

Factors associated with local invasion in infective endocarditis: a nested case-control study

Abarna Ramanathan, James C. Witten, Steven M. Gordon, Brian P. Griffin, Gosta B. Pettersson, Nabin K. Shrestha



Department of Infectious Diseases, Cleveland Clinic, Cleveland, OH, USA

Contact information:
Abarna Ramanathan, MD
9500 Euclid Avenue / G-21,
Cleveland, OH 44195
Tel: 216-952-9151
Fax: 216-445-9446
Email: ramanaa@ccf.org

Abstract (updated)

Objectives
A substantial proportion of infective endocarditis (IE) cases are complicated by local invasion. The purpose of this study was to identify patient and disease characteristics associated with local invasion in surgically treated IE patients.

Methods
This was a nested case-control study. All episodes of IE for patients admitted to Cleveland Clinic from January 1st, 2013 – June 30th, 2016 were identified from the Cleveland Clinic IE Registry. Patients ≥18 years of age who underwent surgery for IE were included. Amongst these, cases were those with local invasion, controls were those without. Local invasion, defined as periannular extension, paravalvular abscess, intracardiac fistula, or pseudoaneurysm, was ascertained from the surgical operative note. Associations of selected factors with local invasion were examined in a multivariable logistic regression model.

Results
Among 511 patients who met inclusion criteria, 215 had local invasion. Mean age was 56 years; 369 were male. Overall 345 (68%) had aortic valve, 228 (45%) mitral valve, and 66 (13%) tricuspid or pulmonic valve involvement. Aortic valve involvement (OR 6.23, 95% CI 3.55 – 11.44), bioprosthetic valve (OR 3.88, 95% CI 2.36 – 6.44), significant paravalvular leak (OR 3.80, 95% CI 1.60 – 9.89), new atrioventricular nodal block (OR 3.77, 95% CI 1.87 – 7.90), infection with streptococci other than viridans group streptococci (OR 7.54, 95% CI 2.42 – 24.87), and presence of central nervous system emboli (OR 1.85, 95% CI 1.13 – 3.04) were associated with local invasion.

Conclusions
Intra-cardiac and microorganism factors, but not comorbid conditions, are associated with local invasion in IE.

Introduction

- Among patients with IE, 20-52% are complicated by local invasion, i.e. extension of infection beyond the valve cusps or leaflets and into the surrounding annulus, including aortic root abscesses, pseudoaneurysms and intracardiac fistulae.
- The aim of this study was to identify patient and disease factors associated with local invasion.

Methods

- All episodes of IE amongst patients admitted to Cleveland Clinic from January 1st 2013 – June 30th 2016 were identified from the Cleveland Clinic IE Registry and screened for inclusion. Patients ≥18 years of age, who underwent surgery for IE, were included. Subsequent episodes of IE were excluded for patients once included.
- All included patients either had histopathological evidence of endocarditis on excised valves or met Duke Criteria for definite endocarditis.
- The presence of locally invasive disease was adjudicated by the description in the surgical operative note.
- IE was coded as non-invasive if infection was confined to the cusps and leaflets and invasive if extending beyond the cusps or leaflets, into the annulus and surrounding structures. The latter included periannular invasion, paravalvular abscess, intracardiac fistula or pseudoaneurysm.
- Associations of various explanatory variables with locally invasive disease were examined in a multivariable logistic regression model.

Results

- Of 732 patients in the IE registry in the specified time period, 201 were excluded because they were treated non-surgically, and 20 were excluded due to having been previously included for a prior episode of IE within the study time frame. Of the remaining 511 included patients, 215 had local invasion.
- Overall 345 (68%) had aortic valve, 228 (45%) mitral valve, and 66 (13%) tricuspid or pulmonic valve involvement. Characteristics of the patients with invasive and non-invasive infections are compared in table 1.
- The variables that remained significant in the multivariable analysis, with the corresponding odds ratios and 95% confidence intervals, are shown in table 2.

Table 1. Characteristics of patients with invasive disease versus non-invasive disease

Characteristic ^a	Non-invasive disease (296)	Invasive disease (215)	P value
Demographics			
Age in years, mean(SD)	54 (17)	58 (15)	0.007
Male sex	201 (68)	168 (78)	0.014
Primary patients	64 (22)	36 (17)	0.208
Comorbidities			
Diabetes mellitus	67 (23)	65 (30)	0.067
COPD	37 (13)	26 (12)	0.999
End stage renal disease	26 (9)	12 (6)	0.234
Cirrhosis	5 (2)	2 (1)	0.731
Malignancy	7 (2)	7 (3)	0.738
Immunosuppression	11 (4)	14 (7)	0.216
Valve affected			
Aortic	154 (52)	191 (89)	<0.001
Mitral	155 (52)	73 (34)	<0.001
Tricuspid or pulmonic valve	51 (17)	15 (7)	0.001
Positive blood cultures	248 (84)	184 (86)	0.666
Microorganism			
Viridans group streptococci	78 (26)	39 (18)	
Staphylococcus aureus	62 (21)	37 (17)	
Coagulase negative staphylococci	29 (10)	38 (18)	
Other streptococci ^b	8 (3)	15 (7)	
Enterococcus	43 (15)	31 (14)	
Fungi	13 (4)	4 (2)	
Pathogen not identified	21 (7)	11 (5)	
Other	42 (14)	40 (19)	
Predisposing factors for IE			
Previous IE	34 (12)	38 (18)	0.063
CIED	31 (11)	27 (13)	0.554
Previous valvular heart disease	66 (22)	33 (15)	0.065
Indwelling vascular catheter	20 (7)	12 (6)	0.721
PWID	58 (20)	24 (11)	0.015
Mechanical valve	11 (4)	40 (19)	<0.001
Bioprosthetic valve	62 (21)	101 (47)	<0.001
Homograft	14 (5)	8 (4)	0.738
Prosthetic ring	16 (5)	9 (4)	0.672
Congenital heart disease	6 (2)	3 (1)	0.845
Complication variables			
Large vegetation	168 (57)	101 (47)	0.036
Significant paravalvular leak	11 (4)	38 (18)	<0.001
Significant regurgitation	216 (73)	117 (54)	<0.001
Leaflet perforation	164 (55)	71 (33)	<0.001
New AV node block	18 (6)	43 (20)	<0.001
CNS emboli	79 (27)	69 (32)	0.218
Other systemic emboli	90 (30)	44 (21)	0.016
CNS hemorrhage	30 (10)	20 (9)	0.871
Infectious intracranial aneurysm	19 (6)	19 (9)	0.391
Metastatic infection	38 (13)	22 (10)	0.445

AV, atrioventricular; CIED, cardiac implantable electronic device; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; IE, infective endocarditis; PWID, persons who inject drugs; SD, standard deviation

Table 2. Effect sizes for variables that remained significant in multivariable analysis

Variable	Odds ratio (95% CI)	P value
Aortic valve involvement	6.23 (3.55 – 11.44)	<0.001
Mechanical valve	1.30 (0.16 – 7.30)	0.778
Bioprosthetic valve	3.88 (2.36 – 6.44)	<0.001
Significant paravalvular leak	3.80 (1.60 – 9.89)	0.004
New AV nodal block	3.77 (1.87 – 7.90)	<0.001
Central nervous system emboli	1.85 (1.13 – 3.04)	0.014
Microorganism (ref:viridans group streptococci)		0.003
Staphylococcus aureus	1.33 (0.65 – 2.73)	
Coagulase negative staphylococci	1.75 (0.80 – 3.85)	
Other streptococci	7.54 (2.42 – 24.87)	
Enterococcus	0.78 (0.37 – 1.62)	
Fungi	0.22 (0.05 – 0.84)	
Pathogen not identified	1.12 (0.38 – 3.11)	
Other	1.13 (0.56 – 2.26)	
Aortic valve × mechanical valve (interaction term)	14.46 (1.95 – 152.60)	0.014

Conclusion

- Our study suggests that local invasion in IE is associated with intra-cardiac and microbiologic factors, but not with comorbid conditions.
- Patients with multiple factors known to be associated with local invasion should be imaged comprehensively with technologies, such as TEE, CT or PET, when invasion is not evident on baseline transthoracic imaging, since such extension of infection is a compelling indication for surgery.

Please see our recently published article at <https://doi.org/10.1016/j.cmi.2020.09.003> for more details.