An-Najah National University
Faculty of Graduate Studies

APPROPRIATENESS OF TIMING OF INITIAL ANTIBIOTIC PRESCRIPTION AND ITS IMPACT ON SEPSIS PATIENT OUTCOMES IN THE ICU AT NABLUS GOVERMENTAL HOSPITALS: A RETROSPECTIVE STUDY

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Dedication

To my father, my first source of strength and inspiration, whose sacrifices and faith in me shaped who I am.

To my mother, the heart of my journey, whose endless love, prayers, and patience carried me through every step.

To my sisters, for their warmth, encouragement, and constant belief in me.

To my brothers, for their support, protection, and motivation.
This work is dedicated to my family—my greatest blessing and strength.

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Finally, I am deeply grateful to my family for their unwavering support, patience, and encouragement throughout my academic journey.

Declaration

I, the undersigned, declare that I submitted the thesis entitled:

APPROPRIATENESS OF TIMING OF INITIAL ANTIBIOTIC PRESCRIPTION AND ITS IMPACT ON SEPSIS PATIENT OUTCOMES IN THE ICU AT NABLUS GOVERMENTAL HOSPITALS: A RETROSPECTIVE STUDY

I declare that the work provided in this thesis, unless otherwise referenced, is the researcher's own work, and has not been submitted elsewhere for any other degree or qualification.

Student's Name **Sarah Mofeed Ghaleb Aqqad**

Signature:

Date: **17/02/2026**

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Abstract

Background: Sepsis is leading cause of mortality in intensive care units (ICUs), especially in low- and middle-income countries (LMICs). Administration of appropriate antibiotics promptly is a cornerstone of sepsis management; neverthless evidence regarding optimal timing is inconsistent, and most available data come from high-resource healthcare settings. This research evaluated the association between initial antibiotic timing and in-hospital mortality among ICU patients with sepsis in Nablus, Palestine. Additional objectives included describing patient characteristics, comorbidity patterns, sources of infection, reasons for delayed antibiotic initiation, and determining factors linked to mortality; these analyses were further categorized by the severity of sepsis.

Methods: This retrospective study examined adult patients (≥18 years) with sepsis/septic shock from January 2023 to June 2025 admitted to the Internal Medicine ICU at Al-Watani Hospital Nablus, Palestine. Information regarding demographics, comorbid conditions, sepsis intensity, source of infection, timing of antibiotics, and outcomes during hospitalization was gathered from electronic medical records. Door-to-antibiotic time was classified as ≤1 hour, 1–3 hours, or >3 hours from the identification of sepsis. The primary outcome of this study was the occurrence of in-hospital mortality. An independent predictor of mortality included risk factors identified by multiple variable logistic regression analyses.

Results: In a study of 297 ICU patients, antibiotics were started within ≤1 hour of sepsis identification for 44.8%, between 1–3 hours for 35.7%, and after >3 hours for 19.5%. Timely antibiotic treatment, administered either within 1 hour (adjusted odds ratio [aOR]

= 1.45; 95% CI: 0.81–2.62) or within 3 hours (aOR = 0.78; 95% CI: 0.38–1.57), was not independently linked to mortality. In contrast, septic shock and a greater burden of comorbidities were independent predictors of mortality. Subgroup analyses consistently showed greater mortality in septic shock patients across all timing categories.

Conclusions: In this ICU cohort with limited resources, the timing of early antibiotic treatment had no independent effect on mortality. The main factors influence outcomes were patient severity and the burden of comorbidities, highlighting the importance of tailored sepsis management and enhanced antimicrobial stewardship in Palestinian ICUs.

Keywords: Sepsis; Septic Shock; Antibiotic Timing; Mortality; Retrospective; ICU; Palestine

Chapter One

Introduction and Literature Review

Over the past years global health has advanced markedly, with declines in mortality from communicable diseases and raise access to healthcare services in low- and middle-income countries (LMICs) (1). Even with these advancements, infectious diseases continue to be a major cause of illness and death globally. In hospital environments, particularly in intensive care units (ICUs), healthcare-associated infections such as sepsis, ventilator-associated pneumonia, and bloodstream infections continue to be significant causes of mortality, even with improvements in diagnostic methods and treatment approaches (2,3).

Among these conditions, sepsis remains one of the most serious and life-threatening outcomes of infection, characterized by organ dysfunction due to an unbalanced host response (4). If not quickly identified and treated, sepsis can result in septic shock, multiple organ failure, and mortality. Despite the numerous supportive care options and antibiotic treatments available today, sepsis still poses a major challenge to health systems globally and hinders the achievement of international health objectives (5). The WHO estimates that around 48.9 million people experience sepsis worldwide annually, with nearly 11 million deaths attributed to sepsis each year globally, primarily in LMICs (6).

The impact of sepsis not only on clinical outcomes. In the United States, it leads to more than 970,000 hospital admissions each year and represents over 50% of all hospital fatalities, resulting in approximately USD 24 billion in healthcare costs (6,7). In environments with scarce resources, these costs increase the burden on already overloaded health systems, underscoring the need for effective, evidence-based solutions.

Prompt and appropriate use of antibiotics continues to be a fundamental aspect of sepsis treatment and one of the key adjustable factors affecting survival. Significant evidence shows that postponements in initiating antimicrobial therapy are strongly associated with elevated mortality rates, longer ICU stays, and greater healthcare costs (8,9). The probability of mortality in individuals with severe sepsis or septic shock increase with each hour delay (10). Despite increased awareness and better diagnostic resources, many healthcare systems still face delays in starting antibiotics, especially in LMICs, where constraints in resources and workflows are more evident.

This chapter provides summary of sepsis, including its definitions, pathophysiology, global burden, and clinical significance in severly ill patients. It then define the specific research problem, presents the research questions and study objectives, and concludes with review of the current literature, thereby establishing the rationale and necessity for the present study.

1.1 Sepsis: Definition and Pathophysiology

1.1.1 Definition and Evolution of Sepsis

Sepsis is a potentially fatal condition that results when the body's immune response to an infection becomes disordered, leading to a state of inflammation throughout the body and failure of one or more organs. The definition of sepsis has changed many times over the last 30 years, the medical understanding of sepsis has evolved, resulting in successive refinements to its definition.

In 1991, the first consensus document, Sepsis-1, classified sepsis into three stages: Sepsis, Severe Sepsis, and Septic Shock. The three stages of sepsis were based on the Systemic Inflammatory Response Syndrome (SIRS) criteria, which encompassed an abnormality in body temperature, tachycardia, tachypnoea, and leukocytosis. Although SIRS was widely used to diagnose and treat sepsis, it had poor specificity because it could be brought on by a non-infectious event, so early cases of sepsis were frequently missed. Additionally, there was no universally agreed-upon definition for organ dysfunction, so the clinical usefulness of SIRS criteria was limited (11).

The definition of sepsis was refined in 2001 when it was called Sepsis-2 while also introducing a new term called severe sepsis; this describes when one or more organs of the body fail as a result of sepsis. There were also the recommendation(s) of using clinical scoring tools/systems (for example; The Sequential Organ Failure Assessment SOFA which evaluates 6 separate organ systems). At that point, SOFA had become the scoring system of choice for determining whether or not a patient has organ dysfunction based on an assessment of the following six organ systems: respiratory, cardiovascular, hepatic, coagulation, renal and neurological systems. In addition to the above, Sepsis-2 continued to lack a clearly defined method for efficient/informal rapid identification/definition of Severe Sepsis in patients and was still interpreted differently in different populations (12).

In 2016, Sepsis-3 was defined using updated clinical parameters for the diagnosis of sepsis with emphasis placed on the identification of organ dysfunction rather than the presence of an inflammatory response (4). Organ dysfunction associated with sepsis will be indicated by an acute (within a 24 hour period) increase of 2 points in the SOFA score. The quick SOFA (qSOFA) tool was also created at this time; qSOFA is used at the bedside and consists of 3 criteria; altered mental status, systolic blood pressure less than 100 mmHg, respiratory rate equal to or greater than 22 breaths per minute. These tools provide clinicians with a mechanism to recognize organ dysfunction at an early stage and subsequently improve risk stratification by utilizing organ dysfunction rather than relying on laboratory analytical data that indicates an inflammatory process. Additionally, Sepsis-3 defined Septic Shock: Septic Shock is a specific subset of sepsis that is characterized as having profound circulatory and metabolic abnormalities and requires the addition of vasopressors to maintain blood perfusion to organs, and is associated with higher mortality (4).

The international benchmark for Sepsis-3 has formed the basis of the majority of current research and clinical practice guidelines worldwide, including The Surviving Sepsis Campaign. To explain the progression of this disease and facilitate timely intervention, it is necessary to understand its pathophysiology.

1.1.2 Pathophysiology and Mechanisms of Organ Dysfunction

The body’s reaction to infection can become imbalanced causing problems in its ability to work properly; this can happen when there is an over-response from one part of the immune system. When this happens, there can be an associated increase in systemic inflammation and tissue damage (4). Under normal conditions the immune system will react in a coordinated manner to respond to an infection through both the innate and adaptive immune response; however when sepsis occurs, the coordination of these two parts of the immune system becomes dysfunctional, resulting in an increase in immune activity causing multiple organs to begin dysfunctioning (13).

One of the most common characteristics of sepsis is the uncontrolled release of pro-inflammatory cytokines which are frequently referred to in the medical community as a "cytokine storm". The immediate result of the presence of a cytokin storm is damaged endothelial cells; this allows excessive amounts of fluid to leave the vessels resulting in excess edema and ultimately multi-organ failure (14). In addition, sepsis also disrupts the normal coagulation processes therefore leading to the development of microvascular thrombi, which decreases overall blood flow to the tissues. There are mechanisms within the body that prevent clotting; however, with the presence of sepsis these mechanisms become suppressed leading to the formation of clots, a decrease in blood flow to the tissue, and an increased risk for developing disseminated intravascular coagulation (DIC)(15).

As the condition continues to advance, there is a reduction in immune function, which contributes significantly to an increased risk of secondary infections (16). In addition, there are dysfunctions in mitochondrial and metabolic processes that prevent oxygen from being utilized effectively in the body, increasing the likelihood of organ failure occurring (17). Immune dysregulation along with problems relating to the clotting process (i.e., coagulopathy) and metabolic disturbances will ultimately result in multiorgan dysfunction syndrome (MODS), which is also considered the leading cause of death from sepsis. Clinically, MODS may present as acute lung injury (i.e., acute respiratory distress syndrome [ARDS]), acute kidney injury, cardiovascular collapse with septic shock, liver dysfunction, or neurological dysfunction (18).

The above pathophysiological processes occur rapidly, which points to the importance of initiating prompt recognition of patients with severe sepsis and commencing antibiotic treatment early—this will also continue to be a key factor influencing survival rates of patients experiencing severe sepsis (19). Early initiation (timely) of antibiotic therapy will help to stop this chain reaction (i.e. cascade), thereby decreasing the chance of developing organ failure and resulting in better overall outcome after severe sepsis.

1.2 Clinical Presentation and Progression of Sepsis

The sepsis is a condition that progresses rapidly. The infection has the potential for causing serious illnesses and death. Rapidly recognizing sepsis and diagnosing it can decrease the likelihood of experiencing problems related to increased morbidity and mortality (20). Clinical tools that assist with this are the (TIME) mnemonics and the (NEWS2) scoring system. These tools have been developed and validated to assess patients who are at higher risk of deteriorating and can be used to encourage early intervention and assure proper monitoring of patients with suspected or established sepsis (21,22).

1.2.1 Early Recognition Tools: TIME™ and NEWS2

The TIME mnemonic, "It's About TIME," describes the four main early symptoms indicative of an infection that can develop into sepsis: Changes in temperature (>38°C and <36°C), Infection (suspected or confirmed), Mental changes (e.g., confusion or lethargy), and Extremely ill appearance (e.g., severe pain). These symptoms are often seen before there is clear evidence of organ dysfunction. Therefore, these signs must be used to guide prompt and adequate clinical response (22).

The NEWS2 score provides a standardized way to perform a bedside assessment of a patient who may have sepsis. The NEWS2 score utilizes vital signs, including respiratory rate, oxygen saturation, temperature, systolic BP, heart rate, level of consciousness using the AVPU scale, and oxygen administration. A NEWS2 score of 5 or greater is indicative of significant risk for clinical deterioration and should prompt immediate escalation of care (21). Both the TIME mnemonic and NEWS2 score are complementary with laboratory test results, e.g., lactate, procalcitonin, C-reactive protein, to improve early detection of sepsis (23).

1.2.2 Stages of Sepsis and Clinical Manifestations

The continuum of severity progresses through three stages: Early Sepsis, Severe Sepsis, and Septic Shock.

Early Sepsis: When first diagnosed with sepsis, many patients present with vague symptoms, fever or hypothermia (low temperatures), fast breathing (tachypnea), mild low blood pressure (hypotension), and changes in their mental status like confusion and agitation. Laboratory tests may show an increase or decrease in number of white blood cells (WBC), elevated C-reactive protein (CRP) or procalcitonin, and early signs of organ "stress" (24). Patients who have sepsis during the early stage have a 10–15% chance of mortality (25).

Severe Sepsis: Patients with Severe Sepsis are characterized by low blood pressure (hypotension), elevated lactate levels, acute kidney injury, low levels of oxygen in the blood (hypoxemia), and Acute Respiratory Distress Syndrome (ARDS); liver dysfunction; Coagulopathy, and neurological dysfunction. Severe sepsis has up to a 20–40% chance of resulting in mortality (25).

Septic Shock: Patients with Septic Shock are diagnosed by low blood pressure (hypotension) following resuscitation despite receiving adequate amounts of fluid or having methylene blue (vasopressor) medications and Lactate > 2 mmol/L. Patients with septic shock may also have cold, mottled fingers; little or no urine; and progressively worsening multi-organ failure. Patients with Septic Shock have an estimated 40-50% chance of mortality; in patients with refractory septic shock, this number could rise to 60% (24,25).

The earlier a patient is diagnosed with sepsis, the better chance the patient has of survival by rapidly recognizing and treating sepsis as soon as possible after diagnosis. Although there are tools available to identify patients who are at risk for sepsis early, starting appropriate antibiotics as soon as possible after diagnosis is the most important factor in decreasing mortality and preventing development of Severe Sepsis or Septic Shock.

1.3 Sources of Infection in Sepsis

Locating the primary source of infection is essential for constraining empirical antimicrobial therapy, determining an initial prognosis and optimizing clinical outcomes. On a global basis, respiratory tract infections (primarily pneumonias) are the leading cause of sepsis and have the highest mortality rate (26). Relatively infrequent, abdominal infections such as peritonitis and intra-abdominal abscesses have similar mortality rates and are very serious when there has been a delay in source control. Urinary tract infections (UTI's) are also a major factor, especially in the older population, but generally have less mortality unless associated with an obstruction or multidrug resistant microorganisms. Infections of the skin and soft tissue (for example, necrotizing fasciitis) have the potential to quickly progress to sepsis; blood infections, especially those caused by resistant organisms, will also continue to be an important cause of severe sepsis and septic shock(26).

Local data from Palestine reflect the same general patterns found globally. In ICU patients enrolled through a retrospective cohort study of patients with respiratory infections, the majority 71.3% were identified as respiratory sources, followed by others with UTI's

47.7% and central line associated bloodstream infection 25.0%. In many cases, patients have several identifiable sources of infection (more than 41.4% of enrolled patients had multiple sources). The distribution of infection sources between patients with sepsis and septic shock was not statistically significant (27).

These results highlight the significance of respiratory infections in causing sepsis and support the following conclusions: identification of the infected source should occur as early as possible; appropriate antimicrobial therapy should be administered as soon as feasible; and targeted source control interventions should begin immediately to improve outcomes.

1.4 Risk Groups of Sepsis

Among all groups, there are people who develop sepsis but some groups of people who have specific health problems are far more at risk for developing and surviving sepsis than others. Advanced age is a major risk factor for adverse outcomes in patients with sepsis due to weaker immune systems (due to aging), the increased amount of other diseases (multimorbidity), and the increased exposure to a hospital or healthcare settings (26). Infants are highly vulnerable to sepsis because their immune systems are still developing (<12 months) (28); thus, the risk of death from sepsis is highest for infants and the elderly. When looking specifically at the group of individuals involved in this study, there was a statistically significant difference in mortality based upon age; those who died were (69 vs. 43 years; $P = 0.003$) therefore older age places elderly persons at increased and/or higher risk of having poor sepsis outcomes (29).

There are sex-based differences in sepsis morbidity and mortality. It is known that men develop sepsis/create sepsis more often than women do, however, it is believed that women have a greater chance to die due to sepsis than men; this may be due to two different immune system responses to infection as well as two very different disease progression pathways of men and women when developing sepsis (26).

The presence of chronic comorbidities significantly heightens the chances of developing sepsis after initial exposure to an individual’s risk factors for other disease processes in their lives. Such chronic comorbidities include diabetes mellitus (DM), chronic respiratory disease, chronic cardiovascular disease, and chronic kidney disease (CKD) which together will decrease an individual’s ability to defend against an invading organism and expose them to multiple healthcare facilities thereby increasing the risk of developing sepsis (30). People with compromised immune systems, such as those receiving chemotherapy, long-term corticosteroids and people living with Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS) are at the greatest risk for developing a rapidly progressing severe infection that ultimately results in the development of sepsis (28).

Another primary contributing factor is healthcare-related; it is estimated that 10-15% of adult patients with sepsis have the infection as a result of receiving care in a hospital. In these cases, the infection was associated with the use of invasive devices, surgical procedures, prolonged hospital lengths of stay and/or mechanical ventilation, and/or renal replacement therapy (28). The physiologic changes that occur during pregnancy and within the postpartum period also place the woman at increased risk of developing sepsis due to immunologic response changes before, during, and after delivery combined with the possibility of developing complications during the peripartum period (28).

Sepsis is a multifactorial disease that results from a complex interaction of the factors of patient's age, sex, presence of comorbidities, patient’s immune system status, and patient exposure to healthcare services. A clear understanding of the populations at increased risk for the development of sepsis is imperative to establish focused prevention efforts, to ensure timely diagnoses of sepsis, and to allow appropriate interventions for the patient being treated for sepsis.

1.5 Management and International Guidelines for Sepsis

Sepsis is a potentially fatal condition that necessitates early identification as well as prompt treatment in order to decrease its morbidity and mortality rates. One of the most successful ways to improve patient death rates from sepsis is through the use of early initiation of proper antimicrobial therapy (31). International guidelines published by the Surviving Sepsis Campaign (SSC) provide clinicians with evidence-based recommendations regarding the timely management of patients suffering from sepsis and septic shock

In 2016 the SSC guidelines indicated that patients presenting with sepsis or septic shock should begin treatment with broad-spectrum antibiotics within one hour of presentation to the emergency department (32). These recommendations were primarily based on retrospective observational studies performed predominately on Intensive Care Unit populations, for example, Kumar et al. (2006) noted an increase in in-hospital mortality by 7.6% for each hour it took to provide the patient with effective antibiotics after development of septic shock, demonstrating the need for rapid initiation of antimicrobial therapy (8).

The timing of antibiotic therapy for septic patients continues to be debated, despite guidelines encouraging early initiation (33,34). The Infectious Diseases Society of America (IDSA) has noted that adherence to the one-hour rule may lead to inappropriate use of antibiotics, misdiagnosis and unnecessary broad-spectrum therapy in patients suspected of having sepsis but who show no signs of shock (35). The IDSA recommended that providers give antibiotics immediately for patients in septic shock while carrying out rapid clinical evaluations for other situations where there is suspicion of infection but no signs of septic shock before ordering antibiotics.

In recognition of these issues, the 2021 SSC Guidelines endorse more flexible and risk-oriented approaches. Antibiotics should be given within an hour for patients with septic shock or patients who likely have sepsis. If there is still suspicion of infection in patients with possible sepsis but no shock, then a rapid diagnostic assessment should be carried out and antibiotics should be started within three hours of completing the assessment. Also, the SSC Guidelines outline that time zero will be the time of first recognition of sepsis. Therefore, time zero can serve as a standardized reference point for the initiation of antimicrobial therapy (36).

1.6 Implementation Frameworks, National Sepsis Programs, and Global Awareness

The Surviving Sepsis Campaign is an example of international guidelines that provide evidence-based recommendations for the management of sepsis. However, the extent to which these guidelines affect sepsis management will depend upon how well they are implemented on a national and regional level. Several countries have already pioneered large-scale programs that can be used as models for improving the quality of sepsis care.

In 2013, New York became the first U.S. state to require sepsis protocols, following the death of 12-year-old Rory Staunton. The law—nicknamed "Rory's Regulation"—requires all hospitals to create and implement standardised and evidence-based protocols for the identification and management of patients with sepsis and to report outcomes back to the Department of Health. Studies have shown that hospitals that followed these mandates significantly reduced their sepsis mortality rate, particularly if the administration of effective antibiotics and complete fluid resuscitation were performed early (37).

In 2011, the Clinical Excellence Commission of New South Wales launched the Sepsis Kills Program in Australia, with the main goal of improving the care of patients with sepsis. This was done through early recognition and prompt escalation in the ED and hospital wards; implementation of a standardized protocol for sepsis identification; education/training of staff; and a process of continuous performance feedback. The implementation of these four strategies resulted in measurable improvements in sepsis-related mortality and length of hospital stay (38).

In England, the NHS has implemented a financial incentive program that rewarded hospitals for achieving targets related to screening patients for sepsis and initiating timely treatment (i.e., administering antibiotic medication) in the emergency department and inpatient setting. This strategy of paying for performance has increased the amount of patients screened for sepsis and the number of patients receiving timely treatment with antimicrobial medication. Financial rewards provided by P4P can significantly improve compliance with evidence-based guidelines (39).

Raising awareness of sepsis among healthcare professionals, policy makers, and the general public is critical to improving the early recognition of the condition and promoting timely interventions. Sepsis has been absent from the agenda of the world's health for much of history, resulting in delayed diagnosis and inadequate treatment practices (40). Educating, advocating and engaging with the community via initiatives like World Sepsis Day allows sepsis to be more visible within the community. A day of observation on September 13, World Sepsis Day encourages professional development, public advocacy, and social media engagement focused on early recognition and best practice preventative measures against sepsis. By analyzing public search patterns, studies have shown that public interest in sepsis peaks around public awareness campaigns like World Sepsis Day and other press coverage, suggesting that these visibility initiatives successfully engage the public (41).

The Global Sepsis Alliance with International partners launched their coordinated effort for an International/Global Response called the 2030 Global Agenda for Sepsis at the World Health Assembly September 2024. This Global Agenda represents a multi-year global strategy that will work to improve sepsis prevention, care, and surveillance worldwide. Through collaboration with over 70 partner organizations from every region, the Global Agenda emphasizes political advocacy, strengthening the healthcare system, conducting research, and implementing a whole-of-society approach to management of sepsis (20).

The 2030 Global Agenda has a strong focus on improving awareness and understanding about sepsis at all levels from all health systems to local communities. More knowledge for doctors, policymakers, and the public helps in early identification of sepsis, providing timely treatment options, and ensure preventive measures are taken - thus reducing sepsis deaths. It also encourages integration of sepsis strategies into national health policies and preparedness plans, which are in alignment with the larger global health objectives established by the Sustainable Development Goals. Through education, advocacy, and evidence-based interventions, the 2030 Global Agenda aims to help reduce the global burden of sepsis and improve patient outcomes for millions of patients around the world by December 31, 2030.

1.7 Problem Statement

Sepsis is one of the leading preventable causes of death across the globe, due to its high prevalence in ICU settings, where patients tend to present with significant physiological instability and can rapidly decline. There is broad agreement among experts that appropriate antibiotics should be started as soon as possible to have the best chance of success in treating a patient with sepsis, however, there remains a lack of consensus on when in fact this should take place. Many systematic reviews of the literature combine heterogeneous groups of patients from both emergency departments and intensive care units using various definitions of "time zero" (the first introduction of antibiotics), such as the patient's time of initial triage in the emergency department or time of sepsis recognition in the hospital, which makes it difficult to reliably evaluate patient mortality outcomes. For example, different mortality outcomes were demonstrated in studies conducted by Leung et al. (2024), compared to Ku et al. (2025), since the study populations in each study were from different clinical settings with different definitions of "time zero." And other research done in 2015 by Sterling showed that there is no relation between initiation of antibiotic timing and patient outcomes especially mortality, mainly due to limitations in study design, which restrict the generalization of their findings (42–44).

Research focused specifically on the timing of antibiotics administration in intensive care unit patients is limited, most of existing data coming from high-resource healthcare systems with rapid diagnostic capability, extensive laboratory support, and efficient clinical pathways. Conversely, low-resource or conflict-affected settings, such as Palestine, have different structural and operational barriers, affecting the timing of antibiotics and, therefore, the patient's clinical outcomes. These barriers include delays in recognizing sepsis, reduced laboratory capacity, and intermittent medication shortages, as well as numerous patients per nurse, and increasing resistance to antimicrobials can further complicate patients' ability to receive timely antibiotics.

To date, no studies have evaluated the impact of earlier initiation of antibiotics—using a standardized protocol to initiate at the time sepsis is recognized—on mortality in critically ill ICU patients in Palestine, despite these challenges. Evidence is needed to provide contextually relevant clinical guidelines, assist healthcare providers in developing antimicrobial stewardship programs, develop appropriate allocation of resources, and improve patient survivability.

1.8 Significance of the Study

Critically ill patients suffer from sepsis and the use of antibiotics is a very important factor affecting their chances of recovery. There is little evidence on the effect that the timing of antibiotics given to patients with sepsis while in a resource-constrained ICU environment, such as Palestine, have on improving patient outcomes. This study standardized time zero as when sepsis was first recognized; therefore, this study may be the first of its kind in Palestine to rigorously assess the effects of timing on in-hospital mortality in relation to the timing of antibiotics given to patients with sepsis.

Several findings have clinical and practical implications. The findings can be used to make ICU treatment decisions at Nablus Governmental Hospitals and provide guidance for developing treatment paths that consider practical and contextual appropriateness rather than simply relying on international guidelines. Determining whether giving antibiotics earlier results in improved survival can be used to improve workflow processes and the prioritization of triage and training of staff to maximize patient outcomes. Providing reliable evidence in support of antimicrobial stewardship by encouraging appropriate use of antibiotics and decreasing the likelihood of unnecessary escalation of antibiotics. Hospital administrators and policymakers can use these findings when planning and allocating resources, including, but not limited to, laboratory capacity, staffing ratios, and medication availability.

This research contributes to the worldwide body of scientific knowledge with regards to underrepresented locations in healthcare by supplying information on how systemic & contextual factors affect sepsis outcomes through exploring a healthcare setting not typical for most studies (hence previously unavailable). It adds to our knowledge base on the association between systemic & contextual factors and sepsis related mortality; therefore, it will also encourage other researchers around the world to conduct additional studies on similar ICUs that are limited by resources. Finally, this study provides support for evidence based strategies to reduce the mortality of critically ill Palestinians, as well as others in developed & undeveloped countries with similar resource-constrained settings.

1.9 Aim of the Study

The study aims to assess the relationship between the timing of the start of initial antibiotic treatment (beginning from sepsis recognition) and in-hospital mortality rates for ICU sepsis patients at Nablus Governmental Hospitals.

1.10 Study Objectives

The study objectives include:

1. Characterizing ICU patients with sepsis (demographic profiles such as age, sex, co-morbid conditions, and immune function) and determining whether there is an association with mortality.
2. Characterizing infection type (e.g., lung infections, urinary tract infections, infections of the skin and soft tissue, or other infections) and determining if these types of infections delay administration of initial antibiotics and their impact on mortality.

3. Identifying factors related to patients and diseases that may be associated with delays in receiving antibiotics in ICU patients with sepsis.
4. Determining the extent to which sepsis severity and patient characteristics can predict the risk of Mortality in the hospital.
5. Exploring the relationship between early antibiotic administration (up to 1 or 3 hours post ICU admission) and Mortality and conducting subgroup analysis by Sepsis Severity (with/without shock).
6. Providing evidence-based recommendations for Sepsis management protocols and Antimicrobial Stewardship Practices for Palestinian ICU's.

1.11 Study Hypotheses

- **H_1:** Earlier administration of initial antibiotics, measured from sepsis recognition, reduces in-hospital mortality in ICU patients with sepsis.
- **H_2:** Demographic and clinical characteristics of ICU patients with sepsis (age, sex, comorbidities, immunosuppressive therapy) are associated with in-hospital mortality.
- **H_3:** The source of infection influences delays in antibiotic administration and is associated with in-hospital mortality.
- **H_4:** Specific patient- and disease-related factors are associated with delayed door-to-antibiotic time.
- **H_5:** Higher sepsis severity and certain patient characteristics predict increased in-hospital mortality.
- **H_6:** Early antibiotic administration (≤1 hour and ≤3 hours from ICU admission) reduces mortality, with effects varying by sepsis severity, including subgroups with and without shock.

1.12 Research Questions

This study seeks to answer the following questions:

1. What are the demographic and clinical characteristics of ICU patients with sepsis, and how are they associated with in-hospital mortality?
2. What are the main sources of infection in ICU sepsis patients, and how do they influence delays in antibiotic administration and mortality?
3. Which patient- and disease-related factors are associated with delayed door-to-antibiotic time in ICU patients?
4. How do sepsis severity and patient characteristics predict in-hospital mortality?
5. Does early antibiotic administration (≤1 hour and ≤3 hours from ICU admission) reduce in-hospital mortality, including subgroup differences by sepsis severity (with shock vs. without shock)?
6. What recommendations based on evidence can be made to improve sepsis management protocols and to enhance practices related to antimicrobial stewardship in Palestinian ICUs?

1.13 Previous Studies and Theoretical Background

One of the most urgent global health problems continues to be Sepsis, estimated to cause up to 20% of yearly deaths globally (45). At this time, the mortality due to sepsis equals or exceeds the mortality from major noncommunicable diseases (NCDs), such as ischemic heart disease, stroke, and cancer (1). Sepsis is typically characterised by a sudden and substantial deterioration in clinical status over a short period of hours to days; consequently, patient outcomes depend almost entirely upon the timeliness and appropriateness of the clinical interventions delivered (46). Among all clinical interventions, the early identification and start of appropriate empiric antibiotics are major factors influencing whether patients survive after developing sepsis.

To develop an adequate theoretical and empirical foundation for conducting the present research, a thorough and structured systematic literature review was performed to examine available evidence from both global and regional datasets related to the timing of initial antibiotic therapy in sepsis. Multiple sources of evidence for inclusion were identified and evaluated, including observational (cohort, case-control), randomized controlled trials (RCTs), systematic reviews, and meta-analyses published in peer-reviewed medical literature, along with guidance documents from major nationally and internationally recognized health organisations. This systematic review will both create a context for the present study by providing an overview of existing research on the timing of initial antibiotic therapy in sepsis as well as highlight important evidence gaps that are specific to low-resource ICU settings such as those found in hospitals located in Palestine.

Research completed before today has significantly affected how sepsis is managed using evidence-based practice and influencing current clinical guidelines; however, published studies on this topic exhibit a large degree of heterogeneity with respect to the outcomes reported between studies. The inherent variability among previously published sepsis studies is largely attributable to the following factors: variability in the methodology used in each study (e.g., methodology varies between studies such as defining the time point being referred to as 'time zero' which may include triage vs. sepsis recognition and the degree of severity of the patient cohort (septic shock vs. without septic shock) vs. clinical setting (e.g., ICU vs ED). Overall, these variations limit direct comparisons between studies and create continuing uncertainty regarding when the best time is to give antibiotics (in particular, patients that are in a critical condition within the ICU).

For the purpose of this review there are two primary themes used to organize the literature that will be reviewed:

1. The timing of the initiation of empirically administered antibiotics and its impact on mortality.
2. Characteristics related to both the patient and disease process associated with mortality.

1.13.1 Timing of Empiric Antibiotic Therapy in Sepsis

The start of empiric antibiotics in a timely manner is generally considered one of the foundation principles of managing sepsis; this is often referred to as the “golden hour” for therapy. Many observational research studies suggest that mortality rates decline when antibiotics are given earlier in patients with sepsis. For instance, Huang et al. (2023) reported that administering antibiotics within 1 hour of recognizing sepsis was associated with decreased mortality and better clinical outcomes (47). However, the potential for significantly increasing a patient's chances of survival with very early antibiotics continues to be debated; the finding that early use of antibiotics may not be conclusive, as there are other factors that may affect the benefits of early use of antibiotics, including, disease severity, patient co-morbidities, and the clinical care setting in which they receive their treatment.

In 2014, Ferrer and colleagues used the Surviving Sepsis Campaign (SSC) database to conduct a major investigation of how the time between initiation of antibiotics and outcomes in patients with sepsis relates to mortality. The authors used a retrospective design and evaluated patients diagnosed with either severe sepsis or septic shock at 165 intensive care units (ICUs) located in Europe, the United States, and South America, making this one of the largest studies of its kind to date (n = 28,150). In patients that received antibiotics after they were identified as having sepsis (n = 17,990), the overall in-hospital mortality rate was 29.7%. This indicates that sepsis represents a major health issue in critically ill patients. The authors of this study demonstrated that there was a statistically significant relationship between each hour of delay in giving antibiotics and increased mortality, irrespective of disease severity, organ dysfunction, source of ICU admission, or geographic location. This research provided the initial evidence to demonstrate that even short delays in the initiation of empiric antimicrobial therapy had an adverse effect on the outcomes of patients and provided an impetus for the timely administration of antibiotics as an essential element of care for patients with sepsis across all types of healthcare systems (9).

In support of these findings, Liu et al. conducted a multi-center retrospective cohort study of over 35,000 ED patients. They identified a time-dependent increase in the risk of death associated with the length of time from registration in the emergency department until the first dose of antibiotics was given. For patients with sepsis, a one-hour delay in the initiation of antibiotic therapy was associated with a 9% increase in the adjusted odds of mortality; for those with sepsis, a 7% increase; and for those with severe sepsis, a 14% increase in adjusted odds of mortality for patients with septic shock, indicating that critically ill patients are at increased risk during times of delayed antibiotic initiation (48).

Recent systematic reviews and meta-analyses have offered a more detailed insight into the various factors influencing the timing of antibiotic treatment in septic patients, such as the treatment setting, the definition of time zero (whether it's the time of sepsis identification or hospital arrival), and the severity of the disease. Leung et al. (2024) conducted a research of forty-two different studies including 190,896 adults from emergency departments (ED) and intensive care units (ICU) who were administered antibiotics after being diagnosed with sepsis or upon arriving at the hospital. They found that the total mortality rate in the entire cohort of patients who received antibiotics within three or six hours of their presentation with septic symptoms was lower than those who did not receive antibiotics within that time frame. They also found that patients who were initially treated in an ICU setting could receive antibiotics within six hours of presenting with septic symptoms and that the difference was not statistically significant when considering the patients overall; however, it was significant for the non-septic shock population. They concluded that the administration of antibiotics within one hour of presentation does not necessarily provide an absolute mortality reduction; therefore, the administration of anti-microbial therapy within one hour of presentation does not universally provide a mortality reduction across all possible patient populations (42).

Further categorization according to disease severity improves this comprehensive perspective. Ku et al. (2025), examining research in both ED and ICU environments with antibiotic timing based on sepsis identification, found that administering treatment within one hour significantly decreased mortality in patients with septic shock, but not in those with sepsis without shock. In contrast, starting antibiotics within three hours was consistently linked to better survival in all patient groups (43). These findings are highly consistent with the 2021 Surviving Sepsis Campaign (SSC) guidelines, which advise that antibiotics be given within one hour for individuals experiencing septic shock or a significant risk of infection, and within three hours for those potentially facing sepsis without shock (36).

Likewise, Tang et al. (2024) performed a meta-analysis of 29 cohorts of patients with sepsis and septic shock that were treated in an emergency department and an intensive care unit setting. By using the time of triage or the time when sepsis was recognized to define the time at which treatment was started, they demonstrated a clear relationship between the duration of time to receive antibiotics and in-hospital mortality, showing that for each hour delay in starting antibiotics, there is a 4.1% increase in risk of in-hospital mortality. Additionally, this association existed in both patients with sepsis and those with septic shock, and there was no evidence of effect modification by the severity of illness. Furthermore, starting antibiotics beyond 1 hour provided significantly higher rates of death than patients who started antibiotics within the first hour, which highlights the importance of not having a delay in starting antibiotics once sepsis has been recognized(49).

However, a prior summary of research collated by Sterling et al. (2015) failed to reveal any significant relationship between administering antibiotics earlier than the initial hour after triage or one hour after recognition of sepsis/shock, based on a Meta-analysis consisting of 11 studies on adult patients diagnosed and treated at an ED with severe Sepsis and Septic Shock. There was no increase in mortality associated with administering the antibiotic greater than 3 hours after being triaged, or greater than 1 hour after being ruled as having either septic shock or severe sepsis, and there was no increase in relative risk of death for every 1-hour delay (up to a maximum of 5 hours) that patients were given antibiotics (44).

Findings from recent studies are helping us determine which patient populations would benefit the most from ultra-early therapy. For instance, Gross et al. (2025) stratified over 34,000 adults who were suspected of having sepsis using deep learning and concluded that patients with high risk would have their 30-day mortality rate significantly decreased by administering therapy within 1 hour. However, they did not see a decrease in short-term mortality for lower-risk patients (50). Im et al. (2022) found similar results in their research with 3,035 ED patients in South Korea. Mortality was reduced by 22% among patients who had septic shock; patients receiving therapy after 1 hour within the first 3 hours would have their mortality risk increase by 35% (51). The data indicate that providing ultra-early treatment is essential for high-risk and unstable patients, whereas therapy timing for lower-risk groups can be tailored to optimize results and promote antibiotic stewardship.

The Middle East and Asia provide useful information about how administering antibiotics at different times in various healthcare settings can affect the outcome of sepsis. Research has found that in these geographical locations, the benefits of giving antibiotics early on to maximize health were mixed depending upon the following factors: the quality of care received prior to illness, the severity of the infection (how serious it is), and the type of clinical environment where one would obtain care.

Patients admitted to an emergency department for treatment have similar mortality rates in the first hour after receiving antibiotics compared with patients treated 3h after arrival (52). The results were likely due to the timely delivery of the baseline medical care received by both of these groups of patients. In contrast, studies in Turkey and Thailand reported that patients admitted to an intensive care unit had stronger associations with the timing of the delivery of antibiotics and improved patient outcomes. For example, Savran et al., (2016) observed in their study of patients admitted to an intensive care unit (ICU) in Izmir, Turkey, that patients had significantly lower rates of mortality when antibiotics were administered to them within three hours after identification as being infected with sepsis. More importantly, receiving antibiotics early was an independent predictor of patient survival when you control for illness severity, using well-established prognostic measures such as the Acute Physiology and Chronic Health Evaluation II (APACHE II) and culture positivity; and Isaranuwatchai et al. (2025) found that studying a large cohort of patients in Bangkok, Thailand, who received timely administration of antibiotics had significantly reduced 28-day mortality rates when compared with patients who received antibiotics after one hour or greater than three hours from presentation. The survival benefit was particularly evident among patients with microbiologically confirmed infections and those with underlying malignancies, groups that are especially vulnerable to rapid disease progression (53,54).

In contrast to the findings of other large-scale studies, there is not a clear indication that ultra-early antibiotic therapy has a mortality benefit in all regional studies. As an example, Abe et al (2019) conducted a prospective observational study which followed 1124 patients with severe/septic shock across 54 Japanese ICUs and found no association with timing categories and adjusted in-hospital mortality. In addition, crude mortality was higher among those who received adequate antibiotics within one hour of sepsis recognition (55).

Similarly, Seok et al (2020) studied 482 patients treated for sepsis in the emergency department of a South Korean hospital and concluded that there were no independent associations between either timing or adequacy of initial antibiotics for 7-, 14- and 28-

day mortality when adjusted for other variables. Rather, markers of clinical severity (e.g., SOFA, serum lactate, and presence of comorbidities) were consistently reliable determinants of patient outcomes (56).

Thus, although there is considerable international evidence to support ultra-early antibiotic therapy as beneficial, the lack of regional data from resource- constrained environments such as Palestine regarding the impact of time to initiate antibiotics on mortality highlights an urgent need for the current study.

1.13.2 Patient- and Disease-Related Factors

The mortality rate of sepsis and septic shock is influenced by many factors. These include patient characteristics such as age, gender, and overall health status; disease and infection related factors; host immune response; severity of organ dysfunction; and clinical outcome. Numerous studies from different global regions have shown that there is a complex combination of factors involved in the cause(s) of sepsis related mortality. This highlights the need to evaluate risk factors comprehensively and implement appropriate clinical management strategies that are based on an individual patient's needs.

Patient-Related Factors

Older adults are one of the most frequently observed indicators of death from sepsis. Chang et al. (2024) demonstrated that non-survivor sepsis patients had a significantly older average (69 years vs 43 years) than survivor sepsis patients, this is believed to be due to dysfunction and diminished physiological reserve caused by natural ageing process through frailty in many older patients; therefore, older age, frailty, and/or physiological reserve will greatly impact mortality (45,57).

Sex-based differences in outcomes for sepsis patients have also been reported; however, findings are still variable. In the United States, Ang et al. (2025) reported that during a hospital admission, men who were diagnosed with septic shock had higher rates of death than women who were diagnosed with septic shock (34.3% versus 32.8%) (58). Rose et al. (2025) also reported that female patients had lower in-hospital and 12-month mortality than male patients in Germany, particularly for patients older than the age of 50 years; this indicates an interaction effect of a patient's age and sex on sepsis outcome (59). However, Wanrooij et al. (2023) found that once the researchers controlled for the severity of the sepsis and the amount of other medical problems, that sex was not an independent predictor of mortality, indicating that the observed differences may be due primarily to differences in baseline health status and the severity of illness and not necessarily due to biological differences between the sexes alone (60).

Comorbidities have a strong impact on death from sepsis. Chronic illnesses including high blood pressure (BP), diabetes (DM), heart disease (CVD), chronic kidney disease (CKD), and chronic liver disease (CLD) will compromise the immune system and decrease the body's reserve and thus, limit the body's ability to compensate for an acute infection. Chang et al. (2024) examined a group of people who had died due to sepsis and noticed that there was a significantly higher amount of high blood pressure (54% of non-surviovor vs 25% of survivors) (29). Whiles et al. (2016) looked at retrospective cohorts and reported 2.4% of individuals without comorbidities will die; however, this rate increases significantly, corresponding to the increase of comorbidities. No significant difference in mortality was found when comparing those without comorbidities to those with 1-3 chronic illnesses. However, it was noted that patients with 4 or more comorbidities had a much higher chance of dying. The most significant single illness contributing to death in these patients was metastatic cancer 17.4% (61). Conversely, Kang and colleagues (2024) found that patients with metastatic cancer had the highest in-hospital mortality rates (38.4%), followed by liver cirrhosis (34.5%). While hypertension is the most common comorbidity for sepsis patients, it has a better associated survival rate, than liver cirrhosis, CKD, or cancer (62).

Larger sampling of the entire population has confirmed previous research results. For example, researchers Stenberg et al (2023) examined a large, nationally representative cohort from a total of more than 6,700,000 Swedish citizens. Researchers found that the age and gender (male), lower education and higher Charlson Comorbidity Index score were all significantly associated with occurrence of sepsis among individuals in this cohort. Older individuals (>80 years old) or individuals who had comorbidities had a significantly greater risk of developing sepsis compared to other individuals in their age group or with similar demographics without chronic illness, suggesting that those disadvantages (i.e., both sociodemographic disadvantage and chronic disease) put people at a higher risk of dying from sepsis (63).

Source of Infection

The location of the infection is also one of the most important factors affecting sepsis-related mortality (26). Pneumonia is the leading cause of sepsis and is associated with the highest risk of death when compared to the other types of infections that can lead to sepsis. Intra-abdominal infections (e.g., peritonitis and intra-abdominal abscesses) are associated with increased mortality and usually require surgical intervention to cure the infection. Urinary tract infections have the lowest associated mortality when compared to the other sources of sepsis. However, soft tissue infections (e.g., cellulitis and necrotizing fasciitis) often progress to severe sepsis or septic shock, and of those, necrotizing fasciitis has the highest fatality rate.

According to Leligdowicz et al. (2014), in their cohort of 10,332 septic shock patients, mortality rates varied significantly based on the site of infection. Patients with respiratory infections and patients with intra-abdominal infections had the highest rates of mortality, and then patients with urinary tract infections had the lowest rates of mortality. Additionally, the source of infection remained an independent predictor of mortality, even after adjustments for demographic factors, pre-existing medical conditions, and illness severity have been made, demonstrating that the source of the infection is an important consideration for risk stratification and clinical management of patients with sepsis (64).

International studies have repeatedly shown how beneficial early empirical antibiotic therapy is in improving outcomes for people who have developed sepsis, and have also identified factors associated with both the patients and diseases that influence mortality. However, research has not yet been conducted in the ICU setting in Nablus Governmental Hospitals regarding either the relative effect of these determinants or the relationship between timing of antibiotic initiation and a patient's survival or not. Therefore, the current study's primary goal is to identify both the frequency of empirical antibiotic administration and how quickly empirical antibiotic therapy is begun; also to assess any association of either/or both of these variables to mortality for patients with sepsis, with or without shock, in the ICU. The ultimate intent is to provide evidence based, locally relevant, clinical decision support; to strengthen antimicrobial stewardship programs; and to facilitate targeted interventions to decrease sepsis related death rates in Palestinian ICUs.

Chapter Two

The Methodology

This chapter outlines the methodology used to achieve the study's objectives. A detailed summary of the research design, setting, and population from which patients were sampled, as well as the inclusion/exclusion criteria for selecting eligible patients. Also, the chapter discusses the ways in which the data will be collected and managed, including the operational definitions of the study's variables, methods for conducting statistical analyses, and how data quality will be maintained. Finally, ethical considerations regarding patient privacy and data security are also discussed; thus, all procedures conducted during this study were guided by principles of ethics that should be followed in conducting clinical research.

2.1 Study Design

A retrospective observational cohort study was conducted to examine the association between door-to-antibiotic duration and hospital mortality rate of patients with septic conditions that were admitted to the Intensive Care Unit (ICU). The use of current electronic medical records (EMRs) permitted the verification of actual treatment methods and patient outcomes for the purpose of this study, without interfering with clinical practice.

2.2 Study Setting and Period

The study was conducted in Nablus, Palestine, which is the location of two governmental hospitals in town that act as major reference hospitals for critically ill patients including septic patients. Two hospitals were initially identified (Rafidia Hospital and Al-Watani Hospital) to be potential locations of patient data collection, however due to a field evaluation, it was determined that Rafidia Hospital did not have a department of internal medicine and septic patients that were admitted to the ICU at Rafidia Hospital on a routine basis had been transferred to Al-Watani Hospital for continued management of sepsis patients. Due to this reason, the study population consisted solely of patients that were managed within the Internal Medicine ICU at Al-Watani Hospital, including any septic patient that had initially been admitted to Rafidia Hospital and subsequently transferred to Al-Watani Hospital for management. Patients were included in the study based on retrospective data collected for a period of time between January 1, 2023 and June 30, 2025, resulting in an adequate sample size with the ability to study the trend of the timing of initiation of empiric antibiotic therapy for ICU septic patients.

2.3 Study Population

The intended research participants included individuals at least 18 years of age who had been diagnosed as having either sepsis or septic shock and who were admitted to the ICU in the Internal Medicine Department of Al-Watani Hospital for the duration of this study. All included participants had a diagnosis of sepsis based on the Sepsis-3 guidelines, which specify that there must be a suspected or proven source of infection and evidence of organ dysfunction at the time of admission to the hospital.

2.3.1 Inclusion Criteria

To be included in this study, patients must have fulfilled each of the following inclusion criteria:

- Age of 18 years or older.
- Identified with sepsis or septic shock necessitating admission to the intensive care unit.
- Was administered at least one dose of intravenous antibiotics while in the ICU.
- Clinical records of sepsis identification and precise timing of first intravenous antibiotic administration.
- Record of their outcome during hospitalization (survival or death).

2.3.2 Exclusion Criteria

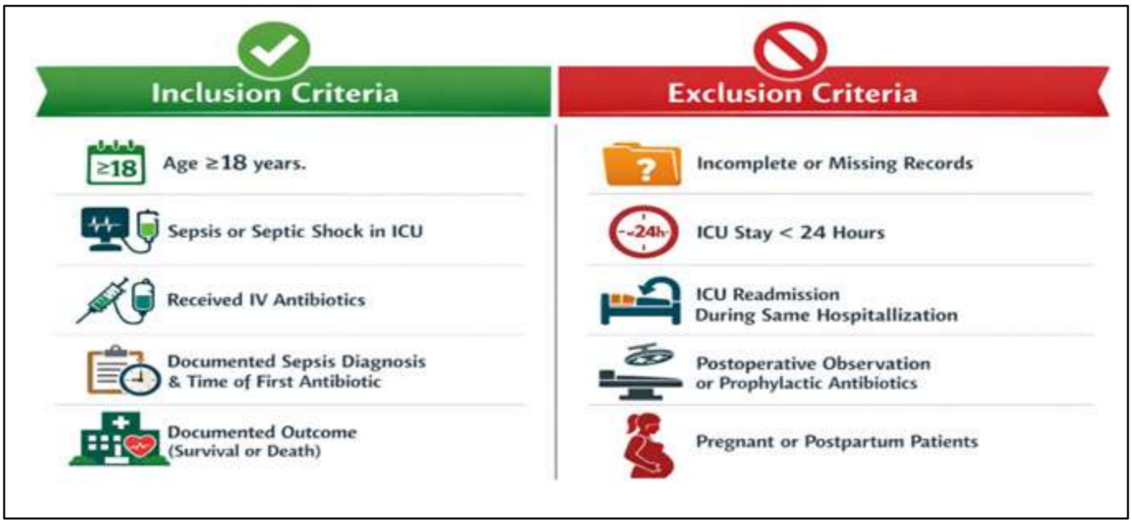
Patients were excluded from this study if they fulfilled any of the following exclusion criteria:

- Incomplete or missing medical records, especially regarding antibiotic timing or clinical outcomes.
- ICU length of stay <24 hours.
- Readmission to the ICU within the same hospitalization (only first admission included).

- Postoperative patients admitted for observation or receiving antibiotics solely for prophylaxis
- Pregnant or postpartum patients

Figure 1

Flow Diagram of Inclusion and Exclusion Criteria for ICU Sepsis Patients



2.4 Sample Size

The total number of patients included in the study was 297 who fulfilled eligibility criteria as well as had adequate medical records. As all eligible cases that occurred during the study period were included in the analysis; therefore, no formal calculation was needed for sample size determination.

2.5 Data Sources and Data Collection Tools

Data sources for this research include multiple hospital sources such as the electronic medical record (EMR) system, ICU admission logs and medication administration records. These sources retrieved all the required clinical and administrative data needed to fully describe the characteristics of each patient as well as the severity of illness, treatments provided and their associated outcomes. Patients eligible for inclusion were identified via ICU admission logs with a documented diagnosis of sepsis, severe sepsis or septic shock so that the sample population would accurately represent the study's original intention.

The data extraction process was developed using a standardized extraction tool and form (Appendix A) for the purpose to systematically collect: demographic information, co-morbidities, sepsis classifications, sources of infections, timing of administering antibiotic therapy and clinical outcomes from patients who had been retained in the ICU-J. The Extraction Form was created to maintain standardization of data collection and to ensure that all key variables were accurately recorded for every patient participating in the study.

The data extraction process took place manually and systemically through ongoing daily visits to the hospital (approximately 8 hours per day) by the researcher throughout the time period of July 7 through August 14, 2025. Manual data extraction allowed for the researcher to have direct access to and verification of the data while also providing an opportunity for the researcher to clarify any ambiguities and to cross-reference the information against multiple sources to reduce the likelihood of missing data or inaccurate data entries.

All patient records were assigned a unique study code in order to maintain confidentiality, with all identifiable information removed from the patient record prior to data entry. Data collected from patients was recorded in an Excel database secured through several methods of verifying accuracy (and/or consistency). This validation of data produced a database of high quality and reliability while also ensuring that patients could be provided with confidentiality as well as providing a reliable dataset for statistical analysis.

2.6 Study Variables and Operational Definitions

2.6.1 Dependent Variable

In-hospital mortality

In-hospital mortality was the primary outcome variable of this study which is defined as death during the same hospital admission when the patient was diagnosed with sepsis. Patient outcomes were categorized as Yes, indicating death during hospitalization, or No, indicating survival to discharge or transfer alive from the hospital.

2.6.2 Primary Independent Variable

Door-to-antibiotic time

Door to antibiotic measurement was the number of hours that have elapsed since sepsis was documented and the administration of the first IV antibiotic order in the critical care setting as a dependent variable for the study. This variable was categorized by the classification system Ku et al. (2025) into three categories (43):

- ≤1 hour.
- 1–3 hours.
- >3 hours.

2.6.3 Other Independent Variables

Demographic Variables

- **Age**: The age of all patients upon admission into ICU was determined from the medical records and categorized into four age groups in accordance to classification used by Paul et al. 2024, Age categories were (7):
  - 18–39 years.
  - 40–59 years.
  - 60–79 years.
  - ≥80 years.
- **Sex:** The sex of each patient was determined using medical record data and categorized into two groups:
  - Male.
  - Female.

Clinical Variables

- **Presence of comorbidity:** The presence of comorbidity was noted for each patient as a yes/no entry based on information documented in patient medical history and consisted of:
  - Heart Failure.

- Diabetes Mellitus.
- Hypertension.
- Chronic Obstructive Pulmonary Disease.
- Hepatic Disease.
- Cerebrovascular Accident.
- Chronic Kidney Disease.
- Other comorbidities.

- **Number of comorbidities:** The total number of documented comorbidities for each patient was calculated. This number was then recorded within three categories based upon Lee et al. (2018) (65):
  - 0 comorbidities.
  - 1–2 comorbidities.
  - ≥3 comorbidities.
- **Immunosuppressive therapy:** Defined as long-term use of immunosuppressive drugs before admission to the Intensive Care Unit (ICU) and recorded as a yes/no variable using documentation from the patient's medical records.
- **Sepsis classification:** Based on clinical documentation in the patient's medical records, each patient was assigned to a classification (e.g. severity of sepsis) according to how severe they were when admitted to the ICU. The classifications were as follows:
  - Sepsis without shock.
  - Sepsis with septic shock.

Source of Infection

Each patient suspected of having a source of infection was documented as to their suspected source. If present, sources of infection were coded as yes and if not, were coded as no, for each type of source:

- Respiratory infection
- Urinary tract infection

- Skin or soft tissue infection
- Other or unspecified infections

2.7 Data Management and Statistical Analysis

IBM SPSS Statistics (Version 21) was utilized for the data analysis; the p-value was set at the 0.05 level of significance for all inferential tests.

2.7.1 Descriptive Statistics

The use of descriptive statistics was employed to summarize the demographic, clinical, and treatment data for the study population. Frequencies and percentiles were used for the categorical variables: age group, gender, comorbidities, immunosuppressive therapy, sepsis classification, infection source, time from door to antibiotic administration, and in-hospital mortality. The descriptive analysis provided a description of the cohort characteristics that assisted in identifying patterns and distributions of the important variables prior to performing inferential testing.

2.7.2 Bivariate Analysis

Bivariate analysis was undertaken to assess the relationships of selected patient characteristics to the outcomes of interest. Chi-squared (a measure of how well the observed outcomes match the expected) tests were conducted to evaluate the following:

1. The relation of patient characteristics including age group, gender, number of comorbidities, immunosuppressive therapy, sepsis classification, and infection source and their relationship to the time from door to when antibiotics were given, to assess what factors may have affected the timely administration of the initial antibiotics.
2. The health-related patient characteristics were evaluated for their association with in-hospital mortality which were done to establish the demographic and clinical characteristics which are related to the risk of mortality for in-hospital patients diagnosed with sepsis.

2.7.3 Ordinal Logistic Regression

Using the ordinal logistic regression approach, potential independent predictors of delayed initiation of antibiotics in patients with sepsis was assessed. The dependent variable in this analysis was door to antibiotic time which was categorized as 3 ordered groups: ≤ 1 hour, 1 - 3 hours and > 3 hours. The independent variables included were: age, sex, number of comorbidities, immunosuppressive therapy, sepsis classification, and source of infection.

The proportional odds assumption (a key assumption of an ordinal logistic regression) was tested using the Test of Parallel Lines to evaluate that the relationship between each pair of outcome categories is parallel. The adjusted odds ratio (aOR) with a 95% CI was used to quantify the strength and direction of association. Statistical significance level set at $p < 0.05$.

2.7.4 Binary Logistic Regression

Two binary logistic regression models were created to find out if there were independent predictors of mortality in patients with sepsis and specifically to see what effect the time taken for the first dose of antibiotics had on mortality risk. The two regression models used different cut-offs for the time between hospital arrival and first antibiotic dose (door-to-antibiotic time) to determine if increasing delay to administration of antibiotics relates to increased mortality risk:

- Model 1: ≤1 hour versus >1 hour
- Model 2**:** ≤3 hours versus >3 hours

Both regression models used the same set of clinically relevant independent variables (age, sex, number of medical problems, type of sepsis, and the amount of time between patient arrival at the hospital and first antibiotic dose at the time of hospital arrival, as defined by each model), so that common demographic, clinical severity, and comorbid factors that are likely to be associated with patient death could be controlled for. The results of both analyses are expressed as the odds ratios (OR) and the associated 95% confidence intervals (CI), allowing for a measure of the strength and directionality of the association between predictor variables and in-hospital mortality. All results were deemed statistically significant if the p-value was < 0.05. By using these two separate logistic regression analyses, we were able to determine whether the time from when a patient with severe sepsis presented to the ICU until they received their first dose of antibiotics was independently associated with increased risk of mortality while controlling for demographic, clinical, and comorbid variables.

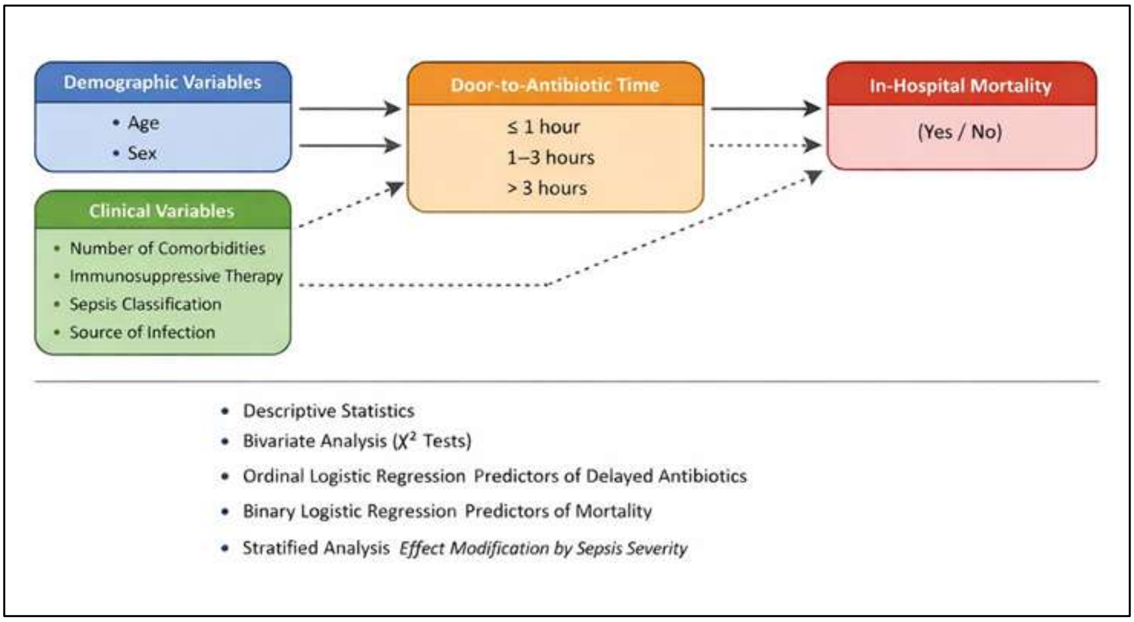
2.7.5 Stratified Analysis

To divide the patients into the two strata, we used the clinical sepsis classifications as reported in their medical record: sepsis without shock and septic shock. By stratifying in this manner, we ensured that we evaluated the effect of antibiotic timing on patient mortality by accounting for the fact that there were differences between the groups in terms of disease severity that could, in and of themselves, affect risk of mortality.

Because we completed the analysis separately for each group, we were able to obtain an improved understanding of how delays in the initiation of antibiotic therapy would influence outcomes for patients with varying degrees of severity of sepsis. Given that our established threshold for statistical significance is $p < 0.05$; this is the cutoff for our analysis.

Figure 2

Conceptual Framework of the Research: The Relationships between Patient Characteristics, Time to Antibiotic administration, and In-Hospital Mortality



2.8 Ethical Considerations

The Institutional Review Board (IRB) for An-Najah National University approved the study ethically on May 12, 2025 (Appendix B). The Health Education and Scientific Research Unit of the Palestinian Ministry of Health allowed your study to utilize patient records on June 25, 2025 (Appendix C). The study was retrospective in design, and therefore, no informed consent was obtained; since all data were previously available in medical record form and no intervention was done with patients. The study did maintain confidentiality and privacy throughout. Each patient record was assigned an individual study identifier number, and no identifiers (including name and national ID number) were stored in the data set to eliminate any potential privacy breach.

The data that was extracted from medical records was stored in a secure Excel (password-protected) file accessible to the research team(s) only. The use of de-identified patient data meant that the study presented minimal risk to patients, while also allowing for a meaningful examination of clinical outcomes and treatment patterns. The results of the analysis of individual patient records are reported as aggregate data therefore there were no means to identify individuals from their records.

Chapter Three

Results

This chapter presents the results of the study examining sepsis patients in an intensive care unit (ICU) with focus on patient characteristics, timing of initiation of antibiotics and in-hospital mortality. The study provides a demographic and clinical profile (age, gender, co-morbidities, sepsis severity and source of infection) of those sepsis patients. Then explores associations between patient characteristics (demographic and clinical factors) and clinical factors (door to antibiotic time and in-hospital mortality) are presented using bi-variate/multi-variable analysis. Finally, in-hospital mortality is examined by different timing intervals of administration of antibiotics in sepsis patients stratified by group of sepsis (i.e., sepsis severity) in order to demonstrate the effect of timely initiation of antibiotic therapy on patient outcomes.

3.1 Patient Characteristics

A total of 297 sepsis patients were included. Most were older adults, with 76.1% aged 60 years or above, while only 5.1% were younger than 40 years. Males comprised 59.6% of the study. Slightly more than half of the patients had three or more comorbidities 58.6%. The most common comorbidities were hypertension 63.3%, DM 51.2%, heart failure 32.7%, and CKD (24.6%). Only a tiny minority were on immunosuppressive therapy 7.7% (Table D.1 in appendix D).

Nearly two-thirds of patients were diagnosed with septic shock at admission (69.7%). Respiratory infections were the most frequent source of sepsis 77.1%, followed by UTI (33.0%), with skin and soft tissue infections and other sources being less common. Multiple sources of infection were identified in a subset of patients, with respiratory and UTI representing the most frequent combination 16.2% (Table 1). Regarding antibiotic timing, 44.8% received antibiotics within ≤1 hour, 35.7% within 1–3 hours, and 19.5% after >3 hours. Overall, in-hospital mortality was 71.4% (Table D.1 in appendix D).

Table 1

Distribution of Sepsis Patients with Sources of Infection (n=297)

Variables	*n* (%)
Respiratory tract infection only	158 (53.2)
Respiratory and UTI infection	48 (16.2)
Urinary tract infection only	37 (12.5)
Other or unspecified infection only	18 (6.1)
Respiratory and Skin/soft tissue infection	11 (3.7)
Skin and soft tissue infection only	7 (2.4)
Respiratory, UTI, and Skin/ soft tissue infection	7 (2.4)
Respiratory and Other/ unspecified infection	5 (1.7)
UTI and Skin/soft tissue infection	4 (1.3)
UTI and Other/ unspecified infection	2 (.7)

3.2 Association of Antibiotic Timing with Patient and Clinical Factors

Early antibiotic administration (≤1 hour) was more frequently observed among younger patients, with 60.0% of those aged 18–39 years receiving antibiotics within the first hour compared with 40.9% of patients aged ≥80 years. The proportion of patients receiving antibiotics within ≤1 hour was similar between patients with septic shock and those without shock (44.0% vs. 46.7%). In contrast, patients with a urinary tract source of infection were less likely to receive antibiotics within the first hour compared with those with non-urinary sources (35.7% vs. 49.2%).

At the bivariate level, antibiotic timing was significantly associated only with UTI. Patients with a urinary source of infection were more likely to experience delayed antibiotic administration ($p = 0.038$). No significant associations were observed between antibiotic timing and other infection sources, including respiratory ($p = 0.533$), skin or soft tissue ($p = 0.694$), or other/unspecified infections ($p = 0.269$). Additionally, antibiotic timing was not significantly associated with age ($p = 0.807$), sex ($p = 0.171$), number of comorbidities ($p = 0.408$), use of immunosuppressive medications ($p = 0.944$), or sepsis classification ($p = 0.185$) (Table 2).

In the multivariate model, the Test of Parallel Lines was non-significant (χ^2 (9) = 6.05, p = 0.735), confirming that the proportional odds assumption was met and the model was appropriate. In the ordinal logistic regression model, UTI as a source of sepsis was the only variable independently associated with door-to-antibiotic timing. Patients without a urinary tract source had lower odds of delayed antibiotic administration compared with those with a UTI source (aOR = 0.55, 95% CI 0.35–0.88). Door-to-antibiotic timing was not independently associated with age (18–39 years: aOR = 0.64, 95% CI 0.20–2.09; 40–59 years: aOR = 0.91, 95% CI 0.46–1.83; 60–79 years: aOR = 1.01, 95% CI 0.60–1.78), sex (male: aOR = 0.68, 95% CI 0.45–1.08), number of comorbidities (no comorbidities: aOR = 1.52, 95% CI 0.53–4.34; 1–2 comorbidities: aOR = 0.74, 95% CI 0.46–1.16), use of immunosuppressive drugs (no: aOR = 0.95, 95% CI 0.42–2.19), or sepsis classification (without shock: aOR = 1.13, 95% CI 0.71–1.82) (Table 3).

Table 2

Bivariate Analysis of Antibiotic Timing and Its Association with Patient and Clinical Factors (n = 297)

Variable	≤1 hr *n* (%)	1-3hrs *n* (%)	>3 hrs *n* (%)	P-Value
Age				
18-39	9 (60.0)	3 (20.0)	3 (20.0)	0.807
40-59	27 (48.2)	19 (33.9)	10 (17.9)	
60-79	70 (43.8)	57 (35.6)	33 (20.6)	
≥80	27 (40.9)	27 (40.9)	12 (18.2)	
Sex of patient				
Male	87 (49.2)	57 (32.2)	33 (18.6)	0.171
Female	46 (38.3)	49 (40.8)	25 (20.8)	
Number of comorbidities				
No comorbidity	5 (33.3)	6 (40.0)	4 (26.7)	
1-2 comorbidities	56 (51.9)	33 (30.6)	19 (17.6)	0.408
≥3 comorbidities	72 (41.4)	67 (38.5)	35 (20.1)	
Using immunosuppressive medication				
No	122 (44.5)	98 (35.8)	54 (19.7)	0.944
Yes	11 (47.8)	8 (34.8)	4 (17.4)	
Sepsis Classification				
Without shock	42 (46.7)	26 (28.9)	22 (24.4)	0.185
With shock	91 (44.0)	80 (38.6)	36 (17.4)	
Respiratory source of infection				
No	27 (39.7)	28 (41.2)	13 (19.1)	0.533
Yes	106 (46.3)	78 (34.1)	45 (19.7)	
Urinary tract source of infection				
No	98 (49.2)	69 (34.7)	32 (16.1)	0.038
Yes	35 (35.7)	37 (37.8)	26 (26.5)	
Skin or soft tissue infection				
No	122 (45.5)	95 (35.4)	51 (19.0)	0.694
Yes	11 (37.9)	11 (37.9)	7 (24.1)	
Other/unspecified infection source				
No	119 (43.8)	97 (35.7)	56 (20.6)	0.269
Yes	14 (56.0)	9 (36.0)	2 (8.0)	

Table 3

Ordinal Logistic Regression Analysis of the Association Between Antibiotic Timing and Patient and Clinical Factors (n = 297)

Variables	Estimate (β)	Std. Error	Wald χ^2	P-Value	Odds Ratio (Exp β)	95% CI for OR	
						Lower	Upper
Thresholds							
Antibiotic time = 1	−0.943	0.542	3.029	0.082	-	−2.006	0.119
Antibiotic time = 2	0.738	0.542	1.855	0.173	-	−0.324	1.799
Age (Reference = Age ≥80)							
18-39	−0.434	0.597	0.528	0.467	0.64	-1.605	0.737
40-59	−0.089	0.353	0.063	0.801	0.91	-0.780	0.603
60-79	0.031	0.278	0.012	0.912	1.01	-0.514	0.575
Sex (Reference = Female)							
Male	−0.366	0.225	2.652	0.103	0.68	-0.807	0.075
Number of comorbidities (Reference = ≥3 comorbidities)							
0 comorbidities	0.419	0.535	.612	0.434	1.52	-0.631	1.468
1-2 comorbidities	−0.318	0.239	1.772	0.183	0.74	-0.787	0.150
Immunosuppressive drugs (Reference = Yes)							
No	−0.046	0.424	.012	0.913	0.95	-0.877	0.785
Sepsis Classification (Reference = With shock)							
Without shock	0.126	0.240	0.277	0.599	1.13	-0.344	0.597
UTI Infection Source (Reference = Yes)							
No (UTI = No)	−0.581	0.234	6.174	0.01	0.55	-1.040	-0.123

3.3 Association of In-Hospital Mortality with Patient and Clinical Factors

In-hospital mortality increased with advancing age, with the highest mortality observed among patients aged ≥80 years 75.8%, followed by those aged 60–79 years 71.9%. Mortality also increased with greater comorbidity burden, reaching 75.3% among patients with three or more comorbidities. Patients presenting with septic shock experienced substantially higher mortality 85.0% than those without shock 40.0%. Regarding the source of infection, mortality was higher among patients with respiratory infections 74.7% compared with those without a respiratory source 60.3%.

At the bivariate level, septic shock ($p < 0.001$) and having respiratory tract infection as a source ($p = 0.021$) were significantly associated with mortality. In contrast, in hospital mortality was not significantly associated with age group (p = 0.587), sex (p = 0.540), number of comorbidities (p = 0.108), use of immunosuppressive therapy (p = 0.841), UTI (p = 0.058), skin and soft tissue infection (p = 0.320), and other or unspecified sources of infection (p = 0.394) (Table 4).

Table 4

Bivariate Analysis of In-Hospital Mortality with Patient and Clinical Factors (n=297)

Variables	Patient died during hospital stay		P-Value
	No *n* (%)	Yes *n* (%)	
Age			
18-39	6 (40.0)	9 (60.0)	0.587
40-59	18 (32.1)	38 (67.9)	
60-79	45 (28.1)	115 (71.9)	
≥80	16 (24.2)	50 (75.8)	
Sex of patient			
Male	53 (29.9)	124 (70.1)	0.540
Female	32 (26.7)	88 (73.3)	
Number of comorbidities			
No comorbidity	7 (46.7)	8 (53.3)	
1-2 comorbidities	35 (32.4)	73 (67.6)	0.108
≥3 comorbidities	43 (24.7)	131 (75.3)	
Using immunosuppressive medication			
No	78 (28.5)	196 (71.5)	0.841
Yes	7 (30.4)	16 (69.6)	
Sepsis Classification			
Without shock	54 (60.0)	36 (40.0)	**<0.001**
With shock	31 (15.0)	176 (85.0)	
Respiratory source of infection			
No	27 (39.7)	41 (60.3)	0.02
Yes	58 (25.3)	171 (74.7)	
Urinary tract source of infection			
No	50 (25.1)	149 (74.9)	0.058
Yes	35 (35.7)	63 (64.3)	
Skin or soft tissue infection			
No	79 (29.5)	189 (70.5)	0.320
Yes	6 (20.7)	23 (79.3)	
Other/unspecified infection source			
No	76 (27.9)	196 (72.1)	0.394
Yes	9 (36.0)	16 (64.0)	

3.4 Factors Associated with In-Hospital Mortality

Two binary logistic regression models were constructed to identify predictors of in-hospital mortality using antibiotic timing thresholds of ≤1 hour (Model 1) and ≤3 hours (Model 2).

3.4.1. Model 1: Factors Associated with In-Hospital Mortality (Antibiotic Timing ≤1 Hour vs 0. >1 Hour)

The number of comorbidities was a significant predictor of in-hospital mortality, with each additional comorbidity associated with a 26% increase in the odds of mortality (aOR = 1.26, 95% CI: 1.03–1.56). Sepsis classification was also associated with mortality; patients presenting with septic shock had substantially higher odds of mortality compared with those without shock (aOR = 0.11, 95% CI: 0.06–0.20).

Antibiotic administration within the first hour was not significantly associated with in-hospital mortality (aOR = 1.45, 95% CI 0.81–2.62). Age (aOR = 1.01, 95% CI 0.99–1.03) and sex (aOR = 0.92, 95% CI 0.50–1.66) were also not significantly associated with mortality (Table 5).

Table 5

Multivariable Binary Logistic Regression Analysis of Factors Associated with In-Hospital Mortality (Antibiotic Timing ≤1 Hour vs. >1 Hour)

Variable	B	p-value	OR	95% CI	
				Lower	Upper
Age (years)	0.116	0.552	1.123	0.766	1.645
Sex	0.078	0.796	1.082	0.596	1.963
Number of comorbidities	0.585	0.020	1.795	1.095	2.942
Sepsis Classification	2.237	<0.001	9.367	5.170	16.980
Antibiotic Timing <1 hr.	-0.391	0.195	0.677	0.375	1.221

3.4.2. Model 2: Factors Associated with In-Hospital Mortality (Antibiotic Timing ≤3 Hours vs 0. >3 Hours)

The number of comorbidities remained a significant predictor of in-hospital mortality, with each additional comorbidity associated with a 26% increase in the odds of mortality (aOR = 1.26, 95% CI 1.02–1.55). Sepsis classification continued to be significantly associated with mortality; patients presenting with septic shock had substantially higher odds of mortality compared with those without shock (aOR = 0.11 for survival, 95% CI 0.06–0.20).

Antibiotic administration within 3 hours was not significantly associated with in-hospital mortality (aOR = 0.78, 95% CI 0.38–1.57). Age (aOR = 1.01, 95% CI 0.98–1.03) and sex (aOR = 0.94, 95% CI 0.52–1.70) also remained non-significant predictors of mortality (Table 6).

Table 6

Multivariable Binary Logistic Regression Analysis of Factors Associated with In-Hospital Mortality (≤3 Hours vs. >3 Hours)

Variable	β	p-value	OR	95% CI	
				Lower	Upper
Age (years)	0.098	0.616	1.103	0.752	1.618
Sex	0.053	0.861	1.055	0.583	1.910
Number of comorbidities	0.574	0.023	1.776	1.082	2.913
Sepsis Classification	2.198	<0.001	9.006	5.002	16.230
Antibiotic Timing (<3 hrs.)	–0.311	0.386	0.733	0.363	1.481

3.5 Mortality by Door-to-Antibiotic Time Stratified by Sepsis Classification

Among patients without shock, in-hospital mortality was highest in those who received antibiotics within the first hour 50.0%, compared with 36.1% in the 1–3 hours group and 13.9% in those receiving antibiotics after more than 3 hours. For patients with septic shock, mortality was 45.5% for ≤1 hour, 36.4% for 1–3 hours, and 18.2% for >3 hours. Overall, patients with shock had higher mortality than those without shock, although the patterns of mortality across antibiotic timing intervals were similar. These differences were not statistically significant in either subgroup (p = 0.138 for patients without shock; p = 0.272 for patients with shock), indicating that door-to-antibiotic time within these intervals was not associated with in-hospital mortality (Table 7).

Table 7

In-Hospital Mortality by Door-to-Antibiotic Time Stratified by Sepsis Classification

Sepsis Group	Door-to-Antibiotic Time	Survived *n* (%)	Died *n* (%)	Total (n)	p-value
Without shock	≤1 hr.	24 (44.4)	18 (50.0)	42	0.138
	1–3 hrs.	13 (24.1)	13 (36.1)	26	
	>3 hrs.	17 (31.5)	5 (13.9)	22	
With shock	≤1 hr.	11 (35.5)	80 (45.5)	91	0.272
	1–3 hrs.	16 (51.6)	64 (36.4)	80	
	>3 hrs.	4 (12.9)	32 (18.2)	36	

Chapter Four

Discussion, Recommendations, and Conclusion

4.1 Discussion

Timely administration of antibiotics is a cornerstone of sepsis management; however, in critically ill ICU patients, its impact may be influenced more by illness severity, comorbidities, and the source of infection than by timing alone. In our cohort at Nablus governmental hospitals, a substantial proportion of patients received antibiotics within the first one to three hours of sepsis recognition. Despite this, variations in timing were not the primary determinant of in-hospital mortality. Rather than being determined by the time at which the antibiotics were given, mortality and other outcomes were more likely to be determined by the presence of septic shock, the presence of comorbid conditions, and the source of the infection. Of the different sources of infection, respiratory infections have the greatest risk of death. This suggests that the timing of when patients with advanced physiological compromise receive antibiotics will have less of an impact on their survival than will the severity of any underlying disease. Therefore, it is important to understand the timing of administering antibiotics in the larger picture of a patient's clinical context.

There's overwhelming support for the use of antibiotics earlier on rather than later in order to increase the outcome of people that have experienced septic shock and sepsis. According to the Surviving Sepsis Campaign (SSC), patients with septic shock or a high probability of infection should be given IV antibiotics within one hour. Those who have been suspected of having sepsis but do not have shock should receive IV antibiotics within three hours (36). Delays associated with the administration of effective antimicrobials have significantly increased the chance of mortality; each additional hour of delay in starting the administration of antibiotics in patients with septic shock has been shown to decrease the chance of survival by a significant amount and the entire in-hospital mortality rate has been shown to increase when antibiotics are not given until after the first hour has elapsed (8,9). The United Kingdom's national Institute of Clinical Excellence (NICE) guidance NG253 further support these recommendations by highlighting the need to have an urgent assessment and provide an infusion of IV antibiotics to adults at very high risk of mortality from sepsis within the first hour. The data supports the need for urgent assessment and initiation of IV antibiotic therapy to prevent progress and improve outcomes (66).

Studies such as Sterling et al. (2015) and Abe et al. (2019) show that the relationship of timely antibiotics and survival demonstrates a lack of conclusive evidence regarding this relationship. Studies conducted by Sterling et al. (2015), in their meta-analysis, concluded that there was no consistent reduction in mortality for timely antibiotic administration when controlling for rate of illness and methodological differences across studies (44). Abe et al. (2019), conducted a large observation study in Japan to assess the effect of timely administration to patient outcomes, found no association in decreased mortality with improved adherence to SSC for those receiving early antibiotics (55). Therefore; the results of this and other studies indicate that the relationship between timing of antibiotic and mortality is likely to vary based upon the following; patient acuity, co-morbidities, source of infection and health care system variables, which align with the patterns observed in our ICU cohort.

Other research indicates a different perspective on time administration of antibiotics. A recent meta-analysis of studies by Ku et al. (2025) shows that patients having septic shock have the greatest advantage in terms of survival if antibiotics are given within the first hour after diagnosis of shock. Patients without septic shock have shown some evidence of improved survival within 3 hours of antibiotic treatment after diagnosis (43). Likewise, Leung et al. (2024) did a systematic review comparing studies evaluating early vs. delayed antibiotic therapy across diverse settings and concluded that all patients receiving antibiotics earlier than three to six hours experienced lower overall mortality (42). These findings demonstrate that how antibiotic administration affects patient outcomes is contextually based and subject to many variables, such as degree of illness severity, characteristics of the host, and the availability of resources in the healthcare system. Given this complexity, decision-making about the optimal timing of antibiotic therapy in different subgroups, the interaction between the type of infection and comorbidities, and how to best implement early antibiotic strategies across different resource-limited ICUs is still uncertain. Therefore, the need for additional research exists to develop a better understanding of timing strategies that will optimize patient care with prompt initiation of therapeutic regimens that are feasible in clinical practice.

Above all, the results of this research must be examined within the framework of a low-resource, conflict-impacted health care system where this study occurred. Late identification of patients with sepsis can hinder the benefits associated with early initiation of antibiotics in these systems; therefore, significant differences in the time between presentation to the hospital and initiation of antibiotics at the starting point race will not necessarily represent early interventions as it pertains to correlation with survival benefits (67).

The effectiveness of early initiation of antibiotics also relies on receiving appropriate, active, and effective empiric treatment. In low-resource settings, this may be limited by restricted formularies, frequent medication shortages, weak microbiological support, and high, or often unknown, antimicrobial resistance patterns (68,69). Consequently, these challenges can undermine microbial coverage of early antibiotics, thereby minimizing timing-related benefits of antibiotic therapy. In effect, patient outcomes in sepsis relies on a bundle of interventions beyond antibiotic administration, including fluids, vasopressors, ventilation, source control, and access to high-quality critical care (36). Therefore, systemic challenges that delay recognition and limit antibiotic appropriateness may also affect the quality of these intervention bundle and thus further undermine impact of antibiotic timing.

To address these structural challenges, door-to-antibiotic time should be interpreted as a process measure instead of an independent predictor of patient outcomes. Stewardship of sepsis workflow should standardize and integrate multiple processes, including protocol for timely identification of sepsis and integration of microbiology into acute care. This includes periodic identification of local resistance patterns to support empiric decision-making. Development of local sepsis protocols should rely on the global consensus on sepsis management and coupled with a clear strategy balancing urgency, when sepsis is probable, with appropriate reassessment, when diagnostic uncertainty is high, to avoid overtreatment with antibiotics.

Finally, when evaluating studies supporting and proposing against early antibiotic administration it is necessary to understand that the most important aspect of an effective outcome after sepsis occurs depends not just on speed of therapy but also on having a timely diagnosis, providing an appropriate antimicrobial and how well the other aspects of critical care have been provided. Future research should be focused less on rigid time thresholds and more on context-sensitive, patient-centred strategies that utilise time-based methods combined with appropriateness and health system capabilities.

To evaluate what factors could predict mortality rates related to sepsis, two different multivariate modeling approaches were taken based upon the timing of antibiotics given for patients with sepsis within either 1 hour (model 1) or 3 hours (model 2). Both models identified presence of septic shock and degree of comorbidity, were predictors for in-hospital mortality. Several large-scale international studies involving thousands of participants by Stenberg et al., Whiles et al., found that patients who have baseline vulnerabilities will also have poorer outcomes following an episode of sepsis. In addition, meta-analyses provide significantly lower estimates of mortality from sepsis and severe sepsis (24-30% for sepsis and > 35-40% for septic shock), as well as indicate that once a patient develops septic shock there is an increase in mortality (much poorer prognosis). These findings are consistent with validation studies done on the Sepsis-3 cohorts (70) and various other epidemiological analyses (25), where shock remains associated with increased mortality rates, adjusted for age, comorbidities, and level of illness.

In our sample population, an increase comorbidity burden contributed independently to higher rates of mortality within our cohort (for every additional chronic condition, the mortality risk increased progressively). The reduced physiological reserve (especially with pre-existing organ dysfunction and impaired immune response), seen in patients with multiple chronic conditions, limits the patient's ability to withstand acute inflammatory and hemodynamic insults associated with sepsis. Additionally, multimorbidity complicates clinical decision-making, and may result in limitations to the ability to provide aggressive ICU intervention (71). Mortality rates were much higher among patients who had a higher comorbidity burden; this was further supported by two studies by Whiles et al. (2016) and Stenberg et al. (2023) which both demonstrate a connection between increasing severity of Charlson comorbidity index and worsening sepsis outcomes – particularly for older adults included in those studies (72,73).

In this cohort, the most frequent reason for sepsis was respiratory infections, which also had the highest mortality rate. This agrees with the results from Palestine that Rabee et al. (2020) found over 66% of the patients with sepsis had respiratory infections as their source (74). The development of pulmonary sepsis has been associated with the development of severe hypoxemia, acute respiratory distress syndrome, and required mechanical ventilation, all of which have been shown to independently increase mortality rates in ICUs (75). Similarly, in critical care, patients with respiratory infection due to multi-drug resistant organisms are delayed in receiving appropriate antimicrobial therapy, which may further deteriorate the outcome of their condition (76).

International evidence confirms that pneumonia continues to be the most common cause of sepsis globally. La Via et al. (2024) demonstrated that the location of an infection is a leading cause for sepsis-related mortality, and patients who have respiratory tract infections have lower rates of survival than patients who do not have respiratory tract infections (26). Leligdowicz et al., in a study published in 2014, also found that patients who had respiratory tract infections and patients who had intra-abdominal infections had a greater hospital mortality (worse outcomes). In contrast, patients whose infections originated from their urinary tracts had a lower hospital mortality (better outcomes) (77).

In this study, no association was found between patient demographics or baseline clinical characteristics -including age, sex, number of comorbidities, use of immunosuppressive medications, sepsis classification, respiratory source of infection, skin infection, or other sources of infection- and the timing of antibiotic administration. At both bivariate and multivariable levels, urinary tract infection (UTI) was the only factor significantly associated with delayed antibiotic administration. This finding suggests that delays were more influenced by differences in clinical presentation and perceived illness severity than by baseline patient characteristics. UTIs often present with subtle early manifestations compared with respiratory or soft tissue infections, which may lead clinicians to underestimate disease severity and postpone antimicrobial initiation while awaiting diagnostic confirmation (78).

4.2 Conclusion

In this retrospective study conducted in Nablus governmental hospitals, ICU patients with severe sepsis and septic shock had a high rate of death while in the hospital. The time from door to antibiotics did not independently affect survival from severe sepsis/septic shock, regardless of whether antibiotics were initiated within 1 hour or 3 hours from identifying the sepsis. Although prompt administration of antibiotics is a cornerstone of sepsis treatment, this data indicate that timing alone does not predict outcomes for critically ill patients in the ICU, especially in low resource environments. The predictors of mortality were the study patients' comorbidities and the presence or absence of septic shock, which shows the vulnerability of those with sepsis to dying of this disease as well as the severity of their illness prior to entering the ICU. The overwhelming prevalence of respiratory infections and mortality from these infections indicate the need for implementing additional prevention efforts, faster recognition of pulmonary sepsis, and improved management of pulmonary sepsis in order to reduce morbidity and mortality from these profoundly serious infectious diseases. The study findings reinforce that we should provide a comprehensive and appropriate approach to providing sepsis care that includes early risk assessment to determine optimal treatment; timely initiation of appropriate antibiotics; aggressive supportive care; and strengthening of health system processes, rather than focusing solely on time-based antibiotic targets.

4.3 Implications

The implications for clinical practice and the organization of health systems from this study's results are substantial. While early administration of antibiotics continues to be considered an essential part of managing patients with sepsis, we found that being strictly focused on adhering to a predetermined time-based target would not be enough to have a significant impact on reducing mortality for critically ill ICU patients. This indicates the need for a much more complex approach which includes providing rapid access to antibiotics, complete patient assessment, timely identification of organ dysfunction, and developing individualized treatment plans based on the patient's risk profile.

The early identification of high-risk patients is extremely important. Tailoring interventions to the severity of a patient's illness, their comorbid conditions, and the source of their infection can improve outcomes to a much greater extent than a uniform, time-based methodology. The unusually high mortality observed in patients with respiratory infections indicates a particular need for improved prevention strategies, earlier detection, and optimized treatment methods for pulmonary sepsis. Potential target interventions include stricter preventative protocols for ventilator-associated pneumonia, prompt diagnostic imaging, and prompt escalation of care for patients who are experiencing deterioration.

The difficulties of providing medical services in low and middle income countries (LMIC) government hospitals are amplified by inadequate human resources, medical supplies and equipment to access rapid diagnostic tests. Improving intensive care unit (ICU) protocols, promoting evidence-based clinical decisions and developing staff capacity through education/training may improve patient outcomes more than concentrating on the timing of antibiotics. The study results also suggest that systems-level interventions such as protocol standardisation, early warning systems, and multidisciplinary teams using coordinated methodologies will facilitate timely, appropriate and context-sensitive care for patients who are critically ill.

The results of this study strongly indicate that optimising sepsis outcomes requires multiple strategies, including rapid initiation of antimicrobial therapy, rational clinical decision making, use of resources conservatively, and support from a systems level (particularly in an environment with limited ICU resources). Future research should examine integrated management strategies (for those at risk) that use timely antimicrobial treatment, targeted patient stratification and early identification strategies.

4.4 Limitations

In interpreting the results of this study, there are various limitations that need to be considered. First, this research was conducted entirely in the intensive care units of the Nablus Governmental Hospitals and at the government's only tertiary care medical center. The ICUs in these hospitals operate in different organizational and resource settings (ICUs staffed with specialists and medical residents as opposed to "staffed with"--meaning there are no specialists in these ICUs) than hospitals with other staffing patterns, clinical workflows, and resources than private hospitals, non-governmental hospitals, and ICUs. This means that the findings and patterns of caring for patients with sepsis and managing their outcomes may not apply to all hospitals.

Second, the retrospective design of the study is a limitation. The data was collected from existing medical records and there was some variability in the amount of information available, and in the amount of detail recorded. Unfortunately, because some of the clinical and organizational characteristics that could potentially affect both the time to antibiotic and patient outcome were missing or incomplete, it did not allow for full adjustment for confounding variables, and therefore potentially affected the association between timing of antibiotics and mortality. Examples of potentially missing information include the severity of illness at the time of presentation (e.g., assessed using the Glasgow Coma Scale, lactate level, acid-base status), as well as other contextual factors (e.g., triage priority, time of day, physician experience/workload, unit-specific sepsis protocol, etc.). Therefore, the study was limited by the inability to adjust for all known confounding variables and may have limited the statistical associations between timing of antibiotics and mortality.

Furthermore, the measurement of the time it took for the antibiotic to be given to the patient (door-to-antibiotic time) was calculated from the time of the provider's documentation of the diagnosis of sepsis and not the actual onset of infection or medical demise. Misclassification of time may also occur due to delays in clinical recognition, documentation practices, and differences in how sepsis has been identified by each individual clinician. Therefore, the documented time may not correspond accurately to every patient's actual clinical course, especially in those with non-classic presentations or those who have had a slow progression of disease.

Although there are limitations, this study offers valuable information about practical ways of treating sepsis in a low-resource ICU. Documentation gaps, delays in sepsis identification, and inconsistency in antibiotic administration have been identified as critical areas for enhancing the system. Additionally, the findings also provide evidence that can be used to inform future prospective studies, quality improvement programs, and the creation of standardized sepsis pathways for similar healthcare systems.

4.5 Recommendations

4.5.1 Recommendations for Practice

- **Implement comprehensive risk stratification in ICUs:** Risk stratification must be used for all patients admitted to an ICU. Patients should be stratified according to their predicted risk for mortality based upon the patient's overall health status with a special focus on patients with multiple chronic disease states or septic shock. Care should be delivered based on how ill a patient is or the complexity of the patient's illness instead of only focusing on time from door to antibiotics (which may underestimate a patient's risk for mortality).

- **Strengthen management of respiratory infections:** Given that respiratory infections are common and associated with high mortality, ICU Management of respiratory infections should include improved identification of sepsis in cases of respiratory infection, optimization of ventilatory support and close clinical monitoring of patients. Antimicrobials administered to patient with respiratory sepsis should be reassessed as patient status changes and as microbiologic culture results become available, as these changes will improve the outcome of patients with respiratory sepsis.
- **ICU Staff Ongoing Training and Curriculum Development:** It is essential that ICU staff are trained to follow a "context-sensitive" approach to managing septic patients; in other words, the healthcare professional must take into account the patient's clinical severity, the source of infection and the patient's comorbidities when providing treatment for sepsis. Education and training will help to promote balanced clinical judgment and adherence to evidence-based clinical practice guidelines for sepsis.
- **Sepsis management should have a Multidisciplinary Team Approach** (MDT): A structured multidisciplinary team approach involving intensivists, ID specialists, pharmacy clinicians, microbiologists, nursing staff, and respiratory therapists should be applied to sepsis management within an intensive care unit (ICU). Collaboration among the team allows for better identification of clinical deterioration, improved selection and adjustment of antimicrobial therapy, and improvement in the control of infectious sources. Regular multidisciplinary rounds will allow for timely review of antibiotic therapy and implementation of antimicrobial stewardship, thus improving overall patient outcomes.
- **Clinical Pharmacy should be Included in the ICU Sepsis Care:** Clinical pharmacy services should participate in antimicrobial stewardship activities by reviewing and evaluating empiric antibiotic selection, optimizing the dose of antibiotics based on pharmacokinetic and pharmacodynamic principles, monitoring potential drug interactions/toxicity, and recommending de-escalation strategies as determined by the laboratory results. Due to the physiology of critically ill patients causing alterations in drug distribution and clearance, the role of the clinical pharmacist is

critical in optimizing the appropriateness of antibiotics and preventing development of resistance, thereby improving rates of survival.

4.4.2 Recommendations for Policy

- **Develop context-appropriate sepsis guidelines:** Standardized sepsis management guidelines should be developed and implemented by health authorities in developing countries. These guidelines should consider the need for timely antibiotic treatment and the patient's unique characteristics (e.g., risk factors, clinical severity of illness) and the local system's limitations in making sepsis management decisions without compromising quality of care.
- **Strengthen ICU capacity and resources**: Investing in ICU infrastructure (e.g., rapid diagnostic tests, appropriate amounts of staff) is necessary to enhance early identification of sepsis and support timely and appropriate interventions
- **Establish continuous monitoring and evaluation systems**: Policies should promote the use of continuous monitoring systems to measure quality of care for sepsis, adherence to established guidelines, and patient outcomes. Continuous monitoring systems can provide evidence-based information to guide decisions about policy development, identify gaps in the quality of sepsis care, and improve the allocation of limited resources.

4.4.3 Recommendations for Future Research

- **Expand prospective, multicenter research**: The focus of future studies should use multi-location future-focused study designs to evaluate how appropriate timing of antibiotics, appropriate therapy and source control of sepsis affect the outcome of sepsis for patients in the intensive care unit (ICU). The use of data from various locations will allow researchers to better determine the impact of clinical variables on patient care and improve the relevance of study results across different healthcare environments.
- **Examine additional determinants of treatment delays:** In this study we did not include all potentially applicable factors, thus future work needs to be conducted to determine other factors that delay time to receive antibiotics. Potential factors relating to time of treatment could include triage priority, physician skill level,

experience and age/skill level of physician on shift, physician workload and the sepsis protocol in the patient's hospital. Understanding these factors might help identify and modify barriers to timely treatment through improvements in hospital systems.

- **Focus on high-risk infection groups**: Future research needs to be directed toward the development and evaluation of targeted interventions to reduce mortality in patients with high-risk, especially respiratory, infections (sepsis). Future research will help improve the delivery of patient care in resource limited healthcare systems. Results from these studies will also help establish new treatment pathways for patients whose care is provided in similar intensive care unit.

List of Abbreviations

Abbreviation	Meanings
ARDS	Acute Respiratory Distress Syndrome
CI	Confidence Interval
CKD	Chronic Kidney Disease
CRP	C-Reactive Protein
DM	Diabetes Mellitus
ED	Emergency Department
EMR	Electronic Medical Record
ICU	Intensive Care Unit
IDSA	Infectious Diseases Society of America
IRB	Institutional Review Board
LMICs	Low- and Middle-Income Countries
MODS	Multiple Organ Dysfunction Syndrome
NEWS2	National Early Warning Score 2
NHS	National Health Service
OR	Odds Ratio
SIRS	Systemic Inflammatory Response Syndrome
SOFA	Sequential Organ Failure Assessment
SSC	Surviving Sepsis Campaign
USD	United States Dollar
UTI	Urinary Tract Infections
WHO	World Health Organization

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Appendices

Appendix A

Sepsis Study – Data Collection Form

1. Patient Demographics & Admission Data

Patient ID	Unique ID (e.g., S001)
Age	Years
Date of Hospital Admission	DD/MM/YYYY
Date of ICU Admission	DD/MM/YYYY

2. Comorbidities (Tick all that apply)

Heart Failure	☐
Diabetes Mellitus	☐
COPD	☐
Hepatic Dysfunction	☐
Renal Failure	☐
Cerebrovascular Accident	☐
Malignancy	☐
Chronic Kidney Disease	☐
On Immunosuppressive Drugs	☐
Others	
Number of Comorbidities	☐ 0 ☐ 1-2 ☐ ≥3

3. Sepsis Classification

Sepsis	☐
Severe Sepsis	☐
Septic Shock	☐

4. Infection Details

Respiratory infection	☐ Yes ☐ No
Urinary tract infection	☐ Yes ☐ No
Skin/soft tissue infection	☐ Yes ☐ No
Other or unspecified infections	☐ Yes ☐ No

5. Diagnosis & Antibiotic Timing

Date & Time of Sepsis Diagnosis	DD/MM/YYYY – HH:MM
Date & Time of 1st Antibiotic Given	DD/MM/YYYY – HH:MM
Time Gap Between Diagnosis & Antibiotic	☐ ≤1 hr. ☐ 1–3 hrs. ☐ >3 hrs.

8. Clinical Outcomes

In-Hospital Mortality	☐ Yes ☐ No

Appendix B

IRB Approval

5/15/25, 12:55 PM IRB Approved Letter.docx - Google Docs

جامعة النجاح الوطنية
An-Najah National University

مكتب مجلس المراجعة المؤسسية
Office of Institutional Review Board (IRB)

Dear Dr. Raya Sawalha,

We are pleased to inform you that your research proposal titled ***"Appropriateness of Timing of Initial Antibiotic Prescription and Its Impact on Sepsis Patient Outcomes in the ICU at Nablus Governmental Hospitals: A Retrospective Study"*** has been approved by the Institutional Review Board (IRB) at **An-Najah National University**.

Here are the approval details:

Submitted by:	Raya Sawalha, Sarah Aqqad.
Approval Date:	12th. May . 2025
IRB Protocol Number:	Fgs/Med. May. 2025/20

Please report any changes to the study protocol to the IRB for review. If you have any questions, contact us at irb@najah.edu. Thank you for your commitment to ethical research.

Best regards,

Naim Kittana, Dr.

IRB, Chairperson

IRB

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AnNajahUni
https:// www.najah.edu

https://docs.google.com/document/d/17sO8P9FxSAKYG4C7ynBzyE1Uz9GV/edit 347/363

Appendix C

تسهيل مهمة

State of Palestine **Ministry of Health** **Education in Health and Scientific Research Unit**		دولة فلسطين وزارة الصحة وحدة التعليم الصحي والبحث العلمي

Ref.: ....
Date:..................

الرقـم: C.Co / ١٥٤٧/١٦٣
التـاريخ: C.Co / ٦/٢٥

الأخ مدير عام الادارة العامة للمستشفيات المحترم،،،

الأخ رئيس وحدة التخطيط والسياسات الصحية المحترمة،،،

تحية واحترام...

الموضـــوع: تسهيل مهمة بحث

يرجى تسهيل مهمة **الطالبة: ساره مفيد غالب عقاد– ماجستير إدارة الصحة العامة/ جامعة النجاح**، وبإشراف د. رايه صوالحة، في عمل بحث بعنوان:

"Appropriateness of Timing of Initial Antibiotic Prescription and Its Impact on Sepsis Patient Outcomes in the ICU at Nablus Governmental Hospitals: A Retrospective Study"

من خلال السماح للطالبة بجمع معلومات من ملفات المرضى المصابين بالإنتان في العناية المكثفة، وذلك في:

– مستشفى رفيديا – مستشفى الوطني

على ان يتم الالتزام باساليب واخلاقيات البحث العلمي، وعدم التعرض للمعلومات التعريفية للمشاركين.

على ان يتم تزويد الوزارة بنسخة PDF من نتائج البحث، التعهد بعدم النشر لحين الحصول على موافقة الوزارة على نتائج البحث.

مع الاحترام...

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Appendix D

Tables

Table D.1

Descriptive Characteristics of Sepsis Patients Admitted to the ICU (n = 297)

Variables	*n* (%)
Age	
18-39	15 (5.1)
40-59	56 (18.9)
60-79	160 (53.9)
>80	66 (22.2)
Sex of patient	
Male	177 (59.6)
Female	120 (40.4)
Heart Failure	
No	200 (67.3)
Yes	97 (32.7)
Diabetes mellitus	
No	145 (48.8)
Yes	152 (51.2)
Hypertension	
No	109 (36.7)
Yes	188 (63.3)
COPD	
No	265 (89.2)
Yes	32 (10.8)
Hepatic Dysfunction	
No	292 (98.3)
Yes	5 (1.7)
CVA	
No	236 (79.5)
Yes	61 (20.5)
Malignancy	
No	246 (82.8)
Yes	51 (17.2)
CKD	

No	224 (75.4)
Yes	73 (24.6)
Number of Comorbidities per Patient	
No comorbidity	15 (5.1)
1-2 comorbidities	108 (36.4)
≥3 comorbidities.	174 (58.6)
Using immunosuppressive medication	
No	274 (92.3)
Yes	23 (7.7)
Sepsis Classification	
Without shock	90 (30.3)
With shock	207 (69.7)
Respiratory source of infection	
No	68 (22.9)
Yes	229 (77.1)
Urinary tract source of infection	
No	199 (67.0)
Yes	98 (33.0)
Skin or soft tissue infection	
No	268 (90.2)
Yes	29 (9.8)
Other/unspecified infection source	
No	272 (91.6)
Yes	25 (8.4)
Door-to-antibiotic time	
≤1 hr	133 (44.8)
1-3hrs	106 (35.7)
>3 hrs	58 (19.5)
Patient died during hospital stay	
No	85 (28.6)
Yes	212 (71.4)

جامعة النجاح الوطنية

كلية الدراسات العليا

مدى ملاءمة توقيت وصف المضاد الحيوي الأولى وتأثيره على نتائج مرضى الإنتان في وحدات العناية المركزة في المستشفيات الحكومية بنابلس: دراسة استعادية

إعداد

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اشراف

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د. عبد السلام الخياط

قدمت هذه الرسالة استكمالا لمتطلبات الحصول على درجة الماجستير في ادارة الصحة العامة من كلية الدراسات العليا في جامعة النجاح الوطنية نابلس- فلسطين.

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الملخص

المقدمة: يُعد الإنتان (Sepsis) من الأسباب الرئيسية للوفيات في وحدات العناية المركزة (ICUs)، ولا سيما في البلدان منخفضة ومتوسطة الدخل. ويُعتبر الإعطاء المبكر للمضادات الحيوية المناسبة حجر الأساس في تدبير الإنتان؛ إلا أن الأدلة المتعلقة بالتوقيت الأمثل لبدء العلاج ما تزال غير متسقة، كما أن معظم البيانات المتاحة مستمدة من أنظمة رعاية صحية ذات موارد عالية. هدفت هذه الدراسة إلى تقييم العلاقة بين توقيت بدء المضاد الحيوي الأولي والوفيات داخل المستشفى لدى مرضى الإنتان في وحدات العناية المركزة في نابلس، فلسطين. وشملت الأهداف الثانوية وصف الخصائص الديموغرافية للمرضى، وأنماط الأمراض المصاحبة، ومصادر العدوى، وأسباب تأخر بدء العلاج بالمضادات الحيوية، والعوامل المرتبطة بالوفيات، مع إجراء تحليلات إضافية وفق شدة الإنتان.

المنهجية :أُجريت دراسة رصدية استعادية شملت المرضى البالغين (≤18 سنة) المقبولين بتشخيص الإنتان أو الصدمة الإنتانية في وحدة العناية المركزة للطب الباطني في مستشفى الوطني بنابلس، فلسطين، خلال الفترة من يناير 2023 إلى يونيو 2025. تم تعريف الإنتان وفق معايير .Sepsis-3 جُمعت البيانات المتعلقة بالخصائص الديموغرافية، والأمراض المصاحبة، وشدة الإنتان، ومصدر العدوى، وتوقيت بدء المضادات الحيوية، والنتائج داخل المستشفى من السجلات الطبية الإلكترونية. وصُنّف زمن الدخول–إلى–إعطاء المضاد الحيوي إلى ≥1 ساعة، أو 1–3 ساعات، أو 3<ساعات من وقت التعرف على الإنتان. وكانت النتيجة

الأساسية هي الوفيات داخل المستشفى. واستُخدم الانحدار اللوجستي متعدد المتغيرات لتحديد المتنبئات المستقلة للوفاة.

النتائج :من بين 297 مريضًا في وحدة العناية المركزة، تم بدء العلاج بالمضادات الحيوية خلال ≤1 ساعة من التعرف على الإنتان لدى 44.8% من المرضى، وخلال 1–3 ساعات لدى 35.7%، وبعد أكثر من 3 ساعات لدى 19.5%. لم يرتبط الإعطاء المبكر للمضادات الحيوية، سواء خلال ساعة واحدة (aOR = 1.45; 95% CI: 0.81–2.62) أو خلال 3 ساعات (aOR = 0.78; 95% CI: 0.38–1.57)، بشكل مستقل بزيادة أو انخفاض الوفيات. في المقابل، كانت الصدمة الإنتانية وارتفاع عبء الأمراض المصاحبة من المتنبئات المستقلة للوفاة. وأكدت تحليلات المجموعات الفرعية وجود معدلات وفيات أعلى بشكل متسق لدى مرضى الصدمة الإنتانية عبر جميع فئات التوقيت.

الخلاصة: في هذه العينة من وحدة عناية مركزة ذات موارد محدودة، لم يؤثر توقيت بدء العلاج بالمضادات الحيوية بشكل مستقل على الوفيات. وكانت شدة المرض وعبء الأمراض المصاحبة هما المحددان الرئيسيان للنتائج السريرية، مما يؤكد أهمية تبني استراتيجيات تدبير للإنتان تراعي السياق المحلي وتعزيز برامج ترشيد استخدام المضادات الحيوية في وحدات العناية المركزة الفلسطينية.

الكلمات المفتاحية: الإنتان؛ الصدمة الإنتانية؛ توقيت المضادات الحيوية؛ الوفيات؛ دراسة أترابية استعادية؛ وحدة العناية المركزة؛ فلسطين.