# In-hospital outcomes and prevalence of comorbidities in patients with infective endocarditis with and without heart blocks: Insight from the National Inpatient Sample

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## ABSTRACT

Infective endocarditis (IE) complicated by heart block can have adverse outcomes and usually requires immediate surgical and cardiac interventions. Data on outcomes and trends in patients with IE with concurrent heart block are lacking. Patients with a primary diagnosis of IE with or without heart block were identified by querying the Healthcare Cost and Utilization Project database, specifically the National Inpatient Sample for the years 2013 and 2014, based on International Classification of Diseases Clinical Modification Ninth Revision codes. During 2013 and 2014, a total of 18,733 patients were admitted with a primary diagnosis of IE, including 867 with concurrent heart blocks. Increased in-hospital mortality (13% vs 10.3%), length of stay (19 vs 14 days), and cost of care ($282,573 vs $223,559) were found for patients with IE complicated by heart block. Additionally, these patients were more likely to develop cardiogenic shock (8.9% vs 3.2%), acute kidney injury (40.1% vs 32.6%), and hematologic complications (19.3% vs 15.2%), and require placement of a pacemaker (30.6% vs 0.9%). IE and concurrent heart block resulted in increased requirement for aortic (25.7% vs 6.1%) and mitral (17.3% vs 4.2%) valvular replacements. Conclusion was made that IE with concurrent heart block worsens in-hospital mortality, length of stay, and cost for patients. Our analysis demonstrates an increase in cardiac procedures, specifically aortic and/or mitral valve replacements, and Implantable Cardiovascular Defibrillator/Cardiac Resynchronization Therapy/ Permanent Pacemaker (ICD/CRT/PPM) placement in IE with concurrent heart block. A close telemonitoring system and prompt interventions may represent a significant mitigation strategy to avoid the adverse outcomes observed in this study.

### Significance of this study

**What is already known about this subject?**
- Infective endocarditis can cause valve abscess.
- Infective endocarditis can result in atrioventricular node blockage.
- Poor outcomes in patients with infective endocarditis include old age, prosthetic valve endocarditis, heart failure, and paravalvular complications.

**What are the new findings?**
- Infective endocarditis with concurrent heart block worsens mortality.
- Infective endocarditis with concurrent heart block increases length and cost of stay.
- Infective endocarditis with concurrent heart block increases the requirement for pacemaker insertion.
- Heart blocks predict worse outcomes in patients with infective endocarditis.

**How might these results change the focus of research or clinical practice?**
- Patients with infective endocarditis and comorbid heart block are at high risk of worse outcomes and immediate surgical intervention should be considered.

## INTRODUCTION

Infective endocarditis (IE) is an infection of a native or prosthetic heart valve, endocardial surface, or indwelling cardiac device.[1 2] It occurs at an incidence of approximately 3–9 cases per 100,000 people per year.[3] In the developing world, rheumatic heart disease is the number one risk factor for the development of IE.[1 2] However, in developed countries, rheumatic heart disease is extremely rare, and risk factors for the development of IE include diabetes, cancer, intravenous drug abuse, degenerative heart valve disease, and congenital heart disease.[2] Although IE is rare, it is among the most common life-threatening infectious syndromes, along with pneumonia, intra-abdominal abscess, and sepsis.[4] In a large prospective cohort study, it was found that the

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**Table 1** Baseline demographics and characteristics

| Characteristics | Infective endocarditis without heart block | Infective endocarditis with heart block | P value |
|---|---|---|---|
| Number of patients | 17,866 | 867 | |
| Age, mean (SD), years | 57.3±19.4 | 58.6±18.6 | 0.054 |
| Female (%) | 39.6 | 31.6 | <0.001 |
| Race (%) | | | |
| White | 72.0 | 70.1 | 0.312 |
| Black | 14.8 | 17.1 | |
| Hispanic | 8.3 | 7.7 | |
| Hypertension (%) | 27.9 | 27.8 | 0.938 |
| Diabetes mellitus (%) | 15.7 | 15.5 | 0.867 |
| Chronic kidney disease (%) | 5.7 | 5.2 | 0.490 |
| Atrial fibrillation (%) | 23.3. | 27.9 | 0.002 |
| Anemia (%) | 18.7 | 17.2 | 0.250 |
| Peripheral arterial disease (%) | 15.6 | 22.4 | <0.001 |
| Teaching hospital (%) | 30.1 | 29.6 | 0.298 |
| Rural location (%) | 37.1 | 37.4 | 0.611 |
| Large hospital bed size (%) | 25.8 | 25.2 | 0.368 |
| Primary payer (%) | | | |
| Medicare/Medicaid | 69.0 | 66.9 | 0.022 |
| Private insurance | 20.7 | 24.3 | |
| 0–25th percentile income (%) | 30.7 | 29.0 | 0.150 |

Statistically significant variables age, gender, atrial fibrillation, peripheral arterial disease, and mode of payment are adjusted in table 2.

most common presenting symptoms include fever, development of a new murmur, or worsening of an old murmur.[5] Less commonly, patients present with symptoms such as vascular embolic events, splenomegaly, Janeway lesions, Osler's nodes, Roth spots, and splinter hemorrhages.[5] Complications of IE include the development of embolism, stroke, intracardiac abscess, congestive heart failure, and new conduction abnormalities.[5] Despite advances in care, the mortality rates of IE have remained stable over the past 20 years, with rates approaching 30% at 1 year after diagnosis.[6]

The high morbidity and mortality associated with IE warrants further investigation into the patterns, clinical course, and outcomes associated with the development of this infectious process. Heart block is a complication of IE that suggests the potential need for early surgical management.[4] According to one study, complete heart block may occur in as many as 14% of cases of IE.[7] Current data are limited regarding trends and outcomes in patients with IE developing heart block as a complication. Using data from the National Inpatient Sample (NIS) databases, we performed a cross-sectional analysis to evaluate several outcomes associated with the development of heart block along with IE. Through this study, we hope to provide further information regarding the impact of developing heart block along with IE and to determine whether this can be used as a predictor of clinical course and outcome in these patients.

## METHODS

### Data source

The NIS has been elaborated in detail in prior studies.[8] The NIS is the largest publicly available database in the USA, which falls under the Healthcare Cost and Utilization Project and is maintained by the Agency for Health Care Research and Quality. It is one of the most useful databases for studying outcomes and trends of various procedures and diseases. It comprised deidentified data collected from 20% of community hospitals in 46 states in the USA. Each hospitalization is representative of one primary diagnosis, up to 29 secondary diagnoses and 15 procedures using the International Classification of Diseases Clinical Modification codes (ICD9 and ICD10). The data include admission status, demographics, admitting diagnosis, comorbidities, healthcare facility status (rural vs urban), discharge diagnosis, outcomes, length of stay and cost during hospitalization. We examined all adult patients who were hospitalized during the years 2013 and 2014 with a diagnosis of IE with and without comorbid heart block using the NIS. Patients were filtered using ICD9 codes. ICD9 codes for IE were validated based on previous studies, and the codes included were 4210, 4211, 4212, 4219, 03642, 09884, 11281 and 1154.[9] ICD9 codes used to identify first-degree, second-degree and third-degree heart blocks were 426.11, 426.12, 426.13 and 426.0. We excluded any hospitalizations with missing demographics, that is, age, gender, admission or discharge diagnosis, and mortality data. We used NIS variables to identify patients' age, gender, race, county location, income, and hospital bed size. Race was divided into three categories: African-American, white and Hispanic. Baseline comorbidities taken into consideration were hypertension, diabetes mellitus, chronic kidney disease, atrial fibrillation, anemia, and peripheral arterial disease using the ICD9 codes. ICD codes for the outcomes are included in the online supplemental file.

### Primary and secondary outcomes

Our objective was to assess the primary and secondary outcomes of patients with a principal diagnosis of IE with and without heart block. The primary outcomes to be analyzed were mortality, length of stay, and cost for all hospitalizations due to IE with and without comorbid heart blocks. The secondary outcomes to be assessed were stroke, acute kidney injury (with and without new hemodialysis), aortic and mitral valve replacement, cardiac arrest, cardiogenic shock, pacemaker implantation, hematologic (thrombocytopenia/coagulopathy) and hepatic (hepatic necrosis/hepatic encephalopathy/hepatitis) complications, cardiac tamponade, sepsis, acquired pneumonia, tracheostomy, and gastrostomy. The ICD9 codes for these outcomes are included in the online supplemental file.

### Statistical analysis

We used survey analyses to stratify and cluster encounters for all continuous and categorical variables. SPSS V27 software was used to perform statistical analyses. We used $\chi^2$ test or analyses of variance to identify differences in categorical variables and two-sample t-test for analysis of continuous variables. Logistic regression model was used to calculate the OR for the outcomes between the two study groups. This was followed by multivariate analyses to account for any confounders between the groups in the form of comorbidities mentioned in table 1 (ie, atrial fibrillation and peripheral arterial disease). P value of <0.05 was considered statistically significant. We audited the analyses

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**Table 2** Clinical outcomes of IE with and without heart block, with adjusted OR

| In-hospital outcomes | IE without heart block | IE with heart block | *a*-OR |
|---|---|---|---|
| In-hospital death (%) | 10.3 | 13.0 | 1.02 (1.01–1.02) |
| Stroke (%) | 13.7 | 17.2 | 1.32 (1.10–1.59) |
| Acute kidney injury (%) | 32.6 | 40.1 | 1.36 (1.18–1.57) |
| Aortic valve replacement (%) | 6.1 | 25.7 | 5.09 (4.30–6.02) |
| Mitral valve replacement (%) | 4.2 | 17.3 | 4.70 (3.87–5.70) |
| New dialysis (%) | 14.8 | 16.6 | 1.15 (0.96–1.39) |
| Pacemaker implantation (%) | 0.9 | 30.6 | 48.55 (39.14–60.24) |
| Cardiogenic shock (%) | 3.2 | 8.9 | 2.81 (2.19–3.60) |
| Cardiac arrest (%) | 2.2 | 7.4 | 3.48 (2.64–4.57) |
| Hematologic complications (%) | 15.2 | 19.3 | 1.33 (1.12–1.59) |
| Hepatic complications (%) | 3.95 | 5.2 | 1.40 (1.03–1.91) |
| Metabolic acidosis (%) | 11.7 | 15.6 | 1.41 (1.16–1.70) |
| Vascular complications (%) | 2.1 | 4.7 | 2.26 (1.62–3.15) |
| Unplanned vascular surgery (%) | 1.3 | 4.4 | 3.54 (2.49–5.03) |
| Cardiac tamponade (%) | 0.5 | 1.2 | 2.20 (1.14–4.25) |
| Acquired pneumonia (%) | 14.4 | 13.5 | 0.95 (0.78–1.16) |
| Sepsis (%) | 44.6 | 40.0 | 0.85 (0.74–0.98) |
| Tracheostomy (%) | 2.3 | 3.1 | 1.46 (0.98–2.17) |
| Gastrostomy (%) | 2.1 | 1.6 | 0.78 (0.45–1.33) |
| Length of stay | 13.8±15.4 | 18.9±16.8 | 2.23 (1.95–2.56)* |
| Mean cost | $146,769±$223,559 | $274,481±$282,573 | 3.52 (3.05–4.05)† |

Adjusted for age, gender, payor, atrial fibrillation, and peripheral artery disease.
*Predicting length of stay greater than 2 weeks.
†Predicting cost greater than $150,000.
*a*-OR, adjusted OR; IE, infective endocarditis.

using the checklist provided by NIS to assess and ensure data analyses are as per rules recommended by the NIS (https://www.hcupus.ahrq.gov/db/nation/nis/nischecklist.jsp).

## RESULTS

We identified a total of 14,191,325 hospitalizations during the years 2013 and 2014. Further, we identified 18,733 inpatient hospitalizations for IE. Out of these, 867 had concurrent heart block. Our final sample had two study groups: IE without heart block (n=17,866) and IE with heart block (n=867). Table 1 shows the background characteristics by study group. We found that patients with IE and heart block were older, with a mean age of 58.6±18.6 (p=0.054). Patients with IE without heart block were more likely to be female compared with those with IE with heart block (39.6% vs 31.6%, p<0.001). The prevalence of atrial fibrillation (27.9% vs 23.3%, p=0.002) and peripheral arterial disease (22.4% vs 15.6%, p<0.001) was significantly higher in patients with IE and heart blocks.

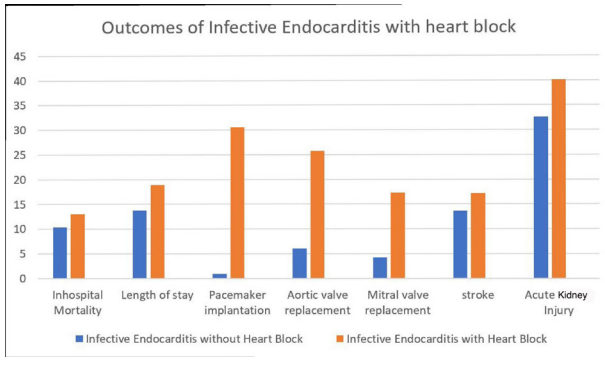


**Figure 1** Outcomes of infective endocarditis with heart block (y-axis denotes percentage; p<0.05).

Table 2 summarizes the results of logistic regression analyses used to calculate adjusted OR (*a*-OR) to control for variables in table 1. IE with heart block had higher mortality (*a*-OR 1.02 (1.01–1.02)), increased length of stay (*a*-OR 2.23 (1.95–2.56)) and higher cost of stay (*a*-OR 3.52 (3.05–4.05)). Patients with IE with heart block had higher odds of stroke (*a*-OR=1.32 (1.10–1.59)), acute kidney injury (*a*-OR 1.36 (1.18–1.57)), aortic valve replacement (*a*-OR 5.09 (4.30–6.02)), mitral valve replacement (*a*-OR 4.70 (3.87–5.70)), pacemaker implantation (*a*-OR 48.55 (39.14–60.24)), cardiogenic shock (*a*-OR 2.81 (2.19–3.60)), cardiac arrest (*a*-OR 3.48 (2.64–4.57)), hematologic complications (*a*-OR=1.33 (1.12–1.59)), hepatic complications (*a*-OR 1.40 (1.03–1.91)), vascular complications (*a*-OR 2.26 (1.62–3.15)) and cardiac tamponade (*a*-OR 2.20 (1.14—4.25)). After controlling for confounding variables in table 1 with statistically significant difference, that is, gender, atrial fibrillation, peripheral arterial disease and primary payer, the severity of outcomes was significantly higher in IE with heart block for all variables except for acute kidney injury leading to hemodialysis (*a*-OR 1.15 (0.96–1.39)), acquired pneumonia (*a*-OR 0.95 (0.74–0.98)), and sepsis (*a*-OR 0.85 (0.74–0.98)). The percentages of outcomes between the two groups are shown in figures 1 and 2.

## DISCUSSION

The primary and secondary outcomes were assessed after adjusting for variables that were statistically significant in table 1, that is, age, gender, atrial fibrillation, peripheral arterial disease, and mode of payment. We



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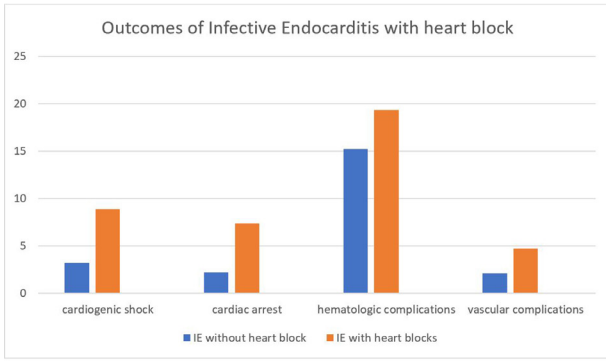


**Figure 2** Outcome of infective endocarditis (IE) with heart block

identified a significant increase in in-hospital mortality when IE is complicated by the development of heart block (*a*-OR=1.02). This could be explained by the pathophysiology of heart block in IE. The development of heart block usually signifies that the infection has spread beyond the valve annulus and into the local tissue.[4] Because of the proximity of the aortic and mitral valves to the conduction system and atrioventricular (AV) node, extension of infection beyond the valve annulus and development of myocardial abscess may impinge on these critical structures, leading to the development of heart block and arrhythmias.[10] This contiguous spread of infection could signify more advanced disease, therefore explaining the increased mortality seen in these patients. We also found that patients with heart block had statistically significant increases in stroke (*a*-OR=1.32), acute kidney injury (*a*-OR=1.36), and vascular complications (*a*-OR=2.26). This could also explain the increased mortality seen in these patients, as patients with heart block are more likely to have multiple organ complications, as demonstrated here. Acute kidney injury could be due to potentially low cardiac output states in heart block leading to low renal perfusion and kidney dysfunction. Further, septic embolization, which is closely correlated to the size of the vegetation and the degree of vegetation spread beyond the annulus, is larger in size and can embolize easily to the kidneys as well as the brain.[4] Lastly, vascular complications may be related to embolization as well. An interesting finding is that the incidence of sepsis was less common in patients suffering from IE with heart block (*a*-OR=0.85). This is unusual, as the data are suggesting that patients with complications secondary to an infectious process are less frequently developing sepsis than in patients without this same complication. One hypothesis for this finding could be that due to the increased incidence of multiple severe comorbid conditions in patients with IE and heart block (eg, valve replacement, pacemaker placement, stroke, cardiogenic shock, cardiac arrest), it is possible that the presence of sepsis is being overlooked and thus coded less frequently. Further research may be necessary to expand on this finding.

Patients with IE and heart block were more likely to require replacement of both the aortic and mitral valves, with *a*-OR of 5.09 and 4.70, respectively. This is likely due to the fact that in order for heart block to develop, the infection must spread beyond the valve annulus via damage to the affected valve.[4] Adhesion of bacterium to the heart valve leads to damage to the endothelium and the subsequent development of an infected thrombus.[1] This leads to an inflammatory response and the release of cytokines, integrins, and tissue factor, thus further propagating valve leaflet distortion and destruction.[1] The destruction may be due to the development of abscess, fistula, valve tears or holes, and prosthetic valve detachment, all of which require surgical reconstruction of the valve.[11] When considering that aortic valve replacement was more common than mitral valve replacement, it is worth noting that the aortic valve is more commonly involved in IE than the mitral valve.[12 13] In addition, the proximity of the aortic valve to the left and right bundle branches means that extension of infection through the aortic valve has a greater likelihood of development of high-grade heart block compared with mitral valve involvement.[13] Lastly, studies have shown that early surgical intervention is associated with reduced mortality and reduced risk of embolic events compared with medical management in patients with endocarditis.[14 15] One multicenter cohort study has demonstrated that surgery conveyed a significant benefit in mortality in patients with *Staphylococcus aureus* endocarditis, the most common bacterium indicated in IE today.[15] Because of this proven benefit, nearly 50% of patients with IE are now undergoing surgical intervention.[4] According the American Heart Association, heart block is an indication for early surgical intervention in cases of IE, thus explaining the increase in valvular replacement in patients with more severe complications such as heart block.[4] It is also worth noting that patients with heart block likely require operations of greater magnitude. For example, surgical management of patients with heart block secondary to periannular extension often involves drainage of abscess cavities, excising necrotic tissue, and closure of any fistula tracts that may have developed secondary to bacterial infection.[16] Reitz *et al*[17] attempted to treat patients with aortic annular abscess via translocation of the aortic valve, closure of the coronary ostia, and saphenous venous bypass grafting to the coronary vessels. VanHooser *et al*[18] found success in treating the same complication in a small cohort of patients (n=3) through the use of composite prosthetic valve-woven Dacron tube graft reconstruction of the aortic root. Lastly, Navia *et al*[19] described the need for reconstruction of the intervalvular fibrosa with double-valve replacement for patients with invasive double-valve IE, a very challenging operation that may provide the only chance for cure in patients with significantly advanced IE. In their study, it was found that patients undergoing reconstruction of the intervalvular fibrosa along with double-valve replacement had postoperative in-hospital death rates as high as 20%, often due to postoperative sepsis-related multiorgan failure.[19] The greater magnitude of the procedures necessary to treat patients with the development of periannular extension and heart block is likely also a contributing factor to poorer prognosis in these patients.

An additional finding that warrants discussion is the increased need for pacemaker implantation in patients with IE complicated by heart block (*a*-OR=48.55). In order to better understand this phenomenon, it is important to recognize that the cardiac conduction system is located within the right atrium as well as the membranous septum. The left bundle branch is often located within the base of the membranous septum, or along the left side of the

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interventricular septum in most cases.[7] The non-coronary sinus of Valsalva is in close proximity to the superior interventricular septum which contains the bundle of His.[7] Finally, the mitral valve is within close proximity to the AV node.[10] Extension of the infectious process into the surrounding tissues in the form of an abscess may lead to interruption of the conduction system due to direct impingement or inflammation.[20] One study by DiNubile *et al*[20] demonstrated that of 211 patients with IE, 20 developed unstable conduction abnormalities. Those with unstable conduction abnormalities were more likely to have aortic valve involvement, consistent with the anatomical proximity of the aortic valve to the conduction system.[21] Patients with AV conduction abnormalities are at risk for the development of serious symptoms related to bradycardia or ventricular arrhythmias, which may also explain the increase in risk of cardiogenic shock and cardiac arrest seen in our study. According to the American College of Cardiology, implantation of a permanent pacemaker should be performed in adults with symptomatic third-degree AV block, type 2 second-degree AV block, and even some cases of type 1 second-degree AV block and first-degree AV block to prevent these complications from occurring.[21]

In the current study, it was found that women were less likely than men to develop heart block as a complication of IE. This is consistent with data seen in previous studies. DiNubile *et al*[20] found that patients with IE and unstable conduction abnormalities were more likely to be male (p=0.04). Furthermore, Wang *et al*[22] found when examining the records of 142 patients with bacterial endocarditis that 6 developed complete heart block. Of those six developing complete heart block, five were men.[22] There are several reasons as to why women are less likely to develop heart block. First, it has been hypothesized that higher levels of estrogen in women may play a protective role against endothelial damage and inflammation.[23] Second, studies have shown that women are less likely than men to have aortic valve involvement, which as discussed previously is known to be associated with higher risk of developing heart block. Sambola *et al*[24] studied the differences between men and women with IE and found that 46% of men with IE had aortic valve involvement compared with only 31% of women. Further, 52% of women had mitral valve involvement compared with 36% of men.[24] Castillo *et al*[25] demonstrated similar findings, with mitral valve involvement being seen in 54% of women compared with 39% of men, and aortic valve involvement more common in men than in women (50% vs 29%). It is likely that the differences in valvular involvement between sexes play a significant role in the development of heart block in these patients. Additional findings that were not of statistical significance but may be of clinical significance are the increased incidence of IE and comorbid heart block in African-American patients (17.1% vs 14.8%) and in rural hospitals (37.4% vs 37.1%). The incidence was slightly lower in patients with hypertension (27.8% vs 27.9%), diabetes mellitus (15.5% vs 15.7%), and chronic kidney disease (5.2% vs 5.7%).

Finally, patients with IE complicated by heart block were more likely to have increased length of stay as well as increased mean cost compared with patients without heart block. This is likely due to an increased need for surgical intervention, valvular replacement, and pacemaker implantation in patients with heart block. The need for these interventions will prolong hospitalization and increased cost for patients due to the cost of the procedures as well as additional costs accrued during the prolonged inpatient course. Moreover, patients with heart block were more likely to develop complications such as stroke, acute kidney injury, hematologic complications, hepatic complications, vascular complication and metabolic acidosis. This increased likelihood of multiorgan involvement likely plays a significant role in increased length and cost of hospitalization.

### Limitations

There are limitations to utilization of the Healthcare Utilization Project database, including errors in relation to the ICD9 and ICD10 coding system. In order to prevent this, we have used codes that have been validated in previous studies. We have performed a retrospective analysis and give insight into an association between the two conditions rather than proving causation between these conditions and the studied outcomes. An additional limitation is that the ICD coding system is unable to identify when patients are readmitted with the same condition. Because of this, every admission is considered a separate case and therefore a new patient encounter. A final limitation of the paper is that the model used for data analysis was performed using statistically significant variables as confounders, as opposed to a full comorbidity adjustment.

## CONCLUSION

The development of heart block in patients with IE worsens in-hospital mortality, length of hospitalization and cost of stay. Patients with IE and heart block are more likely to require surgical interventions, including valvular replacement and pacemaker implantation. In addition, these patients are more likely to develop multiple organ dysfunction, which likely contributes to the increased mortality as well as length/cost of hospitalization. Patients with IE should be closely monitored with telemetry in order to recognize the development of heart block. Doing so may lead to more prompt recognition of the conduction abnormality as well as earlier intervention to avoid the adverse outcomes observed in our study.

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