ORIGINAL ARTICLE

Assessment of the Process of Initial Antibiotic Therapy for Patients with Sepsis in the Emergency Department of a Tertiary Hospital in the Philippines: A Mixed Methodology

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ABSTRACT

Background. Sepsis is a life-threatening organ dysfunction in response to an infection, and immediate administration of the first antibiotic dose, along with other resuscitative efforts, improves patient outcomes. This paved the way for the development of evidence-based sepsis pathways in different health institutions.

Objectives. This study aims to assess the process of initial antibiotic therapy, from the time the loading dose of antibiotic was ordered to the time it was administered, for adult patients with sepsis admitted at the Emergency Department (ED) of the University of the Philippines – Philippine General Hospital (UP-PGH).

Methods. In phase 1 of the study, a review of medical records was done to identify all adult patients diagnosed with sepsis in the ED from February 1 to August 31, 2022. A variant of time-motion analysis was used wherein three points in the sepsis pathway were identified: the time of diagnosis of sepsis/first chart order of antibiotics (point A), the time the chart order was noted by the nurse-in-charge (point B), and the documented time of first dose administration (point C). The mean and median duration (in hours) were then computed between these points. As an additional aim, we briefly presented the outcome of the population used. In phase 2, individual interviews and focused group discussions were done, involving key medical personnel in the sepsis pathway: physicians, nurses, pharmacists, and utility personnel. The data transcribed from these interviews was analyzed through a thematic examination.

Results. A total of 508 adult patients were diagnosed with sepsis on record review, 442 of whom met the inclusion criteria. The median time it took for the nurse-in-charge to acknowledge the antibiotic order (points A to B) is 0.73 hours (IQR 0.27-1.7). Meanwhile, the median time between acknowledgment of the order to administration of antibiotics is 1.94 hours (IQR 0.83-6.63). More importantly, the median time from diagnosis-to-first dose (points A to C) is 3.53 hours (IQR

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1.59–7.96), while the corresponding mean duration is 5.72 hours. In all cases, 44.6% and 12.4% of loading doses were given within three hours and within one hour after diagnosis, respectively. The all-cause mortality of all qualified cases was 64.7%. A total of 28 key medical personnel were recruited for phase 2. Issues regarding governance, information systems, finances, service delivery, and human resources were identified. In particular, the electronic chart system, a more stable supply of antibiotics, and the new pharmacy at the ER helped facilitate antibiotic delivery. Lack of personnel, gaps in information, and repetitive paperwork were cited as areas for improvement in the existing system.

Conclusion. In more than half of the study population, the target time from diagnosis to loading dose of at least 1 hour was not reached. The significant delays in sepsis treatment call for system-wide improvements to hasten the process of antibiotic delivery and reduce the poor outcomes associated with sepsis.

Keywords: thematic analysis, time motion studies, sepsis

INTRODUCTION

According to the CDC, sepsis is a potentially fatal, dysregulated immunological response to an infection.[1] According to the most recent WHO data on sepsis, the direct and indirect illness burden is approximately 48.9 million cases and 11 million sepsis-related deaths globally.[2] The Surviving Sepsis Campaign has recommended the administration of appropriate broad-spectrum antibiotics within one hour for patients with definite or probable sepsis with or without shock.[3] This poses a challenge to doctors and allied health-care workers working in government institutions around the country, especially if the patient-to-healthcare worker ratio surpasses the ideal ratio. In one study by Pruinelli et al., short delays in implementing the sepsis bundle had a great impact on the mortality of patients.[4] According to a literature review, for every 1-hour delay in antibiotic administration, it is associated with a 3-7% increase in the odds of a poor outcome.[5-9] Therefore, institutions find ways to improve health service delivery. One such way is the creation of clinical pathways (CPWs).[10] These are tools based on the latest evidence to improve care and outcomes.[11]

In our institution, the sepsis pathway was developed in 2019 to provide efficient and timely management of patients diagnosed with sepsis (defined as qSOFA = >2). In the sepsis pathway, there are bundles of care, both diagnostic and therapeutic, that need to be instituted within one hour upon recognition of sepsis. There are a multitude of ways to assess the effectiveness of clinical pathways, one of which is time-motion studies.[11] Its main purpose in our study is to determine the duration between pre-determined points along the sepsis pathway. By knowing how much time it takes for a task to be completed, we can therefore suggest solutions to improve delivery of that task. Its main aim is to set a standard time for each process and to improve efficiency.[9] Improvement of health service delivery, hopefully, comes with improvement of patient outcomes.

OBJECTIVES

General Objective

To assess the process of initial antibiotic therapy, from the time an antibiotic was ordered to the time the loading dose of the antibiotic was administered, for adult patients diagnosed with sepsis admitted to the Emergency Department (ED) of the University of the Philippines – Philippine General Hospital (UP-PGH).

Specific Objectives

1. To document and outline the current process of initial antibiotic therapy in the Emergency Room of the UP-PGH: request for an antibiotic, procurement, distribution, and administration of the loading dose.
2. To determine the average duration between the important points along the process of initial antibiotic therapy through a review of records.
3. To identify factors affecting the duration from the time antibiotics were first ordered to the time they were administered through chart reviews and interviews.

METHODS

This is a mixed methodology involving a time and motion analysis of the antibiotic procurement and loading dose, and a thematic analysis on the factors that affect the mean/median duration. A descriptive study which determined the mean/median time intervals between important pre-identified points along the process of treating sepsis in the newly-opened emergency room: time sepsis from any etiology was diagnosed by the physician (point A), to the time nurses acknowledge the physician's order and inform the pharmacy of the antibiotic order by way of logging through the electronic system (point B), and the time the antibiotic has been actually administered and logged as given in the electronic record system (point C). The time period covered by the study was from February 1, 2022, to August 31, 2022. This study is divided into two phases and is further described in Table 1.

Setting

The research was carried out in UP-PGH located in the center of Manila, Philippines. The focus group discussion (FGD) and interview took place in certain rooms throughout the institution.

Rationale for Study Site

The emergency room of UP-PGH was identified and designated as the appropriate study site since most patients

Table 1. Workflow of Antibiotic Process and Designated Points

PHASE 1: Time-and-motion study			
1	Time of diagnosis/Time antibiotic ordered (point A)	→	Time physician orders noted by nurse-in-charge (point B)
	When a physician diagnosed sepsis of any origin and ordered antibiotics	→	When the nurse-in-charge acknowledges a doctor's order by entering it into the EMR
2	Time physician orders noted by nurse-in-charge (point B)	→	Time antibiotic was given (point C)
	When the nurse-in-charge acknowledges a doctor's order by entering it into the EMR	→	When the antibiotic was administered to the patient by the nurse-in-charge

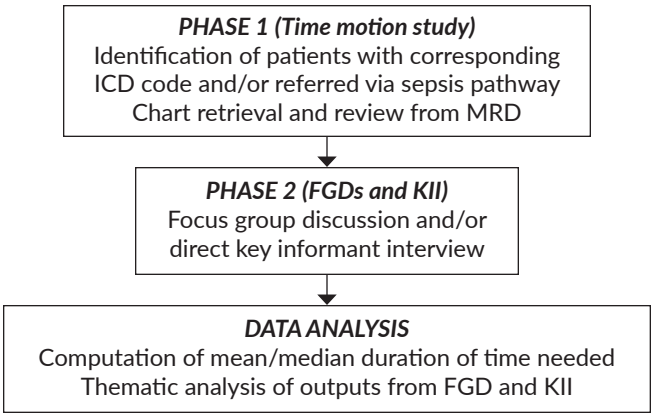

Figure 1. Flow chart of activities.

were newly tagged or diagnosed with sepsis at the ER. It was also chosen since the objective of this study was to identify system and human factors such as the first diagnosis of sepsis and the time antibiotics were ordered by the attending physician and the time they were given by the nurse-in-charge. Interviews and group discussions were conducted throughout UP-PGH for convenience.

Inclusion Criteria for Phase 1

1. Patients aged 19 years old and above
2. Patients diagnosed with sepsis from any infectious etiology, as defined by quick sequential organ failure assessment (qSOFA)
3. Patients who were tagged with ICD code A41.9 (septicaemia unspecified, septic shock) and/or referred to the Infectious Diseases Service via the sepsis pathway
4. Patients admitted to the UP-PGH Emergency Room from February 1 to August 31, 2022

Inclusion Criteria for Phase 2

Hospital staff directly and indirectly involved in dispensing and administering antibiotics will be included in the one-on-one interview and FGD.

1. Physicians-in-charge
2. Nurses-in-charge
3. Pharmacist
4. Institutional workers

Exclusion criteria

1. Patients who have been diagnosed with a certain infection but do not qualify to be diagnosed with sepsis according to the qSOFA definition
2. Patients not admitted to the Emergency Department
3. Cases who received antibiotics before a formal chart order was entered by the physician

Data Management and Analysis

Data Collection

Phase one of our research included patients who were tagged with ICD code A41.9 (septicaemia unspecified, septic shock) and/or referred to the Infectious Diseases Service via the sepsis pathway from February 1 to August 31, 2022. Their charts during the admission were retrieved from the medical records and reviewed thereafter. The following data were obtained from the review of medical records and encoded in a password-protected electronic data collection form:

1. Patient details; name, age/sex, diagnosis, and outcome (discharge, mortality, home against medical advice)
2. Interval from the time sepsis was diagnosed and an antibiotic has been ordered (point A) by the attending physician to the time it was acknowledged by nurse-in-charge/nurse-on-duty (point B).
3. Interval from the time the nurse-in-charge acknowledged the physician's order (point B) to the time it was actually given/logged time (point C).

Phase two of our research focused on group discussions and interviews of direct key informants (KII) who are involved in direct and indirect patient care (Figure 1). Focused group discussions and interviews lasted for around 30 minutes and 15 minutes, respectively. During the interview, a questionnaire (provided in both Filipino and English) explored the informant's practices and experience when procuring and subsequently administering the antibiotic loading dose in septic patients at the emergency room. Different questionnaires were used depending on their designated position (physician, nurse, pharmacist, etc.; see Appendix). From the data gathered, thematic analysis was done to create common themes by identifying texts, words, and phrases that were similar in essence transforming them into codes and eventually themes that would be central to discussion. No video or audio were recorded during the session and data were directly lifted from the collection instrument (questionnaire) which did not change throughout.

Sampling Design and Sample Size

The researchers conducted a time-and-motion study and focused group discussions/one-on-one interviews with nurses, pharmacists, paramedical staff, physicians, and institutional

workers. The study employed an all-comers design wherein all patients tagged with ICD code A41.9 and/or referred via the sepsis pathway from February 1 to August 31, 2022 were included as long as they met the inclusion criteria. Minimum sample size requirement for estimation of mean and median duration between two points of interest was computed using R version 4.0.3. A sample size of at least 385 is needed, to estimate: 1. the mean/median time from sepsis diagnosis to time noted by NIC; 2. Time from NIC noted the order of antibiotics being administered with half-width precision of 2 minutes and 95% confidence level, in a population expected to have a standard deviation of 20 minutes.

Phase two of the study, since it is the descriptive part, the target was at least 5-10 representatives from each identified group – physicians and allied healthcare workers mentioned in the inclusion criteria. For phase two, an all-comers and convenience design was employed to maximize participation in the group discussions. However, the data gathered still cannot be generalized into conclusions.

Study Outcomes

The primary outcome of a time-and-motion analysis is the determination of the amount of time (in hours) it takes for an antibiotic loading dose to be given from the first medical recognition of sepsis to its actual administration. For phase two, collated inputs and development of themes via a thematic analysis.

Data Handling, Processing, Storage, and Protection

Data and other study-related documents collected during the study period, both from phase 1 and phase 2, were stored in a password protected Microsoft excel file and secured folder, respectively. Microsoft Excel was used to make a standardized electronic data form. These are only available to the primary investigator and co-investigator/s. The accumulated data was stored for three months after the research has been completed.

Qualitative Approach and Research Paradigm

The study group utilized a combination of field research, grounded theory, and narrative research. In phase 1 of the study, as the group establishes that there is indeed a delay in antibiotic loading doses in septic patients, we tried to establish linkages between factors using data gathered from observation by key personnel (pharmacists, nurses, physicians, and institutional workers). Coding was employed to categorize qualitative data into common themes. When decoding and analyzing the data, a 'pragmatist paradigm' was practiced, focusing on outcomes and combining both qualitative and quantitative data to form insights on the matter.

Data Analysis Plan

Data gathered were from chart and log book review. The mean and median duration, in minutes and hours, between intervals from specified points in the procurement and administration of antibiotics was described as mean and standard deviation or median and interquartile range. The normality of distribution of the dataset was assessed by the Shapiro-Wilk test of normality which showed a non-normal distribution pattern. Data was tabulated in MS Excel file in the format of date (mm-dd-yyyy) and time (hh:mm). Output from the focused group discussion and direct key informant interviews were obtained then analyzed using thematic analysis via coding with the help of a third-party professional statistician. These codes actually allowed us to sort information easily, and to analyze data which uncovered similarities, differences, and relationships among segments to develop our themes. The questionnaire was not validated and was created just for this research's purpose.

Ensuring Quality of Qualitative Data

The risk of handling qualitative data is in its nature that it is subjective. As part of the researchers' effort to minimize bias, we recognize the benefit of understanding the pillars of trustworthiness in qualitative data. Close observation and comprehensive study of the process were done to ensure we get the correct data and regularly communicate with each other to recognize personal biases. Triangulation was also used during data collection, involving both physicians (residents and fellows) and our allied healthcare workers to get different perspectives. An audit trail was also created during data collection through attendance checking, documenting details of the interview and group discussion, and how discussions were conducted.

Ethical Considerations

Our study is divided into two phases. In the first phase, which is the time-and-motion analysis, there are no direct or indirect interactions between the patient and the researchers. Only chart reviews were done and researchers looked at time stamps on the electronic record. In the second phase, the participants who went with the interview were oriented and signed an informed consent prior to proceeding with the study. Only hospital case numbers or ID numbers were collected as subject identifiers which were stored in password-protected master list and were only accessible to the investigators and our adviser. The files were eventually deleted as part of the measures to prevent leakage of private information. Both phases of the study were approved by the institution's ethical review committee (UPM-REB). This analysis is also in accordance with the Declaration of Helsinki, the 2012 Data Privacy Act, and the 2017 National Ethical Guidelines for Health and Health- Related Research.

Researcher Characteristics and Flexibility

We recognize that a wide range of circumstances, such as overcapacity and a high staff-to-patient ratio, influence the result. Therefore, versatility was applied when drawing the conclusion. Additionally, we would like to make it clear that we do not specialize in combining qualitative and quantitative

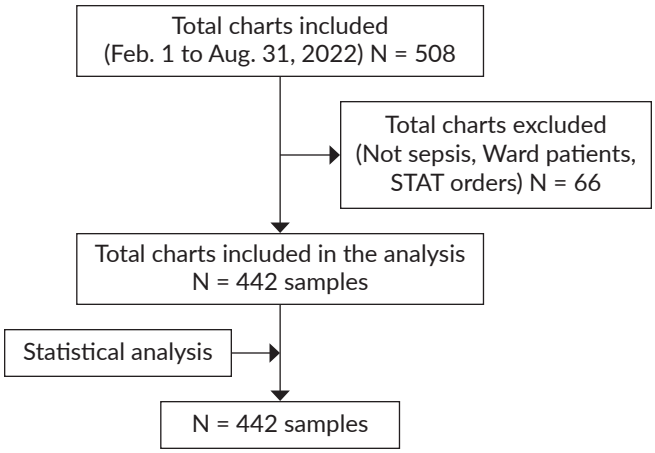

Figure 2. Data collection.

approaches. The authors also assert that they have no personal connection to the study subjects.

Informed Consent

Approval from the institution's ethical review board was requested for charts to be reviewed from medical records. It was the responsibility of the group to ensure anonymity of the patient's data and ensure data protection. Informed consent was obtained from interviewees – nurses, pharmacists, paramedical staff, physicians, prior to interview.

RESULTS

The clinical characteristics of the participants of the study were summarized by descriptive statistics in Table 2. Age was described as median and interquartile range. Sex and disposition were described as frequency and percentage. A total of 508 adult patients referred via the sepsis pathway and/or those tagged with ICD code A41.9 (septicaemia unspecified, septic shock) were identified. Only 442 of them met the inclusion criteria while 66 were excluded for various reasons (Figure 2). The all-cause mortality of all qualified cases was 64.7%.

Three points in the sepsis pathway were designated as follows: Point A: time of sepsis diagnosis and antibiotic was first ordered, Point B: time nurse noted the order, Point C: time of administration of antibiotic. The time elapsed between these designated points were described as median with interquartile range. Data analysis was performed using Stata version 17. The distribution of normality of numerical variables was assessed by the Shapiro-Wilk test of normality. Missing values were neither replaced nor imputed. The median time it took for the nurse-in-charge to acknowledge the antibiotic order (point A to B) is 0.73 hours (IQR 0.27-1.7). Meanwhile, the median time between acknowledgment of the order to administration of antibiotics is 1.94 hours (IQR 0.83-6.63). The median time of diagnosis-to-first dose (point A to C) is 3.53 hours (IQR 1.59-7.96), and the corresponding mean duration (point A to C) is 5.72 hours (Table 3). From all cases, 44.6% and 12.4% of antibiotics were first loaded within 3 hours and within 1 hour after diagnosis, respectively.

Table 2. Baseline Characteristics and Disposition of the Participants in the Study

	Median/ Frequency	IQR/ %
Age	59	21
Sex		
Male	229	50.66%
Female	213	51.70%
Disposition		
Discharged	132	26.90%
Home per request	40	8.10%
Transfer to other hospital	1	0.20%
Mortality	335	64.70%

Table 3. Duration (hours) between the Important Points along the Process of Initial Antibiotic Therapy

Motion	Median	IQR
Time from sepsis diagnosis and antibiotic was first ordered to nurse noting the order	0.73	1.38
Time from nurse acknowledging the order to antibiotics administration	1.94	4.67
Over-all	3.53	5.72

A total of two FGDs were conducted - one with residents together with the fellows and another one with pharmacists. A total of 12 allied healthcare workers (pharmacists, nurses, and institutional workers) were interviewed and recruited for phase 2. A swim lane diagram on the antibiotic procurement and administration (Figure 3) was presented to the group or interviewee. Identification of redundant processes and barriers to effective healthcare delivery was done and inputs from the direct key informant interviews were collated.

Collated data was then analyzed and interpreted with thematic analysis to develop three central themes. Theme 1 discusses how we request antibiotics and our common practices while the second and third themes tackle strong and bad qualities of procurement of antibiotics and treatment of sepsis, respectively (Table 4).

DISCUSSION

In the management of overwhelming infection or sepsis, studies have established that timely administration of antibiotic loading dose improves patient outcomes (i.e., mortality).[3] Hence, health institutions have constructed ways on improving health service delivery such as creation of clinical pathways. For this reason, the sepsis pathway was developed to improve and guide management at the ER level. Part of the 1-hour bundle (both diagnostics and treatment) is for the antibiotic loading dose be given within one hour from recognition of sepsis. Our research showed that all loading doses of antibiotics ordered from February to August

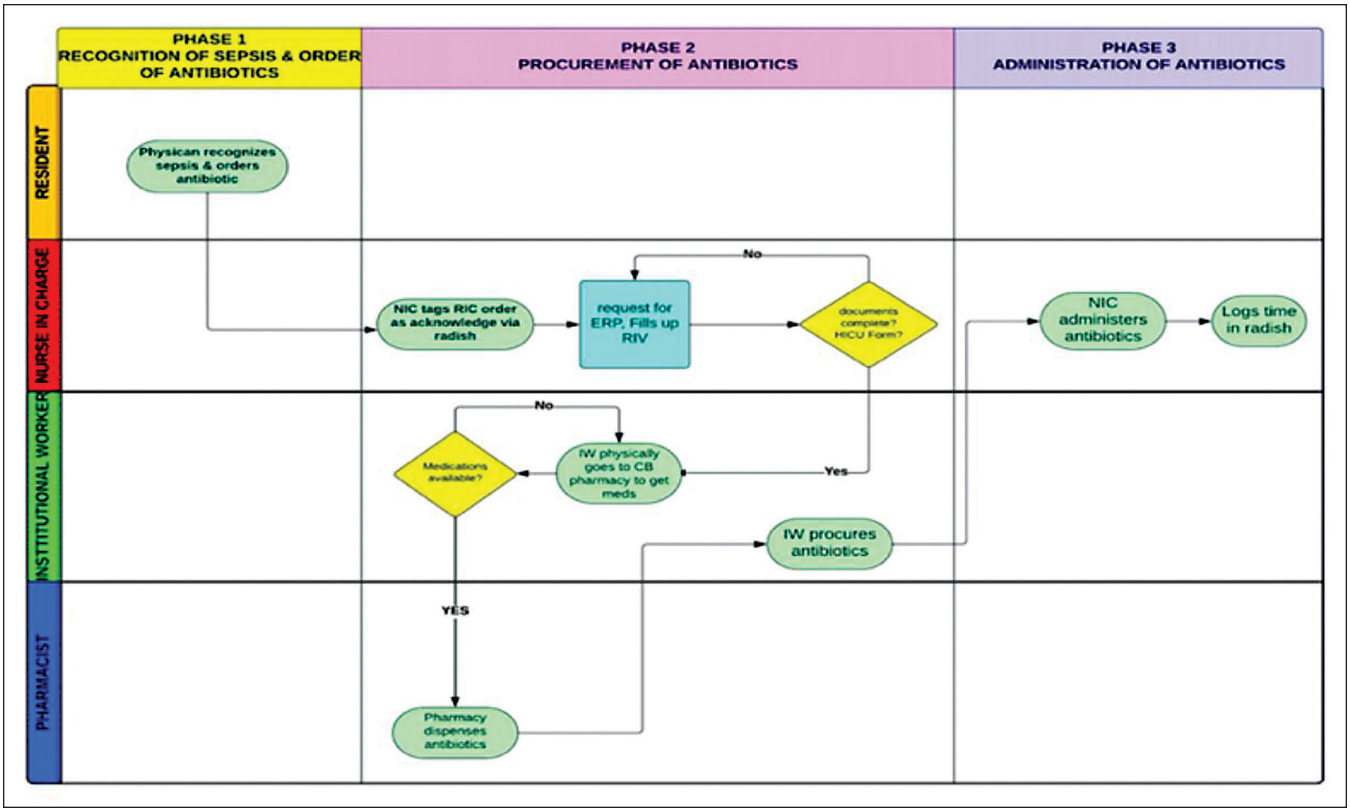

Figure 3. Swimlane diagram showing the antibiotic procurement to administration.

Table 4. Description of Themes and Summarized Points of each Theme

Theme	Descriptions	Points raised
THEME 1. Requesting Antibiotics: Common Practices	The first theme focuses on the common practices of the healthcare workers in requesting antibiotics for sepsis patient.	• Most commended the current system as it entails the use of electronic • medical records. Fellow #2 mentioned "easy access for ordering of antibiotics at the ER" as a way to describe our EMR. • Some prefer to communicate personally with the hospital staff to ensure that the antibiotics are immediately given. Resident #1 mentioned "Occasionally, if really needed to personally communicate with staff to carry out orders."
THEME 2. Processing Requests for Antibiotic Use: Boosters and Bottlenecks	Once the antibiotics are requested, the process for procuring them ensues. In this part of the system, there are facilitators and barriers to the immediate access and dispensing of these medications.	• Dispensed in a fast manner due to the electronic records system which also • enables the tracking of these medication requests until their dispensing at the hospital pharmacy. • Hospital pharmacy is very accessible and can be easily contacted via phone call to confirm the dispensing of the medications. • 4 out of 7 nurses mentioned that they encountered delays from the • hospital's infection control unit in their approval of the requested medications for dispensing. • Practice of some nursing staff to only request all patient medications after they have ended their shift, which leads to delays in the logging of these medication requests.
THEME 3. The System of Antibiotic Treatment for Sepsis in the Emergency Room: The Good and the Bad	After the much-needed medications are dispensed, it is only vital to look at the overall system of antibiotic treatment for sepsis patients in the hospital, pointing out those that facilitate system efficiency and those that hinder the system from working toward the same purpose.	• For beneficial factors, it was regarded by most of the healthcare workers that the electronic recording of antibiotic requests and dispensing makes the administration of antibiotics to sepsis patients easier and more accessible. • Favorable stock of medications, which enables immediate dispensing of these medications to patients especially those in urgent need of it. • Everyone interviewed agreed that the existing human resources of the hospital must be augmented. Especially nurses who want to improve "Nurse-patient ratio" and "Manpower".

2023, only 12.4% were given within an hour and 44.6% were given within 3 hours of sepsis diagnosis. Notably, 25.3% of antibiotics were given for more than 8 hours after sepsis diagnosis. Breaking down the sepsis pathway into designated points that has time stamps in the electronic medical record allows us to identify where the delay is longer. The point A to B (recognition of sepsis-to-acknowledgement of order) is approximately less than an hour in more than half of cases (60%) and from point B to C (time of acknowledgement to administration of medication) lasts around 2 hours, which is relatively longer than the former. These findings are alarming considering the 65% all-cause mortality rate among patients with sepsis admitted during this period. However, no conclusion should be made since no analysis on correlation was done between delays in antibiotic administration and all-cause mortality.

Improvement of a system starts with acknowledging that there are indeed problems that need to be addressed. Hence, efforts were made to discuss the data with identified key informants - institutional workers, nurses, and physicians. Among those discussed were things that hinder and elevate the process. There were mentions of the electronic medical record (EMR) system as a means of accelerating communication among doctors, nurses, and pharmacists compared to traditional use of hand written orders. This has allowed multiple users to access patients' charts simultaneously within the hospital. The electronic recording, requesting, and dispensing of antibiotics were also commended by the interviewees in this study, as it eliminated the traditional practice of filling out long paper forms and physically dropping them to a designated area in the hospital. However, the over reliance on the EMR can be disadvantageous at times of power outages or the occurrence of technical errors or bugs, as mentioned, particularly by our nurses and residents. Other concerns were about human resources, governance, information, service delivery, and finances. Work practices among allied healthcare workers significantly impact the pace of antibiotic dispensing at the different levels. Pharmacist respondents mentioned that incomplete forms and chart orders with incomplete details (for example, unclear frequency or dosages) resulted in delays in dispensing antibiotics, particularly the restricted ones. This necessitated the pharmacists to follow up with the nurse or doctor who submitted the form with missing information, causing further delays. Some resident physicians interviewed observed that, in some instances, medication orders across all patients handled by a nurse were consolidated and requested from the pharmacy only at the end of each shift. As a result, antibiotics, including those ordered early in the shift, would not be formally requested from the pharmacy until hours later. As staff have higher workload than recommended, grouping similar tasks tends to improve efficiency at the expense of urgent delivery of some interventions, such as antibiotics. Consistent among all healthcare workers was the issue on human resources or personnel. This was recurrently mentioned as the main root of delays in sepsis management at the ER. It must also be underscored that such a lack will not occur without the day-to-day high influx of patients at the ER.

Studies on health services are of high value in terms of improving delivery and ultimately improving outcomes. In our study, we have, at least, identified that there are gaps despite guideline-based delivery of health services. Change always starts with acknowledging there are things that need improving.

Limitations of the Study

Limitations include its reliance on the patient's electronic records for completeness and accuracy. Only those patients referred to the sepsis pathway and those tagged with an appropriate ICD code were identified and included in the study. Failure to assign cases of sepsis with the appropriate ICD code may lead to non-inclusion of the case in the study. The time period covered in this study is only from February to August 2023, which may not be reflective of the current situation, as systems may have changed through time. Improper documentation of assessment and management as well as discrepancies in time stamps also led to exclusion of such cases from the study. In retrospect, it was imperative to involve hospital administrators in future focus group discussions or interviews.

Despite these limitations, they do not significantly change the study's findings and conclusions.

CONCLUSIONS

In more than half of the study population, the target time from diagnosis to loading dose of less than one hour was not reached. The discussions made with ER team members underscored issues concerning human resource, information, service delivery, and governance as possible reasons for the outcomes. Ultimately, the significant delays in sepsis treatment at the ER call for system-wide improvements to hasten the process of antibiotic delivery and reduce the poor outcomes associated with sepsis.

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Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

All authors declared no conflicts of interest.

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REFERENCES

1. Srzić I, Nesek Adam V, Tunjić Pejak D. SEPSIS DEFINITION: WHAT'S NEW IN THE TREATMENT GUIDELINES. Acta Clin Croat. 2022 Jun;61(Suppl 1):67-72. doi: 10.20471/acc.2022.61.s1.11. PMID: 36304809; PMCID: PMC9536156.
2. World Health Organization, Sepsis [Internet]. 3 May 2024 [cited 2024 Oct 1]. Available from: https://www.who.int/news-room/fact-sheets/detail/sepsis
3. Khan P, Divatia JV. Severe sepsis bundles. Indian J Crit Care Med. 2010 Jan;14(1):8-13. doi: 10.4103/0972-5229.63028. PMID: 20606903; PMCID: PMC2888324.
4. Pruinelli L, Westra BL, Yadav P, Hoff A, Steinbach M, Kumar V, et al. Delay Within the 3-Hour Surviving Sepsis Campaign Guideline on Mortality for Patients With Severe Sepsis and Septic Shock. Crit Care Med. 2018 Apr;46(4):500-505. doi: 10.1097/CCM.0000000000002949. PMID: 29298189; PMCID: PMC5851815.
5. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006 Jun;34(6):1589-96. doi: 10.1097/01.CCM.0000217961.75225.E9. PMID: 16625125.
6. Ferrer R, Martin-Loeches I, Phillips G, Osborn TM, Townsend S, Dellinger RP, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. Crit Care Med. 2014 Aug;42(8):1749-55. doi: 10.1097/CCM.0000000000000330. PMID: 24717459.
7. Kalil AC, Johnson DW, Lisco SJ, Sun J. Early goal-directed therapy for sepsis: a novel solution for discordant survival outcomes in clinical trials. Crit Care Med. 2017;45(4):607-14. doi:10.1097/CCM.0000000000002235.
8. Seymour CW, Gesten F, Prescott HC, Friedrich ME, Iwashyna TJ, Phillips GS, et al. Time to Treatment and Mortality during Mandated Emergency Care for Sepsis. N Engl J Med. 2017 Jun 8;376(23):2235-2244. doi: 10.1056/NEJMoa1703058. Epub 2017 May 21. PMID: 28528569; PMCID: PMC5538258.
9. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021 Nov;47(11):1181-1247. doi: 10.1007/s00134-021-06506-y. Epub 2021 Oct 2. PMID: 34599691; PMCID: PMC8486643.
10. Rotter T, de Jong RB, Lacko SE, Ronellenfitsch U, Kinsman L. Clinical pathways as a quality strategy. editors. Improving healthcare quality in Europe: Characteristics, effectiveness and implementation of different strategies [Internet]. Copenhagen (Denmark): European Observatory on Health Systems and Policies (Health Policy Series, No. 53.). 2019 [cited 2023 Nov 8]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK549262/
11. Kalne PS, Mehendale AM. The Purpose of Time-Motion Studies (TMSs) in Healthcare: A Literature Review. Cureus. 2022 Oct 3;14(10):e29869. doi: 10.7759/cureus.29869. PMID: 36348835; PMCID: PMC9629289.