ORIGINAL PAPER

Nagoya J. Med. Sci. **87**. 546–557, 2025
doi:10.18999/nagjms.87.3.546

Optimal surgical timing for non-urgent surgery patients with active infective endocarditis

Tomonari Uemura, Hideki Ito, Ryota Yamamoto, Toshikuni Yamamoto, Sachie Terazawa, Tomo Yoshizumi, Yoshiyuki Tokuda, Yuji Narita and Masato Mutsuga

Department of Cardiac Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan

ABSTRACT

While preoperative antibiotic therapy is generally recommended in non-emergency surgery cases of infective endocarditis, delaying surgery may lead to a deterioration in patient condition. This study examined deterioration of condition during preoperative antibiotic therapy and associated clinical characteristics to clarify the optimal timing for non-emergent infective endocarditis surgery. We retrospectively analyzed 65 patients (mean age 57.1 ± 16.9 years) with active left-sided infective endocarditis (57 with native valves, 8 with prosthetic valves) initially considered suitable for combined antibiotic therapy and non-emergent surgical treatment. Causative organisms were *Streptococcus* spp. (n=31), *Staphylococcus* spp. (n=15, including 5 resistant strains), and Gram-negative bacteria (n=4). Twelve patients (18%) required unexpected urgent operations shortly after starting antibiotics (median 5.5 days, interquartile range 3–8 days). Another 12 patients (18%) experienced deterioration of condition 20–30 days after starting antibiotics, including worsening heart failure (n=5), new embolic events (n=3), new perivalvular extension of infection (n=3), and worsening infection parameters (n=1). A leukocyte count >7900/μL one week after starting antibiotics predicted late deterioration (sensitivity 91%, specificity 76%, area under the receiver operating characteristic curve 0.866). Among patients with active infective endocarditis who initially received maximal antibiotic therapy and were considered for non-emergent surgery, 18% required urgent operation and another 18% experienced late deterioration. A high leukocyte count despite one week of antibiotic therapy was associated with late deterioration. For these patients, earlier surgical intervention might be beneficial to avoid a deterioration in conditions.

Keywords: infective endocarditis, non-urgent surgery, prognostication

Abbreviations:
IE: infective endocarditis
WBC: white blood cell

Received: January 9, 2025; Accepted: February 3, 2025
Corresponding Author: Tomonari Uemura, MD
Department of Cardiac Surgery, Nagoya University Graduate School of Medicine,
65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan
Tel: +81-52-741-2111, Fax: +81-52-744-2785, E-mail: uemura.tomonari.p5@f.mail.nagoya-u.ac.jp

INTRODUCTION

Infective endocarditis (IE) is an uncommon infectious disease with an annual incidence of 3–7 per 100,000 person-years in most contemporary population surveys.[1] Despite advances in diagnosis, infection control, and surgical techniques, IE still carries high mortality and morbidity rates.[2] The appropriate timing of surgical intervention is widely debated and no consensus guidelines have yet been developed to define the appropriate timing in most settings.

Emergent or urgent surgery is generally indicated in cases of uncontrollable congestive heart failure, refractory sepsis, or embolic complications, with a recommendation for surgery within a few days. In contrast, no clear recommendations have been made for the appropriate timing of non-urgent surgery.

For non-urgent surgery, the 2023 European Society of Cardiology guidelines state that surgery should be performed 'within the same hospital admission'.[3] American College of Cardiology/American Heart Association guidelines similarly state that surgery should be performed during initial hospitalization and before the completion of a full course of antibiotics.[4] Basically, unless emergency surgery is indicated, all patients initially receive appropriate antibiotic therapy at maximum doses prior to IE surgery according to the guidelines.

The present study reviews the clinical course of patients with active IE, with a particular focus on the deterioration of condition occurring during the period of guideline-orientated preoperative antibiotic therapy. This study also evaluated possible predictors of deterioration based on initial findings shortly after the commencement of antibiotic therapy. The intention was to clarify the appropriate timing for IE surgery in individual patients.

PATIENTS AND METHODS

Ethical statement

This retrospective review study was approved by review board of Nagoya University Graduate School of Medicine (approval no. 2019-0179; date of approval, 2019/08/23). The need to obtain informed consent was waived based on the retrospective nature of the investigation.

Inclusion and exclusion criteria and patient care protocols

Between January 2007 and December 2022, 93 patients required valvular surgery in our department for left-sided active IE. All patients met the modified Duke criteria for definite or possible endocarditis. Among these, 28 patients were deemed to need emergency surgery (surgery within 24 hours after admission) at the time of initial presentation and were excluded from the study. The remaining 65 patients who were not immediately indicated for emergency surgery were included in the study. These patients were diagnosed with active left-sided IE and were initially considered suitable for combined antibiotic therapy followed by non-emergent surgical treatment.

All patients received appropriate antibiotic therapy at maximum doses according to the guidelines. Patients were closely monitored for signs of deterioration and the potential need for urgent surgery. During initial antibiotic therapy, patients who developed 1) hemodynamic instability, 2) impending risk of embolic events, 3) uncontrollable infection, or 4) perivalvular extension of IE were indicated for prompt urgent surgery, which was performed within 3–5 days of developing these conditions. If none of these conditions arose, a full course of antibiotic therapy was continued with the aim of achieving maximal control of the infection. Patients who did not require emergency or prompt urgent surgery were defined as the non-urgent group, and deterioration occurring in this group was defined as late deterioration. In this study, late deteriora-

tion was defined as follows: 1) new embolic events; 2) worsening heart failure; 3) worsening infection parameters; or 4) new perivalvular extension of infection. The clinical course of the 65 patients was reviewed retrospectively, with a particular focus on deterioration during antibiotic therapy prior to IE surgery. A flowchart of inclusion and exclusion criteria and patient flow in this study is shown in Figure 1.

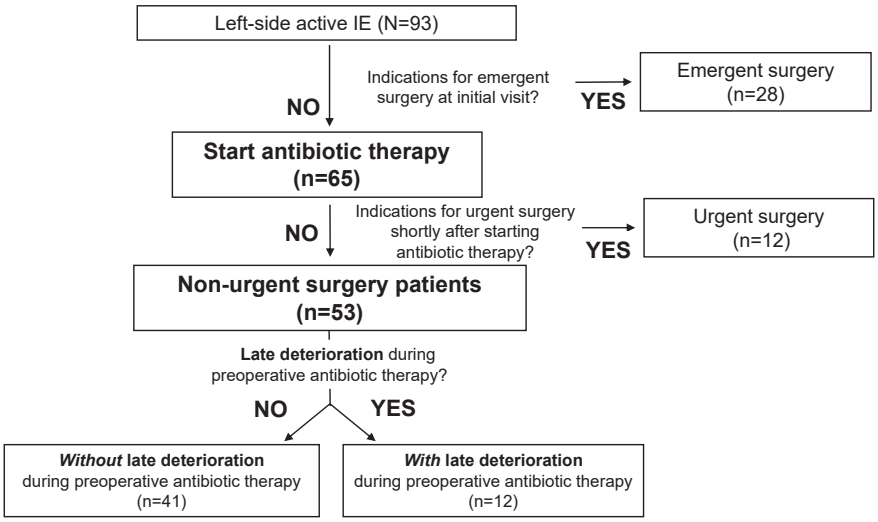

Fig. 1 Flowchart of patient selection for this study
IE: infective endocarditis

Outcomes

The primary endpoint of this study was the timing of deterioration during preoperative antibiotic therapy before IE surgery. Secondary endpoints were the risk factors for late deterioration among non-urgent surgery patients.

Data analysis

Missing data. Missing baseline data were infrequent (<10% for most variables) and were handled using multiple imputation.

Statistical analysis. Continuous variables are reported as mean ± standard deviation or median and interquartile range (IQR) and were examined using Student's t test or the Wilcoxon rank-sum test. Categorical variables are presented as the number and percentage and were examined with the chi-squared test or Fisher's exact test between two groups.

Unless otherwise specified, definitions of preoperative characteristics and postoperative outcomes followed the Japan Adult Cardiovascular Surgery Database protocols (definitions are available online at http://www.jacvsd.umin.jp). Laboratory data were collected at three time points: on admission, one week (7±1 days) after initial diagnosis, and just before surgery. For patients diagnosed at referring hospitals, blood test data from the referring facilities were obtained to ensure consistent timing of data collection across the entire cohort. Composite preoperative risk was assessed using European System for Cardiac Operative Risk Evaluation (EuroSCORE) II.[5] Event-free rates were estimated using the Kaplan–Meier method, and differences between groups were determined using log-rank analysis. Values of $p<0.05$ were considered statistically significant.

In addition, factors predicting the occurrence of late deterioration during antibiotic therapy were evaluated among patients who did not initially undergo urgent surgery. A multiple logistic regression model, adjusted for confounders, was developed based on results from univariate analyses using a stepwise forward-selection method. The probability threshold for removal from the logistic regression was set at 0.25. Subsequently, the cutoff value was evaluated by receiver operating characteristic (ROC) curve analysis.

Not only in-hospital results focusing on a deterioration in conditions but also long-term results (namely the rate of freedom from IE-related death or recurrent IE) were also evaluated using Kaplan–Meier methods.

All analyses were performed using JMP version 17 software (SAS Institute, Cary, NC, USA).

RESULTS

Patient characteristics

The 65 patients not indicated for emergency surgery at the time of initial visit showed a mean age of 57.1 ± 16.9 years, and 46 (70.8%) were male. *Streptococcus* spp. was the most frequent causative organism, found in 31 cases (47.7%). Other causative organisms included methicillin-sensitive *Staphylococcus aureus* (MSSA) in 10 cases (15.4%), methicillin-resistant *S. aureus* (MRSA) in 5 cases (7.7%), *Enterococcus* spp. in 4 cases (6.2%), Gram-negative bacteria in 4 cases (6.2%), and no pathogen detected in 10 cases (15.4%).

Native valve endocarditis was present in 57 cases (87.7%), with 26 (40.0%) in the aortic valve position, 39 (60.0%) in the mitral valve position, and 8 (12.3%) involving both valves. Prosthetic valve IE accounted for the remaining 8 cases (12.3%). Preoperative symptomatic stroke was detected in 5 cases (7.7%), and 5 patients (7.7%) had cerebral hemorrhage at the initial visit (Table 1).

Clinical course during antibiotic therapy

Twelve of the 65 patients (18%) required unexpected urgent surgery shortly after starting maximal antibiotic treatment, due to hemodynamic instability (n=7), impending risk of embolic events (n=3), uncontrollable infection (n=1), and perivalvular extension of IE (n=1). The median time to urgent surgery in these 12 patients was 5.5 days (IQR 3–8 days) after initiation of antibiotic therapy. Table 2 shows the characteristics of the remaining 53 patients who did not undergo urgent IE surgery. Twelve of these 53 patients experienced late deterioration, comprising worsening heart failure (n=5), new embolic events (n=3), new perivalvular extension of infection (n=3), and worsening infection parameters (n=1). Table 2 also includes a comparison based on the presence or absence of deterioration. Figure 2 illustrates the estimated freedom from unexpected urgent surgery or late deterioration using the Kaplan–Meier method. The curve indicates that late deterioration typically occurred 20–30 days after starting antibiotic therapy.

Table 1 Characteristics of the 65 patients

Variables	Values
Background	
Age, y, mean ± SD	57.1 ± 16.9
Male, n (%)	46 (70.8)
Hypertension, n (%)	16 (24.6)
Diabetes, n (%)	10 (15.3)
Chronic renal failure, n (%)	13 (20.0)
Hemodialysis, n (%)	3 (4.6)
Ejection fraction < 50%, n (%)	8 (12.3)
Pathogens	
Blood culture positive just before surgery, n (%)	6 (9.2)
Streptococcus spp., n (%)	31 (47.7)
MSSA, n (%)	10 (15.4)
MRSA, n (%)	5 (7.7)
Enterococcus spp., n (%)	4 (6.2)
Gram-negative bacteria, n (%)	4 (6.2)
Not detected, n (%)	10 (15.4)
Vegetation site	
Native valve, n (%)	57 (87.7)
Aortic valve, n (%)	26 (40.0)
Mitral valve, n (%)	39 (60.0)
Both aortic and mitral valves, n (%)	8 (12.3)
Prosthetic valve, n (%)	8 (12.3)
Cerebral infarction (symptomatic), n (%)	5 (7.7)
Cerebral hemorrhage (at admission), n (%)	8 (12.3)
EuroSCORE2 logistic, %	3.81 [1.70–11.4]

Values are given as mean ± SD, n (%), or median [interquartile range].
MRSA: methicillin-resistant *Staphylococcus aureus*
MSSA: methicillin-sensitive *Staphylococcus aureus*
EuroSCORE2: European System for Cardiac Operative Risk Evaluation II

Table 2 Characteristics of patients not undergoing urgent IE surgery: presence or absence of late deterioration

	Overall	**With late deterioration**	**Without late deterioration**	***p***
	N=53	n=12	n=41	
Background				
Age, y	55.8 ± 17.0	56.8 ± 17.4	55.8 ± 17.4	0.859
Male sex	37 (69.8)	6 (50)	31 (75.6)	0.150
Hypertension	13 (24.5)	3 (25.0)	10 (24.4)	1.000

Diabetes	8 (15.1)	3 (25.0)	5 (12.2)	0.361
Chronic renal failure	7 (13.2)	1 (8.3)	6 (14.6)	1.000
Hemodialysis	1 (1.9)	0	1 (2.4)	1.000
Ejection fraction < 50%	4 (7.5)	3 (25.0)	1 (2.4)	*0.033**
Pathogens				
Blood culture positive just before surgery	2 (3.8)	1 (8.3)	1 (2.4)	0.405
Streptococcus spp.	27 (50.9)	7 (58.3)	20 (48.8)	0.745
MSSA	9 (17.0)	3 (25.0)	6 (14.6)	0.400
MRSA	2 (3.8)	0	2 (4.9)	0.435
Enterococcus spp.	3 (5.7)	0	3 (7.3)	0.335
Gram-negative bacteria	3 (5.7)	0	3 (7.3)	0.335
Not detected	9 (17.0)	2 (16.7)	7 (17.1)	0.974
Vegetation site				
Native valve	47 (88.7)	11 (91.7)	36 (87.8)	0.710
Aortic valve	18 (34.0)	5 (41.7)	13 (31.7)	0.769
Mitral valve	35 (66.0)	8 (66.7)	27 (65.9)	0.958
Both aortic and mitral valves	6 (11.3)	2 (16.7)	4 (9.8)	0.883
Prosthetic valve	6 (11.3)	1 (8.3)	5 (12.2)	0.710
Cerebral infarction (symptomatic)	3 (5.7)	2 (16.7)	1 (2.4)	0.649
Cerebral hemorrhage (on admission)	5 (9.4)	4 (33.3)	1 (2.4)	0.882
EuroSCORE2 logistic, %	3.40 [1.68–8.19]	2.79 [1.59–7.53]	5.48 [1.95–34.7]	0.076
Blood values on admission				
ALB, g/dL	3.20 [2.65–3.55]	2.70 [2.58–3.30]	3.40 [2.70–3.50]	0.208
Hb, g/dL	11.5 [9.85–13.1]	9.80 [8.80–12.4)	11.6 [10.6–13.0]	0.188
WBC count, ×1000/μL	10.0 [7.70–14.4]	10.5 [8.50–16.2]	9.90 [7.55–11.7]	0.218
PLT count, ×1000/μL	210 [127–257]	220 [175–268)	208 [107–251]	0.230
CRP, mg/dL	7.66 [5.45–11.2]	8.25 [5.24–11.0]	7.66 [5.74–11.1]	0.923
Blood values one week after admission				
ALB, g/dL	2.80 [2.50–3.10]	2.65 [2.50–2.77]	3.00 [2.50–3.30]	0.125
Hb, g/dL	10.5 [9.2–11.9]	10.1 [8.25–10.8]	10.7 [9.4–12.0]	0.192
WBC count, ×1000/μL	7.16 [5.70–9.65]	10.7 [8.60–14.4]	6.55 [5.60–7.88]	*0.006***
PLT count, ×1000/μL	263 [203–334]	276 [232–304)	258 [202–334]	0.552
CRP, mg/dL	2.82 [0.92–5.06]	5.21 [2.08–10.1]	2.09 [0.92–4.39]	0.063

Values are given as mean ± SD, n (%), or median [interquartile range].
ALB: albumin
CRP: C-reactive protein
Hb: hemoglobin
MRSA: methicillin-resistant *Staphylococcus aureus*
MSSA: methicillin-sensitive *Staphylococcus aureus*
PLT: platelet
WBC: white blood cell
IE: infective endocarditis
EuroSCORE2: European System for Cardiac Operative Risk Evaluation II

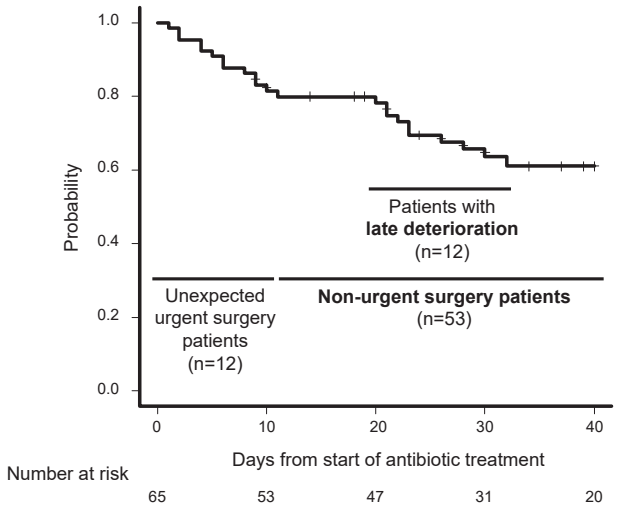

Fig. 2 Kaplan–Meier curve for freedom from unexpected urgent operations or late deterioration
Patients after 10 days of antibiotic treatment were defined as the non-urgent surgery group. The curve indicates that late deterioration typically occurred 20–30 days after starting antibiotic therapy.

Predictors of late deterioration before IE surgery

Factors predicting late deterioration during antibiotic therapy were evaluated among patients who did not undergo initial urgent surgery, and for whom laboratory data after initial antibiotic therapy were available. Based on the data in Table 2 and univariate analyses, ejection fraction (EF) <50% and a high white blood cell (WBC) count after one week of antibiotic therapy were associated with late deterioration. Multivariate analysis identified elevated WBC count as the single independent predictor of late deterioration, with an odds ratio of 1.61 (95% CI 1.14–2.25; $p<0.01$; Table 3). ROC curve analysis revealed that a WBC count >7900/μL at one week after starting antibiotics offered a clear cutoff value for predicting late deterioration, with 91% sensitivity and 76% specificity (area under the receiver operating characteristic curve [AUC], 0.866; 95% CI, 0.757–0.975; Figure 3).

Figure 4 illustrates the trajectory of WBC counts at three time points: on admission; one week after admission; and just before surgery. Notably, most patients who did not experience late deterioration showed a WBC count <7900/μL one week after initiating antibiotics, with a further decline observed just before surgery. In contrast, patients who experienced late deterioration exhibited consistently elevated WBC counts that did not decrease across the three time points.

Table 3 Predictors of late deterioration in non-urgent surgery patients

Parameters	Univariate *p*-value	Multivariate *p*-value	OR (95% CI)
EF <50%	0.033	0.592	–
WBC count 1 week after admission	*<0.01***	*<0.01***	1.61 (1.14–2.25)

CI: confidence interval
EF: ejection fraction
OR: odds ratio
WBC: white blood cell

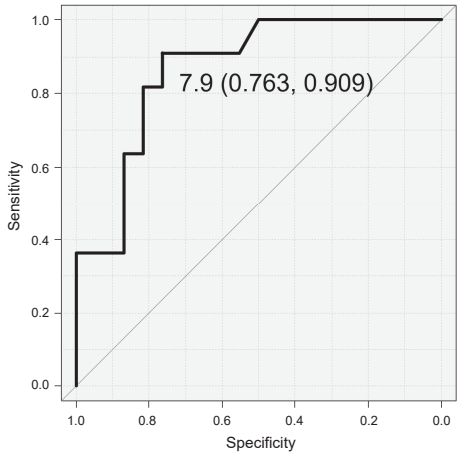

Fig. 3 Receiver operating characteristics curve generated for WBC counts at one week after starting antibiotic therapy against late deterioration among 53 non-urgent surgery patients

A cut-off of 7900/μL was found to have 91% sensitivity and 76% specificity with an AUC of 0.866 (95% CI, 0.757–0.975).

AUC: area under the receiver operating characteristic curve

CI: confidence interval

WBC: white blood cell

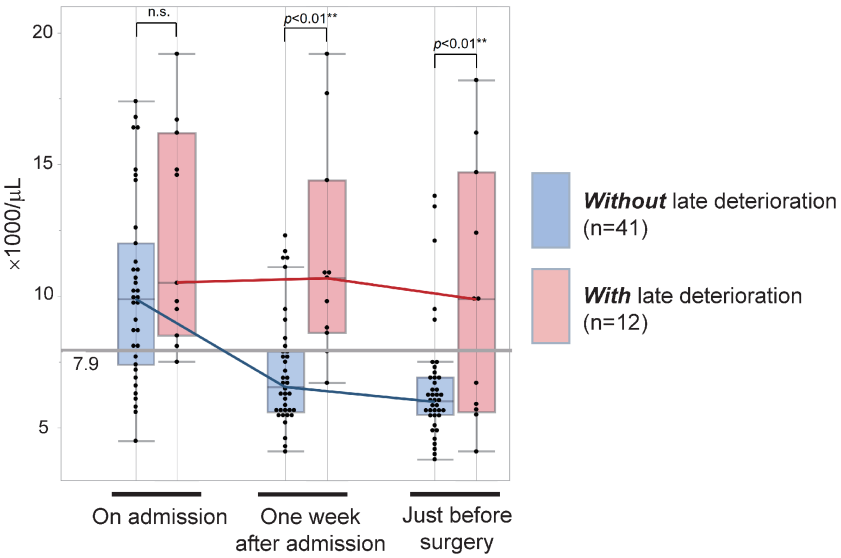

Fig. 4 The trajectory of WBC counts at three time points

The bold gray line represents the cut-off WBC count at one week after admission, as determined by ROC curve analysis. The bold blue and red lines indicate median WBCs for each group. The box shows the interquartile range (IQR).

n.s.: not significant

ROC: receiver operating characteristic curve

WBC: white blood cell

Long-term results for non-urgent surgery patients

Median follow-up was 1235 days (IQR 420–2380 days). The rate of freedom from IE-related death was significantly higher in patients without late deterioration compared to those with late deterioration (p=0.015). However, no significant difference in rate of IE recurrence was seen between these two groups (p=0.551; Figure 5).

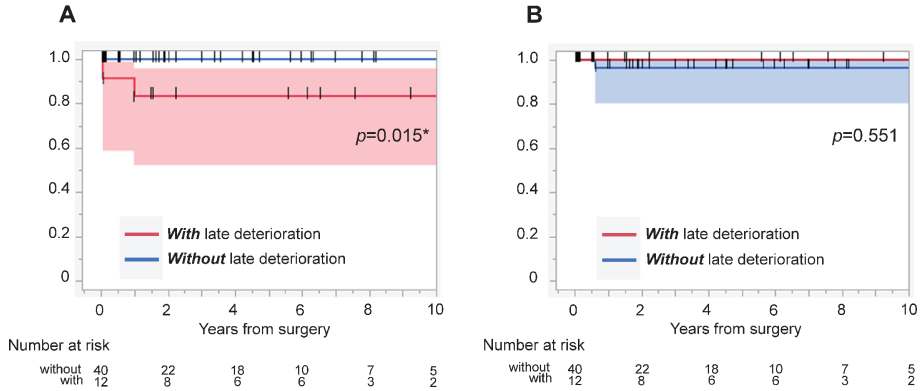

Fig. 5 Kaplan–Meier curves in patients with and without late deterioration
A, Freedom from IE-related death; and B, Freedom from recurrence of IE. The rate of freedom from IE-related death was significantly higher in patients without late deterioration compared to patients with late deterioration (p=0.015). No significant difference in rate of IE recurrence was seen between groups (p=0.551).
IE: infective endocarditis

DISCUSSION

Various guidelines specify indications for emergency surgery and its timing, but do not clearly define the optimal timing of surgery for patients who do not meet the criteria for emergency surgery. This study is the first to examine in detail the deterioration of condition occurring during antibiotic treatment for active IE indicated for surgery, and to propose appropriate timing for non-urgent surgery cases not clearly described in current guidelines.

Deterioration of condition during antibiotic therapy

Although guidelines[3,4] specify indications and timing for emergency surgery, they do not clearly define the optimal timing for surgery in patients who do not meet the criteria for emergency surgery. The present study demonstrated that among patients with active IE who received maximal antibiotic therapy and were initially considered for elective surgery, 18% eventually required an unexpected urgent operation, while another 18% experienced late deterioration. These significant proportions underscore the dynamic nature of IE and the potential for rapid changes in patient status.

Even when an elective operation was deemed appropriate at initial presentation, a significant number of patients experienced unexpected deterioration. Consequently, not a small number of patients did not complete the full course of preoperative antibiotic therapy as initially planned. In fact, the need for these unexpected urgent operations generally arose shortly after initial presentation, most often within the first week. Moreover, even when urgent surgery was not indicated, deterioration in other forms—such as heart failure or embolic events—could still occur at a relatively later stage, typically 20–30 days after starting antibiotic therapy. These findings

suggest the need to closely monitor patients for signs of deterioration throughout the entire course of antibiotic treatment.

Predictors of late deterioration

The present study identified several risk factors for late deterioration in non-urgent surgery patients through univariate analyses, including cardiac dysfunction and elevated WBC counts one week after starting antibiotics. Multivariate analysis revealed elevated WBC counts as the single independent predictor of late deterioration in this patient group. Specifically, a WBC count >7900/μL at this time demonstrated high sensitivity (91%) and specificity (76%) for predicting late deterioration. This finding provides clinicians with a valuable tool for risk stratification and surgical planning.

Previous research has demonstrated the utility of C-reactive protein (CRP) levels in predicting mortality, complication rates, embolism, and the need for emergency surgery in IE management.[6-8] Those studies highlighted the prognostic value of inflammatory markers, particularly CRP, for postoperative outcomes of IE. Our study complements such findings by identifying elevated WBC count as a predictor of late deterioration.

Clinical implications for surgical timing

The present results indicate that elevated WBC counts following initial antibiotic therapy are predictive of patient deterioration. Based on this finding, we suggest that for patients who do not achieve normalization of WBC count within one week of starting antibiotic therapy, surgery should be considered before completing the full course of antibiotics, ideally within 20 days of presentation. This strategy aims to prevent late deterioration of condition, such as new embolisms or worsening heart failure, which tend to occur after 20 days. The recent literature supports the benefits of early surgery regarding perioperative mortality and recurrence rates,[9-11] likely via the prevention of embolic events within the first week following diagnosis and antibiotic initiation.[12]

On the other hand, completing a full course of preoperative antibiotic therapy is often beneficial for infection control prior to surgery. Our protocol involves administering a full course of antibiotics at maximum doses to patients not immediately requiring emergency surgery, with close monitoring for potential urgent surgical needs. In our study, while many patients eventually required unexpected urgent surgery, those who responded well to antibiotics and completed the therapy without deterioration achieved very favorable outcomes. No cases of death were encountered and only one case among these patients showed recurrent IE.

Previous research also underscores the advantages of extended preoperative antibiotic therapy. García-Granja et al found that positive intraoperative valve cultures are associated with increased postoperative mortality.[13] Halavaara et al reported that after two or more weeks of antibiotic therapy, valve cultures often become negative, and the polymerase chain reaction (PCR) yield for valve bacteria significantly decreases.[14] In addition, a longer preoperative antibiotic period increases the likelihood of negative valve cultures intraoperatively.[15]

Decisions thus need to balance the benefits of a full course of preoperative antibiotics for infection control with the potential advantage of early surgery to avoid late deterioration. Our results advocate a personalized approach based on WBC count as an inflammatory marker. If urgent surgery is not indicated, patients may initially complete a full course of antibiotics. However, for those with persistently high WBC counts after one week of therapy, deterioration may be anticipated and earlier surgery should be performed—ideally within 20 days of presentation. Continuous monitoring for signs of deterioration and the potential need for urgent surgery throughout the antibiotic treatment course is essential.

Study limitations

Our study has the limitations inherent to a single-institution, retrospective design. As with any retrospective study, there may be unknown confounding factors that could not be adjusted for, potentially influencing our results. In addition, we collected data on surgical cases over a 15-year period, and the indications and timing of surgery may have changed over this time. Definitions of criteria for urgent surgery and deterioration may vary between institutions, potentially affecting the comparability of results.

To address these limitations and validate our findings, large-scale, multi-center prospective studies are warranted. Such studies would provide a more comprehensive understanding of the optimal timing for surgical intervention in patients with IE and help establish more generalizable guidelines for clinical practice.

Despite these limitations, this study contributes valuable insights to the management of non-urgent surgical patients with IE and provides a foundation for future research in this area.

CONCLUSIONS

This study provides important insights into the management of non-urgent surgical patients with IE. Among patients with active IE who initially received maximal antibiotic therapy and were considered for non-emergent surgery, 18% required an urgent operation and another 18% experienced late deterioration. A WBC count >7900/μL after one week of antibiotic treatment emerged as a significant predictor of late deterioration, suggesting that earlier surgical intervention may be beneficial in such cases to prevent adverse outcomes.

CONFLICT OF INTEREST

None declared.

FUNDING

None.

ACKNOWLEDGEMENTS

The authors would like to express their sincere gratitude to all those who supported this clinical study. The authors also thank FORTE Science Communications (https://www.forte-science.co.jp/) for English language editing.

REFERENCES

1 Duval X, Delahaye F, Alla F, et al. Temporal trends in infective endocarditis in the context of prophylaxis guideline modifications: three successive population-based surveys. *J Am Coll Cardiol.* 2012;59(22):1968–1976. doi:10.1016/j.jacc.2012.02.029

2 Mylonakis E, Calderwood SB. Infective endocarditis in adults. *N Engl J Med.* 2001;345(18):1318–1330. doi:10.1056/NEJMra010082

3 Delgado V, Ajmone Marsan N, de Waha S, et al. 2023 ESC Guidelines for the management of endocarditis.

Eur Heart J. 2023;44(39):3948–4042. doi:10.1093/eurheartj/ehad193
4 Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation.* 2021;143(5):e72–e227. doi:10.1161/CIR.0000000000000923
5 Nashef SA, Roques F, Sharples LD, et al. EuroSCORE II. *Eur J Cardiothorac Surg.* 2012;41(4):734–744;discussion 744–745. doi:10.1093/ejcts/ezs043
6 Mohanan S, Gopalan Nair R, Vellani H, C G S, George B, M N K. Baseline C-reactive protein levels and prognosis in patients with infective endocarditis: A prospective cohort study. *Indian Heart J.* 2018;70 Suppl 3:S43–S49. doi:10.1016/j.ihj.2018.05.001
7 Heiro M, Helenius H, Sundell J, et al. Utility of serum C-reactive protein in assessing the outcome of infective endocarditis. *Eur Heart J.* 2005;26(18):1873–1881. doi:10.1093/eurheartj/ehi277
8 Heiro M, Helenius H, Hurme S, et al. Short-term and one-year outcome of infective endocarditis in adult patients treated in a Finnish teaching hospital during 1980–2004. *BMC Infect Dis.* 2007;7:78. doi:10.1186/1471-2334-7-78
9 Kousa O, Walters RW, Saleh M, et al. Early vs late cardiac surgery in patients with native valve endocarditis-United States Nationwide Inpatient database. *J Card Surg.* 2020;35(10):2611–2617. doi:10.1111/jocs.14854
10 Liang F, Song B, Liu R, Yang L, Tang H, Li Y. Optimal timing for early surgery in infective endocarditis: a meta-analysis. *Interactive Cardiovasc Thorac Surg.* 2016;22(3):336–345. doi:10.1093/icvts/ivv368
11 Papadimitriou-Olivgeris M, Guery B, Ianculescu N, et al. Risk of embolic events before and after antibiotic treatment initiation among patients with left-side infective endocarditis. *Infection.* 2024;52(1):117–128. doi:10.1007/s15010-023-02066-z
12 Kang DH, Kim YJ, Kim SH, et al. Early Surgery versus Conventional Treatment for Infective Endocarditis. *N Engl J Med.* 2012;366(26):2466–2473. doi:10.1056/NEJMoa1112843
13 García-Granja PE, López J, Vilacosta I, et al. Impact of Valve Culture in the Prognosis of Active Left-sided Infective Endocarditis. *Clin Infect Dis.* 2019;68(6):1017–1023. doi:10.1093/cid/ciy684
14 Halavaara M, Martelius T, Järvinen A, et al. Impact of pre-operative antimicrobial treatment on microbiological findings from endocardial specimens in infective endocarditis. *Eur J Clin Microbiol Infect Dis.* 2019;38(3):497–503. doi:10.1007/s10096-018-03451-5
15 Gisler V, Dürr S, Irincheeva I, et al. Duration of Pre-Operative Antibiotic Treatment and Culture Results in Patients With Infective Endocarditis. *J Am Coll Cardiol.* 2020;76(1):31–40. doi:10.1016/j.jacc.2020.04.075