:1 ratio to the early-surgery group or the conventional-treatment group with the use of a Web-based interactive response system. The protocol specified that pts who were assigned to the early-surgery group should undergo surgery within 48 h after randomization. Pts assigned to the conventional-treatment group were treated according to AHA guidelines, and surgery was performed only if complications requiring urgent surgery developed during medical treatment or if symptoms persisted	The 1° endpoint (composite of in-hospital death and embolic events that occurred within 6 wk after randomization) occurred in 1 pt (3%) in the early surgery group as compared with 9 (23%) in the conventional-treatment group (HR: 0.10; 95% CI: 0.01–0.82; p=0.03). There was no significant difference in all-cause mortality at 6 mo in the early-surgery andconventional- treatment groups (3% and 5%, respectively; HR:0.51; 95% CI: 0.05–5.66; p=0.59). The rate of the composite en point of death from any cause, embolic events, or recurrence of IE at 6 mowas 3% in the early-surgery group and 28% in the conventional-treatment group (HR: 0.08; 95% CI: 0.01–0.65; p=0.02).	As compared with conventional treatment, early surgery in pts with IE and large vegetations significantly reduced the composite endpoint of death from any cause and embolic events by effectively decreasing the risk of systemic embolism.

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Eishi, 1995 (38)	To establish guidelines for the surgical treatment of pts with IE who have cerebrovascular complications	Retrospective study of 181 pts with cerebral complications among 2523 surgical cases of IE	181 pts	Predominately left sided IE; 37.5% PVE and 62.5% NVE with neurological complicationis of IE	Questionnaire consisting of 2 parts: (1) Each center was asked for a summary of the number and outcome of pts with IE according to the types of IE 1 (active/healed and native valve/prosthetic valve) and the presence of cerebral complications; (2) the other portion inquired about each pt with cerebral complications, asking for details such as age, gender, AF, anticoagulant therapy, diseased valve, organism, effectiveness of antimicrobial therapy, reason for early cardiac operation, interval between the onset of symptoms and the cardiac operation, type of cerebral complication, cerebral aneurysm, prior cerebral surgery, severity, influence of operation on cerebral damage, and outcome.	To study the influence of cardiac surgery on preoperative cerebral complications, we analyzed the interval between the onset of cerebral complications and performance of the cardiac operation, as well as other preoperative variables. The effectiveness of antimicrobial therapy was ranked in 3 grades (1 = ineffective, 2 = effective, and 3 = well controlled). A correlation between the interval and the exacerbation of cerebral complications was evaluated by means of the Spearman rank correlation coefficient. The intervals were then classified in several groups, and variability between the groups for the exacerbation was estimated by Scheffe's F procedure for post-hoc comparisons, according to the Kruskal-Wallis test. To analyze the risk factors affecting exacerbation of cerebral complications, we expressed preoperative variables as mean ± standard error. The difference between the groups with and without exacerbation was tested for significance by the unpaired t test, and incidence was expressed as percentage of pts having the variable compared with the entire group of pts and then compared by $\chi 2$ analysis. Moreover, all variables and incidence (transformed to continuous variables) were estimated by stepwise regression analysis. Statistical significance was accepted at a p level of <0.05. These analyses were done with the Stat View system (Abacus Concepts, Inc., Berkeley, Calif.).	The rate of exacerbation of cerebral complications decreased to 10% in pts who underwent surgical treatment more than 15 d after cerebral infarction and to 2.3% in those operated on more than 4 wk later. Preoperative risk factors were severity of cerebral complications, interval from onset of symptoms to operation, and uncontrolled HF as the indication for cardiac surgery. More than 15 d after cerebral hemorrhage, the risk of the progression of cerebral damage is still significant, and this risk persists even 4 wk later.
Garcia-Cabrera, 2013 (39)	Assess the incidence of neurological complications in pts with infective endocarditis, the risk factors for their development, their influence on the clinical outcome, and the impact of cardiac surgery	Retrospective analysis of prospectively collected data on a multicenter cohort	1345pts	Consecutive Left sided endocarditis cases from 8 Centers in Spain	Specific variables from registries were analyzed including the date of IE dx; pts age and sex; type of endocarditis (native or prosthetic); location and size of vegetations on echocardiography; infecting microorganism; date, type, and extent of neurological complications; anticoagulant therapy given; date of the start of antimicrobial treatment; date of surgery (if performed); and outcome.	Determine the risk factors associated with the development of all neurological complications	Predictors of neurological complications were vegetation size ≥3 cm (HR: 1.91; 95% CI: 1.07–3.43; p=0.029), S aureus as the cause of IE (HR: 2.47; 95% CI: 1.94–3.15; p<0.001), anticoagulant therapy at IE dx (HR: 1.31; 95% CI: 1.00–1.72; P=0.048), and MV involvement (HR: 1.29; 95% CI: 1.02–1.61; p=0.03). Further analysis showed that elderly pts (≥70 y) had lower complication rates than younger ones, and only hemorrhagic events showed statistical significance (HR: 0.36; 95% CI: 0.16–0.83; p=0.014). Anticoagulant treatment was particularly associated with cerebral hemorrhage (HR: 2.71; 95% CI: 1.54–4.76; p=0.001).

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Barsic, B, 2013 (40)	Examine the relationship between the timing of surgery after stroke and the incidence of in-hospital and 1-y mortalities.	Post-hoc review of the International Collaboration on Endocarditis –Prospective Cohort Study of with definite IE who were admitted to 64 centers June 2000–December 2006	198 pts	198 pts of 857 pts with IE complicated by ischemic stroke who underwent valve replacement surgery post-stroke	Data were obtained from the International Collaboration on Endocarditis–Prospective Cohort Study of 4794 pts with definite IE who were admitted to 64 centers from June 2000 through December 2006. Multivariate logistic regression and Cox regression analyses were performed to estimate the impact of early surgery on hospital and 1-y mortality after adjustments for other significant covariates.	Estimate the impact of early surgery on hospital and 1-y mortality after adjustments for other significant covariates.	After adjustment for other risk factors, early surgery was not significantly associated with increased in-hospital mortality rates (OR: 2.308; 95% CI: .942–5.652). Overall, probability of death after 1-y follow-up did not differ between 2 treatment groups (27.1% in early surgery and 19.2% in late surgery group, p=.328; adjusted HR: 1.138; 95% CI: .802–1.650).

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