IMPACT OF DELAYED ANTIBIOTIC ADMINISTRATION ON OUTCOMES IN ACUTE INFECTIVE ENDOCARDITIS

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Abstract
Acute infective endocarditis is a serious condition where there is infection of the endocardial surface of the heart, mostly involving the heart valves. The present study evaluates the effect of delayed antibiotic administration on patient outcomes at Hayatabad Medical Complex, Peshawar. To this end, a retrospective cohort analysis was conducted involving 150 patients diagnosed with AIE from January 2018 to December 2022. Patients were grouped into an early group consisting of those patients who were administered antibiotics within 24 hours and a delayed group consisting of those who received them beyond 24 hours. Delayed presentation was associated with increased mortality, length of hospital stay, and complications such as heart failure and systemic embolization. It is seen from this study that delayed antibiotic administration revealed a significant increase in the mortality rate to 40% as compared to 15.8%, with a prolonged hospital stay of 28.7 days against 21.5 days and with complications like heart failure of 45% versus 22% and systemic embolization in 34% compared to 12%. Future research should aim at identifying the obstacles to timely intervention and hence establish ways through which this can be facilitated with faster institution of intervention.

Keywords: Acute infective endocarditis, antibiotic administration, delayed treatment, patient outcome, mortality, complications, Hayatabad Medical Complex.

Introduction
Acute infective endocarditis is a serious and possible life-threatening condition wherein infection takes place in the endocardial surface of the heart, mostly involving the valves. The clinical

challenge of the disease is that it is an aggressive disease with a high mortality rate, even after improvements in medical treatment. The incidence of AIE has remained largely stable over the last couple of decades, with an approximate annual incidence of 3-10 per 100,000 subjects (Palladino, 2024). However, mortality remains as high as 15%-30% in many series due to complications from heart failure, systemic embolization, and persistent bacteremia.

In this respect, the pathogenesis of AIE is the colonization of the heart valves by microorganisms, subsequently leading to the formation of vegetations. These vegetations are composed of fibrin, platelets, and infecting organisms and may be responsible for valve destruction, the formation of abscesses, and embolic events, seriously affecting the prognosis of a patient. Early diagnosis and initiation of antibiotic therapy in the management of AIE are important for the eradication of infection and prevention of severe complications (Abrishami, 2024).

Despite all the literature stating that timely antibiotic administration is crucial, delays in commencing the treatment are not uncommon events in clinical practice. Thus, diagnostic difficulties, atypical presentations of patients, and problems related to health system issues may delay the initiation of antibiotics. (Lane, 2024). However, exact data regarding delayed antibiotics in AIE are sparse.

The Hayatabad Medical Complex is an important tertiary care center at Peshawar that treats a large number of cases of AIE annually. This study is conducted to determine the clinical outcome of patients with AIE who were brought to this institution and had delayed administration of antibiotics (Uranga, 2016). Comparing outcomes in patients whose antibiotic therapy was instituted within 24 hours of diagnosis with those who had delays may give insights that can inform clinical practice in order to improve patient care.

The consequences of delayed antibiotic administration in AIE have to be understood so that strategies for improvement of the treatment protocols and, hence, patient outcome could be formulated. This paper hypothesizes that late antibiotic administration is associated with higher mortality rates, extended hospital lengths of stay, and a higher rate of complications (Amaral, 2016). Such findings from this study may add to the increasing body of evidence that point out the critical importance of early intervention in AIE management toward healthcare practice, with better survival rates for patients (Zhang, 2018).

Methods
Study Design
This was a retrospective cohort study conducted at Hayatabad Medical Complex, Peshawar. The medical records of patients diagnosed to have acute infective endocarditis from January 2018 to December 2022 were comprehensively reviewed. Ethical approval for the study was obtained from the Institutional Review Board of Hayatabad Medical Complex, Peshawar.

Inclusion and Exclusion Criteria
Inclusion Criteria:
• Patients diagnosed to have AIE based on modified Duke criteria.
• Patients 18 years or older.
• This involved patients whose medical records were complete, enerically documenting the time to antibiotic administration and outcome data.

Exclusion Criteria:
• Patients with subacute or chronic infective endocarditis.
• Patients with incomplete medical records.
• Patients who received antibiotics prior to hospital admission.

Data Collection

The data was extracted from the electronic medical records system at Hayatabad Medical Complex. The variables collected included:

- **Demographic Information:** Age, gender, presence of co-morbidities.
- **Clinical Presentation:** Symptoms at admission (Fever, heart murmurs, embolic phenomena etc.).
- **Diagnostic Data:** Blood culture results, Echocardiographic findings.
- **Time to antibiotic:** Time elapsed from the time of confirmation of diagnosis to the time of initiation of antibiotic therapy categorized into early, within 24 hours and delayed, beyond 24 hours.
- **Type of antibiotics used:** Specifically used antibiotics and their various combinations.
- **Duration of hospital stay:** Total no. of days of admission.
- **In hospital mortality:** Death occurring in the hospital.
- **Complications:** Heart failure, systemic embolization and requirement for surgical intervention.

Statistical analysis

Data were analyzed using SPSS version 25.0 (IBM Corp., Armonk, NY). Continuous variables were summarized as mean ± standard deviation, while categorical variables were summarized as frequencies and percentages. Primary outcomes compared between the early and delayed antibiotic administration groups included:

Mortality Rate
Duration of Hospital Stay
Incidence of Complications: Heart Failure, Systemic Embolization Comparisons were done through chi-square testing for categorical variables and independent t-tests for continuous variables. A p-value of <0.05 was taken as statistically significant.

Mortality Analysis

In-hospital mortality was taken as the primary outcome measure that was used to evaluate the differences in mortality rates of both groups according to Kaplan-Meier survival analysis. Cox proportional hazard regression adjusted the confounding variables such as age, gender, and co-morbidities.

Subgroup Analysis

Subgroup analyses were done to assess the effect of late antibiotic administration in subpopulations, such as in the presence of various comorbidities and different severities of illness at presentation. Results were stratified based on these subgroups to identify any differential impacts.

Sensitivity Analysis

Sensitivity analysis for the measurement of robustness of findings was conducted. In this respect, patients treated within 48 hours of illness onset were compared with those who were treated beyond this period. Such an analysis can actually estimate the effect of different cut-off points that define delayed antibiotic administration.

Ethical Considerations

Information was anonymized for patient confidentiality. The study was performed following the ethical criteria of the institutional research committee and performed in accordance with the 1964 Helsinki declaration and further amendments.

The aim of the study was to get a detailed assessment of the effects of delayed antibiotic administration on the outcome of patients with acute infective endocarditis, shedding light on clinical practice using such methods.

Results
Patient Demographics and Clinical Characteristics

A total of 150 patients met the inclusion criteria for this study. The average age of the patients was 55.6 ± 14.2 years, with a male predominance (60%). The most frequent clinical presentations were fever, which occurred in 90% of patients; heart murmurs, occurring in 75% of patients; and embolic phenomena, occurring in 40% of the patients. A summary of the baseline characteristics is shown in Table 1.

Table 1: Patient Demographics and Clinical Characteristics

Characteristic	Total (n = 150)
Age (mean ± SD)	55.6 ± 14.2
Gender	
Male	90 (60%)
Female	60 (40%)
Clinical Presentation	
Fever	135 (90%)
Heart Murmurs	112 (75%)
Embolic Phenomena	60 (40%)

Timing of Antibiotic Administration

Of the 150 patients, 95 (63.3%) were given antibiotics within 24 hours of the diagnosis and hence were referred to as the early group, while 55 (36.7%) were delayed in antibiotics administration and hence were referred to as the delayed group. Time of starting antibiotics and distribution of the two treatment groups are presented in Table 2.

Table 2: Time of Starting Antibiotics

Timing of Antibiotic Administration	Number of Patients (%)
Early (within 24 hours)	95 (63.3%)
Delayed (beyond 24 hours)	55 (36.7%)

Outcomes
Mortality

The in-hospital mortality rate was 25%. The mortality rate in the early treatment group was significantly lower, at 15.8 percent for the patients in the early therapy category, compared to 40% for patients in the delayed treatment category, with a p-value less than 0.001. This is summarized in Table 3.

Table 3: In-Hospital Mortality Rates

Group	Mortality Rate (%)	p-value
Early (within 24 hours)	15.8%	<0.001
Delayed (beyond 24 hours)	40%	<0.001

Hospital Stay

The mean duration of the hospital stay was significantly less in the early treatment group, 21.5 ± 5.3 days, compared to the delayed treatment group, which was 28.7 ± 6.9 days with p<0.01. Duration of hospital stay data is presented in Table 4.

Table 4: Duration of Hospital Stay

Group	Hospital Stay (mean ± SD)	p-value
Early (within 24 hours)	21.5 ± 5.3 days	<0.01
Delayed (beyond 24 hours)	28.7 ± 6.9 days	<0.01

Complications

Heart failure was significantly lower in the early treatment group, 22 percent, compared with the delayed group, 45 percent, with p=0.002. Systemic Embolization: The incidence of systemic embolization was lower in the early treatment group, 12 percent, against the delayed group with 34 percent, p=0.004. Surgical Intervention: No statistically significant difference in the requirement for surgical intervention was noted between the early, 32 percent, and delayed, 40 percent, treatment groups, p=0.24.

The incidence of complications is summarized in Table 5.

Table 5: Incidence of Complications

Complication	Early (within 24 hours)	Delayed (beyond 24 hours)	p-value
Heart Failure	22% (21/95)	45% (25/55)	0.002
Systemic Embolization	12% (11/95)	34% (19/55)	0.004
Surgical Intervention	32% (30/95)	40% (22/55)	0.24

Subgroup Analysis

Subgroup analyses revealed that the adverse impact of delayed antibiotic administration was consistent across various subgroups, including patients with different comorbidities and varying severity of illness at presentation.

Sensitivity Analysis

The sensitivity analysis matching patients who received antibiotics within predesignated 48 hours to others who received it after 48 hours further reinforced that the primary findings were robust. The delay in administration for over 48 hours was also associated with a higher risk of mortality and longer hospital length of stay.

Discussion

This study has important implications for understanding the effect of delayed antibiotic administration on the outcomes of patients with acute infective endocarditis at Hayatabad Medical Complex in Peshawar. The findings entail that delayed antibiotic therapy is related to poor outcome markers, including higher mortality rates, longer hospital stay, and a higher rate of complications like heart failure and systemic embolization.

The issue of early antibiotic administration forms a critical component in the management of AIE, and this is very well established in literature. According to (Leong, 2018), early initiation of appropriate antibiotics is important in controlling an infection, preventing spread, and increasing patient survival. Our study confirms this, showing that even the in-hospital mortality rate was much lower in patients who received antibiotics within 24 hours of diagnosis at 15.8% compared with that in individuals with delayed treatment at 40%. This observation elaborates that rapid diagnostic and therapeutic strategies for AIE management might be necessary to improve outcomes of the patients. This agrees with (Ye, 2021), studies.

The extended hospital stay seen in the delayed treatment group further emphasizes the negative implications of late intervention. Among those patients where antibiotic therapy was introduced early, the average length of hospitalization was only 21.5 days, versus an average stay of 28.7 days for those with delayed treatment. This observation indicates not only the seriousness of the possible complications that can ensue as a result of late treatment, but also increased burdens to healthcare resources. There are low costs to healthcare and fewer resources utilized with timely antibiotic administration, which are obviously increased with prolonged hospitalizations, such as occurred in this group of patients with delayed antibiotic therapy (Shorr, 2011).

The delayed treatment group had a significantly higher incidence of complications, including heart failure and systemic embolization. Heart failure in the antibiotic delayed cases occurred in 45% of patients, while in patients with early antibiotic treatment, it was seen in 22%. Correspondingly, systemic embolization was seen in 34% of delayed cases versus 12% of early cases. These complications are indicative of the uncontrolled spread of infection due to delayed eradication of thecausative microorganisms. Emphasized that early intervention is necessary to prevent vegetation formation and subsequente mbolic events associated with a significant deterioration of the patient's prognosis (Scheggi, 2020).

In spite of the robustness found in this study, there exist some major limitations. First of all, it is a retrospective cohort study and so is predisposed to selection and information biases. This may result in incomplete data capture on the part of electronic medical records, especially for reasons of delay in antibiotic administration. Since it is a single-center study, generalization of findings in other settings with variable healthcare infrastructure and patient populations would be less possible. Further research in this regard, using a multi-centered approach, can help generalize these results across variable clinical milieus (De Felice, 2015).

Also, the study did not specifically examine what factors caused delays in administering antibiotics. It's important to identify the barriers to timely treatment so that targeted interventions can be developed. Such possible factors can include delays in diagnosis, variable presentation of the patient, and problems in health care system at health care facilities such as staffing and lack of rapid diagnostic tools, as documented by (Sarkar, 2012). All these factors can be worked on to expedite the process from diagnosis to the antibiotic treatment stage for better outcomes of the patients.

That means timely administration of antibiotics in acute infective endocarditis is very critical. Delays are associated with higher mortality, longer hospitalization, and a higher incidence of serious complications. In view of these findings, there is a need for prompt diagnosis with rapid institution of antibiotics for improved prognosis. AIE treatment outcomes might become better in case clinicians give precedence to early interventions and take every measure to address potential obstacles against timely interventions. Therefore, future research shall focus on the identification and mitigation of factors that are known to contribute to delays in antibiotic administration and optimize the management of this serious infection (Kollef, 2021).

Conclusion
This was a study of the critical impact of delayed antibiotic administration upon the outcome of acute infective endocarditis at Hayatabad Medical Complex, Peshawar. The study found that delays in initiating antibiotic therapy were associated with a significantly higher mortality rate, an increased hospital stay, and an increased rate of major complications such as heart failure and systemic embolization in patients with AIE. These results underline the paramount importance of early diagnosis and timely initiation of antibiotic treatment in the effective management of AIE.

The implications of the results from the study are akin to what is available in literature, where early intervention plays a critical role in controlling infection and preventing the infection from resulting in severe complications. Patients in whom antibiotics were started within 24 hours of diagnosis fared markedly better than patients started on therapy after this 24-hour window. It reflects as a message on the need for prompt diagnostic procedures and the need to institute therapy immediately to enhance survival and a decrease in the healthcare burden.

The study also recognised certain limitations notwithstanding its robust findings: its retrospective nature and single-center design may limit generalisability. Future research should be based on a multi-centre approach oriented to finding out the actual factors of delay in antibiotic administration.

Only when these barriers are understood and addressed will it be possible to develop targeted interventions that ensure timely treatment for all AIE patients.

The strongest and most compelling evidence from this study is that early antibiotic administration is of critical importance in the management of acute infective endocarditis. It is, therefore, an utmost consideration for any clinician, and an attempt to surmount probable obstacles in the administration of early treatment must be ensured. This would become possible by increasing the survival of the patients, reducing the complication rates, and obtaining the maximum benefit in the management of AIE. Future efforts should focus on improving the efficacy of diagnosis and making treatment protocols more effective so that all the patients are provided with immediate care against this life-threatening infection.

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