Pontifícia Universidade Católica
do Rio de Janeiro

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Assessing outcomes of critically ill patients with Sepsis using Process Mining

Dissertação de Mestrado

Dissertation presented to the Programa de Pós-Graduação em Engenharia de Produção of PUC-Rio in partial fulfillment of the requirements for the degree of Mestre em Engenharia de Produção.

Advisor: Prof. Fernanda Araujo Baião
Co-advisor: Prof. Igor Tona Peres

Rio de Janeiro
September 2024

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Bibliographic data

Costa, Rayane Silva

Assessing outcomes of critically ill patients with sepsis using process mining / Rayane Silva Costa ; advisor: Fernanda Araujo Baião ; co-advisor: Igor Tona Peres. – 2024.

61 f. : il. color. ; 30 cm

Dissertação (mestrado)–Pontifícia Universidade Católica do Rio de Janeiro, Departamento de Engenharia Industrial, 2024.

Inclui bibliografia

1. Engenharia Industrial – Teses. 2. Mineração de processos. 3. Sepse. 4. Análise de conformidade. I. Baião, Fernanda Araújo. II. Peres, Igor Tona. III. Pontifícia Universidade Católica do Rio de Janeiro. Departamento de Engenharia Industrial. IV. Título.

CDD: 658.5

Acknowledgements

I would like to express my deep gratitude to everyone who made this dissertation possible. First, I thank my advisor, Fernanda Baião, and my co-advisor, Igor Peres, for their guidance, patience, and invaluable support throughout this academic journey.

I would like to dedicate a special thanks to my parents, Izabel and Marcos, and my sister, Ana Júlia. You are my foundation and my safe harbor. Thank you for all the love, understanding, and unconditional support you have always given me. Without you, I would not have come this far.

To my fiancé, Tiago, my eternal gratitude for your companionship, patience, and encouragement. Your constant presence in my life, even in the most challenging moments, was essential for the completion of this work. I am immensely grateful to have you by my side.

To my in-laws, Tania e José, thank you for your welcome and affection. Your support and encouragement were fundamental throughout this process. I am very grateful to be part of such a special family.

I also thank my classmates, especially Rafaela, for the collaboration and exchange of ideas that enriched my academic journey and whose friendship has extended into life.

To the professors and staff PUC-Rio, I appreciate the technical and administrative support, always willing to help.

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001.

Finally, I dedicate this dissertation to all those who, in some way, contributed to my personal and professional growth.

Thank you very much!

Abstract

Costa, Rayane Silva; Baião, Fernanda Araujo (Advisor); Peres, Igor Tona (Co-Advisor). **Assessing outcomes of critically ill patients with Sepsis using Process Mining.** Rio de Janeiro, 2024. 61p. Dissertação de Mestrado - Departamento de Engenharia Industrial, Pontifícia Universidade Católica do Rio de Janeiro.

Sepsis is the leading cause of death in intensive care units (ICUs) worldwide. In Brazil, the mortality rate in ICUs reaches 65%. This study evaluated the behavior of the care pathways for patients with sepsis and in a critical status of the Beth Israel Deaconess Medical Center, Boston-USA intensive care units, from the MIMIC-IV database. This available database contains data from more than 200,000 patients registered between 2008 and 2019. After applying the selection criteria, 7,790 cases were studied. Using process mining techniques, the conformance of treatment executions with therapeutic recommendations was analyzed, followed by a comparative analysis of outcomes concerning the adherence to the sepsis protocol. The results showed an overall average compliance of 92%. The observed LOS was less than the expected LOS, and the mortality rate was higher than the expected mortality rate. An analysis of SMR and SRU indicators confirmed the variation from expected values, suggesting that the sepsis treatment process in this unit requires some adjustments and that compliance analysis may not be the best way to evaluate this type of process.

Keywords

Process mining, Sepsis, Conformance analysis.

Resumo

Costa, Rayane Silva; Baião, Fernanda Araujo (Orientadora); Peres, Igor Tona (Co-Orientador). **Análise de desfechos de pacientes críticos com sepse usando Mineração de Processos.** Rio de Janeiro, 2024. 61p. Dissertação de Mestrado - Departamento de Engenharia Industrial, Pontifícia Universidade Católica do Rio de Janeiro.

A sepse é a principal causa de morte em unidades de terapia intensiva (UTIs) no mundo. No Brasil, a taxa de mortalidade nas UTIs atinge 65%. Este estudo teve como objetivo avaliar o comportamento dos processos de atendimento a pacientes com sepse em unidades de terapia intensiva do Beth Israel Deaconess Medical Center, Boston-EUA, a partir da base de dados MIMIC-IV. Esta base de dados está disponível publicamente e contém dados de mais de 200.000 pacientes registrados entre 2008 e 2019. Após aplicação dos critérios de inclusão 7.790 casos foram estudados. Usando técnicas de mineração de processos foi analisada a conformidade das execuções de tratamento com as recomendações terapêuticas e, em seguida, foi realizada uma análise de comparação dos desfechos em relação ao atendimento do protocolo de sepse. Os resultados mostraram uma média geral de 92% de conformidade. O LOS observado foi menor que o LOS esperado e a taxa de mortalidade foi maior que a mortalidade esperada. Uma análise sobre indicadores SMR e SRU confirmou a variação em relação aos valores esperados, sugerindo que o processo de tratamento de sepse desta unidade precisa de algumas adequações e que a análise de conformidade pode não ser a melhor forma de avaliar este tipo de processo.

Palavras-chaves

Mineração de processos, Sepse, Análise de conformidade.

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1 Introduction

Sepsis is one of the leading causes of death in intensive care units (ICU). There were 48,9 million sepsis cases and 11 million deaths related in the world in 2017, with 240,000 deaths in Brazil alone, which reveals a mortality rate of 65% (Rudd et al. 2020; Gao et al. 2024). These numbers exceed, for example, the number of myocardial infarctions or all cases of death combined with cancer in the lungs, breasts, and prostate (Bao, Deng, and Zhao, 2023).

Sepsis is a health condition that is necessarily treated in ICUs. In sepsis, the patient's immune system has an extreme response to an infection. The body's reaction to fight infection triggers inflammation, causing damage to several organs; this behavior differentiates sepsis from an infection. In some cases, the body's aggressive response can trigger a systemic reaction, inducing several organs to malfunction, leading to sepsis shock, which is one of the most severe conditions of the disease (Singer et al. 2016). Considering this serious scenario, ICU functioning is essential for good patient outcomes.

Considering the sepsis treatment as a process, another perspective of ICU well-functioning could be the evaluation of its actual process executions. Considering the conformance analysis of sepsis treatment as a process, which is still a research opportunity, this work aims to (i) evaluate the conformance of the real process compared with literature guidelines of sepsis treatment. Then, (ii) analyze how process conformance is related to patients outcomes.

This work will be applied at MIMIC-IV, a freely available database of patients who were admitted to the critical care units of the Beth Israel Deaconess Medical Center, Boston (Johnson et al. 2023; A. L. Goldberger et al. 2000). To achieve this, the complementary objectives of this research are:

- Design the standard process of sepsis treatment, based on literature guidelines.
- Develop an RD (relational diagram) to expand MIMIC-IV comprehension.

Following this introductory section, the research is divided as follows: Chapter 2 describes the main subjects in literature; Chapter 3 comprises the research steps, tools, and methods used in this research; Chapter 4 presents the main results and discusses them; and finally, Chapter 5 states the conclusion and final considerations for future work, followed by the References and Appendixes.

2 Background

This section presents the main subjects of this work.

2.1. Process mining

Organizations are inherently process-oriented, with each product or service following a sequence of activities and steps for its delivery (Ulrich and Eppinger, 2016). Organizations often rely on BPMN tools to maintain standardization and clearly define these processes. These tools map the processes and provide a structured framework, instilling confidence in the standardization of the activities (Ter Hofstede et al., 2010). These tools describe how the process should be structured imperatively (Pesic, Schonenberg, and Van Der Aalst 2007).

Although these tools fulfill their role of mapping the expected standard process, day-to-day executions (hereafter also named traces) can reveal a different behavior. Process mining comprises a set of data science techniques that can discover the actual process, verify compliance based on a standard, or even promote its improvement from the systemic records of their executions (W. M. P. van der Aalst 2011).

Process mining techniques execution needs an event log structure. At least three elements are necessary as components of an event record in the log: a unique identifier of the trace, the event title, and a timestamp; this is illustrated in Figure 1. According to W. M. P. van der Aalst (2011), a process event represents the register of an activity execution. An event can include other attributes, such as costs, the name of the agent, their respective role in the process, etc. A process trace, or case, is a set of events describing its sequence and representing an instance of the process execution. An event log comprehends a set of process traces of a unique business process execution.

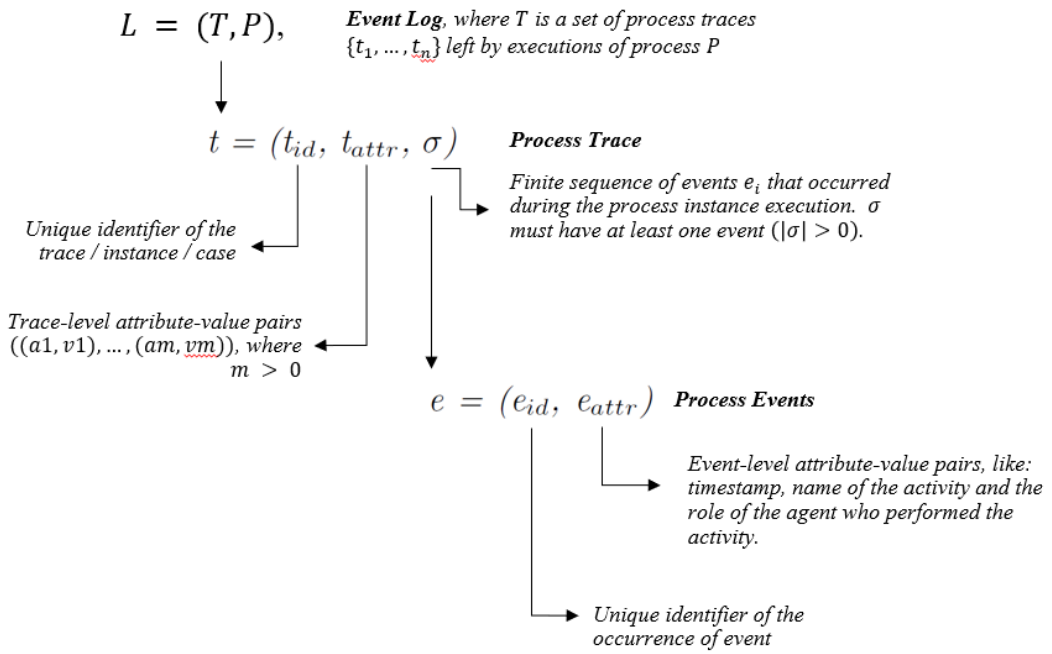

Figure 1 - Event log composition - adapted from W. M. P. van der Aalst (2011). Considering an event log $\boldsymbol{L}$, composed of a set of traces $\boldsymbol{T}$ of a business process P, $\boldsymbol{t}$ has a unique identifier ($\boldsymbol{t_{id}}$), a set of events $\boldsymbol{\sigma}$, and the trace's attributes. On the other hand, $\boldsymbol{e}$ is a set of events with a unique identifier ($\boldsymbol{e_{id}}$) and its attributes.

Table 1 illustrates an example of an event log. The case_id is the trace identified as “20811838_36577352", and a set of nine events is described with their timestamp attribute. In this example, the patient is admitted to the ICU at 21/08/2117 02:02, a set of treatments are executed, and at 11/09/2117 11:53, the patient is discharged from the ICU.

Table 1 - Event log example

Case_id	Event id	Activity	Timestamp
20811838_36577352	ppw00001	#01-ICU admission	21/08/2117 02:02
20811838_36577352	ppw00002	#02-Check blood lactate	04/09/2117 03:17
20811838_36577352	ppw00003	#03-Perform blood culture	02/09/2117 15:32
20811838_36577352	ppw00004	#03-Perform blood culture	04/09/2117 09:13
20811838_36577352	ppw00005	#04-Administrate antibiotics	02/09/2117 20:00
20811838_36577352	ppw00006	#04-Administrate antibiotics	02/09/2117 21:00
20811838_36577352	ppw00007	#04-Administrate antibiotics	04/09/2117 09:00
20811838_36577352	ppw00008	#04-Administrate antibiotics	11/09/2117 10:00
20811838_36577352	ppw00009	ICU discharge	11/09/2117 11:53

A set of traces with at least one common attribute and an equal sequence of events comprehends a variant. With a set of variants, the business process can be analyzed in order to identify, for example, patterns, deviations, or gaps (W. Van der Aalst 2016).

2.1.1. Process Mining and sepsis research

The study of process mining in health care has increased in the last few years, but there are still few studies relating to process mining and sepsis. Bakhshi, Hassannayebi, and Sadeghi (2023) used process mining through heuristic miner and inductive miner methods to discover the process of emergency, admission, and discharge of patients with sepsis diagnosis from a hospital in the Netherlands. They highlighted the difficulties of obtaining a concrete comprehension of the process structure and identifying the relevant process.

Noshad, Rose, and Chen (2022) proposed a mixed graphical and quantitative process mining approach to identify patterns and best practices from electronic health records event logs. Their results enable the visualization of processes' status and most common paths. They also enable conformity evaluation based on internal hospital guidelines.

From the events recorded by the hospital's ERP system, Kukreja and Batra (2017) examined the event log of sepsis cases to investigate the healthcare process, identify the control flow, and evaluate conformance. The results provide an update on hospital internal procedures.

Neira (2018) in order to study the optimization of care pathways in sepsis treatment, had identified a lack of process mining techniques supporting this kind of study. The author developed a technique capable of identifying and highlighting a set of activities that provide positive and negative outcomes considering multiple criteria simultaneously.

Mannhardt and Blinde (2017) worked to discover a process model of patient trajectories from a Dutch hospital. The authors highlighted how process mining can be useful in understanding patient flow; however, process discovery can also produce unsuitable models that interfere with understanding.

This work aims to go beyond the proposals addressed in these previous works and evaluate the relationship between process conformance and sepsis treatment outcomes.

2.1.2. Process Mining Tools

Some computational tools can be used to support process mining and its applications. Three of them, ProM, Disco, and PM4Py, were used in this work. These tools are described below.

ProM is a framework that supports a variety of process mining techniques in the form of plugins (Van Dongen et al. 2005). It is a free-of-charge platform, and researchers and developers can contribute to creating new plugins. The plugins can be installed according to demand using the ProM Package Manager. This platform allows researchers to, for example, convert event log to a .XES file and execute process mining discovery, and conformance checking. This tool, however, does not have a user-friendly interface.

Disco is a process mining platform from Fluxicon with a more friendly interface and no need for knowledge of a programming language (Günther and Rozinat 2012). However, Disco is not a free tool, and the academic license has some limitations, such as the low number of events processed in a unique event log and the lack of a conformance-checking analysis tool.

PM4Py is a free-access Python library that offers everything from process discovery to conformance analysis and evaluation (Berti, van Zelst, and Schuster, 2023). It also offers support for BPMN tools and streaming processes; however, the user needs previous knowledge in Python and a more solid knowledge of process mining. PM4Py has a variety of implemented approaches, including support to BPMN and process tree creation, Alpha Miner and Inductive Miner to process discovery, and for evaluation of the log model in conformance checking, Fitness token-based replay, for example. The use of this last one will be presented in this work and is defined by Berti and van der Aalst (2020) as one of the most important techniques that act on Petri nets; it promotes a comparison of the behavior of a process execution with the behavior allowed by a process model. The replay considers the activities of the trace in order and matches the current activity with the model. After calculating the number of arcs, the same number of tokens is added to the count. The algorithm tries to match the transitions in the model with the activities in the event log; if the activity is not in the current marking, the algorithm starts searching for a transition in the model that corresponds with this activity. Considering that the transition of the current marking could not be fired, the marking is

modified to enable it by inserting the token(s). At the end of the replay, if the marking reached differs from the final one, then missing tokens are inserted to enable the conclusion. The number of missing tokens is used to calculate the percentage of conformance.

2.2. Sepsis

Sepsis is a life-threatening organ dysfunction caused by an aggressive body response to an infection (Singer et al. 2016). Early diagnosis of sepsis is essential for the immediate start of treatment, increasing the patient's recovery expectation.

To enable this, a task force was conducted by Singer et al. (2016) to update definitions and expand the list of diagnostic criteria. This work was called Sepsis-3 and presents an update on sepsis and septic shock definitions from previous publications (Levy et al. 2003; Bone et al. 1992). The authors analyzed the Sequential Organ Failure Assessment (SOFA), a scoring mechanism for rapid diagnosis of sepsis. SOFA is widely used to quantify abnormalities observed through clinical analysis and laboratory data leading to the diagnosis of sepsis (Singer et al. 2016). However, it is essential to note that it does not intend to predict results but rather to describe a sequence of typical and known complications of this disease (Vincent et al. 1996). To establish an even faster mean for diagnosis and, consequently, rapid start of the appropriate treatment, the SOFA was adapted to a version with three indicators and was called quickSOFA (qSOFA), a rapid sequential assessment of organ failure.

The qSOFA consists of three indicators that can be analyzed in the patient's bed and indicate a high probability of sepsis. Singer et al. (2016) highlight that the qSOFA analysis should consider the sum of one point (from zero) for each indicator whose reference value is reached. A diagnosis of sepsis is highly likely if the final sum shows two or more points. Table 1 presents the indicators of qSOFA and their reference values.

Table 2 - qSOFA Indicators (Adapted from de Singer et al. (2016)).

Indicator	Reference
Respiratory frequency	≥ 22/min
Systolic blood pressure	≤ 100mmHg
Altered mental status	Glasgow coma scale < 15

A point is summed for each indicator whose reference value has reached. The sepsis diagnostic is highly likely if the final sum equals or exceeds two.

2.2.1. SRU and SMR

In the comparison of different ICU efficiencies, a bias can be produced considering differences among the patient populations; these two standardized indicators try to eliminate this bias (Walton and Padkin 2007).

The SRU is the quotient of the observed length of stay (LOS) and expected LOS. Expected LOS is calculated as the total number of days of patients' stays divided by the number of surviving patients. SMR is obtained by calculating the quotient of the number of observed deaths for an ICU and predicted mortality, severity-adjusted by SAPS3 (Walton and Padkin 2007;Rothen et al. 2007). Both indicators will be explored in Chapter 3.

2.3. SAPS3

SAPS3 deals with risk factors and outcomes in an intensive care unit (ICU) to promote a risk adjustment model (Moreno et al. 2005). SAPS3 is composed of 21 items distributed since ICU admission to body conditions, surgical information, and comorbidities. The sum of all these conditions indicates a score of the patient risk:

1 ICU admission
2 Age, years
3 Comorbidities
4 Length of stay before ICU admission, day
5 Intrahospital location before ICU admission
6 Use of major therapeutic options before ICU admission
7 Planned or unplanned ICU admission
8 Reason(s) for ICU admission
9 Surgical status at ICU admission

10 Anatomical site of surgery
11 Acute infection at ICU admission
12 Glasgow Coma Scale/Score
13 Total bilirubin, mg/dL (µmol/L)
14 Body temperature, °C (°F)
15 Creatinine, mg/dL (µmol/L)
16 Heart rate, beats/min
17 Leukocytes, G/L
18 Hydrogen ion concentration (lowest), pH
19 Platelets, G/L
20 Systolic blood pressure, mm Hg
21 Oxygenation

3 Methods

This study performed an ICU conformance analysis on data from patients diagnosed with sepsis and in critical condition at Beth Israel Deaconess Medical Center. Medical Information Mart for Intensive Care (MIMIC)-IV, containing retrospective deidentified medical data of patients admitted to the emergency department or intensive care unit (Johnson et al. 2023; A. Goldberger et al., n.d.).

Beyond the objectives set out in this work, a script to create the event log and a script to calculate SAPS 3 based on MIMIC-IV were developed. All the algorithms are publicly available at https://github.com/raycosta-s/mimic_iv.

The scripts to create an event log and to calculate the SAPS3 score were developed using R Studio 4.3.1 and MS Power BI 2.127.1327.0. The conformance analysis was performed using the PM4Py library in Python 3.11. Petri net was developed in Yasper 1.0 and the process mining was performed using Disco 4.0.8 and ProM 6.12. A relational diagram was created using a canvas tool called Miro®.

This study encompasses the following six macro steps that will be explored: the creation of relational diagrams, data collection and preparation, descriptive analysis, creation of event logs, conformance analysis, and sensitivity analysis using severity-adjusted measures, as shown in Figure 2. These steps will be described below.

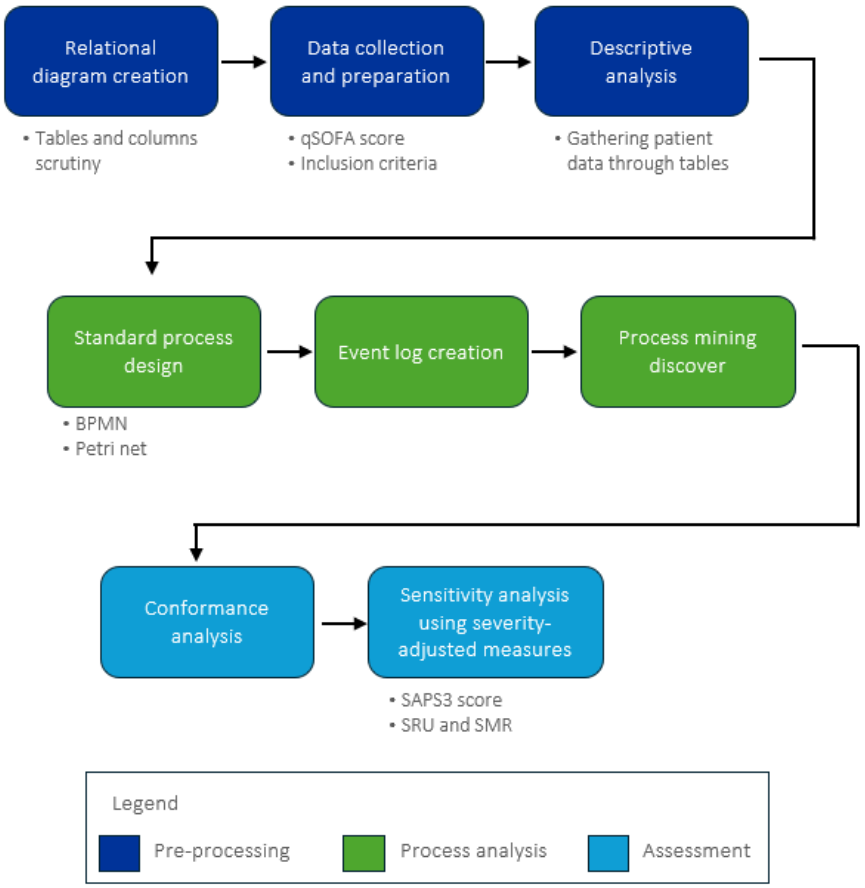

Figure 2 - Study macro steps

3.1. Relational diagram - RD

MIMIC-IV is an extensive database composed of three modules and many tables (Johnson et al. 2023; A. Goldberger et al., n.d.). To help understand how the tables are related to each other and to better detect how these relations could be used in data analysis, a relational diagram (RD) was created.

An RD is composed of elements that describe the relationships these entities have with each other, following the RD data model (Elmasri and Navathe 2015). Figure 3 presents some of these elements that were used to represent the relationships in the MIMIC tables.

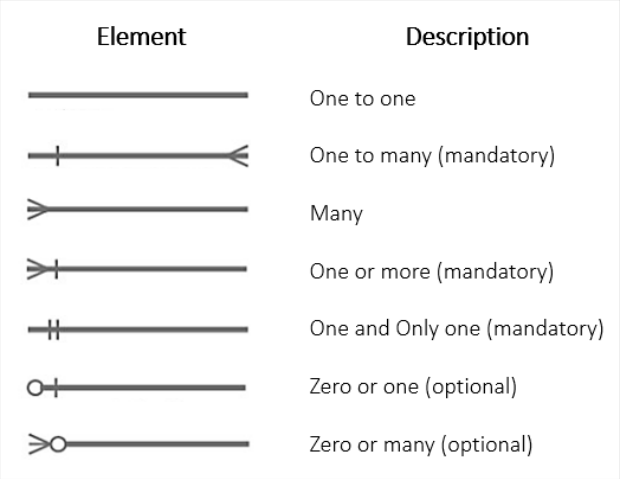

Figure 3 - RD Elements

The model was developed using an online canvas tool called Miro®, which allows you to develop a diagram from zero or from a pre-existing model. Since the connections and tables make the diagram a huge figure, Figure 4 shows only an overview of the model. The complete diagram is openly available at the website: https://miro.com/app/board/uXjVM205PAg=/?share_link_id=312243665788.

All the tables and respective columns are represented. The column data type is also presented. The tables are grouped by color, indicating the module. The blue tables belong to the ICU module, the green ones belong to the Hospital module (HOSP), and the orange ones are from the Emergency Department (ED) module. The darker colored tables represent important tables from each module, according to this work, mainly due to the connections they establish to track the path taken by the patient during their hospital stay. In the ICU module, the main table selected is the icustays, which contains the stay_id of the patient, i.e., the identifier of the patient's stay at the ICU, the date and time of the admission and discharge from ICU, the first and last care unit of the patient's stay and the length of stay (LOS). In the ED module, the main table is edstays, which contains similar information about the patient's stay, including gender and race. In the HOSP module, two tables were selected: admissions and patients. The admissions table contains equal data from patients' stay at the hospital but also provides additional information such as type and location of admission, language, race and marital status of the patient, data on insurance, and date and time of death. The patient's table adds data on the age and year of the treatment. In the same way, the darker lines represent connections between the modules.

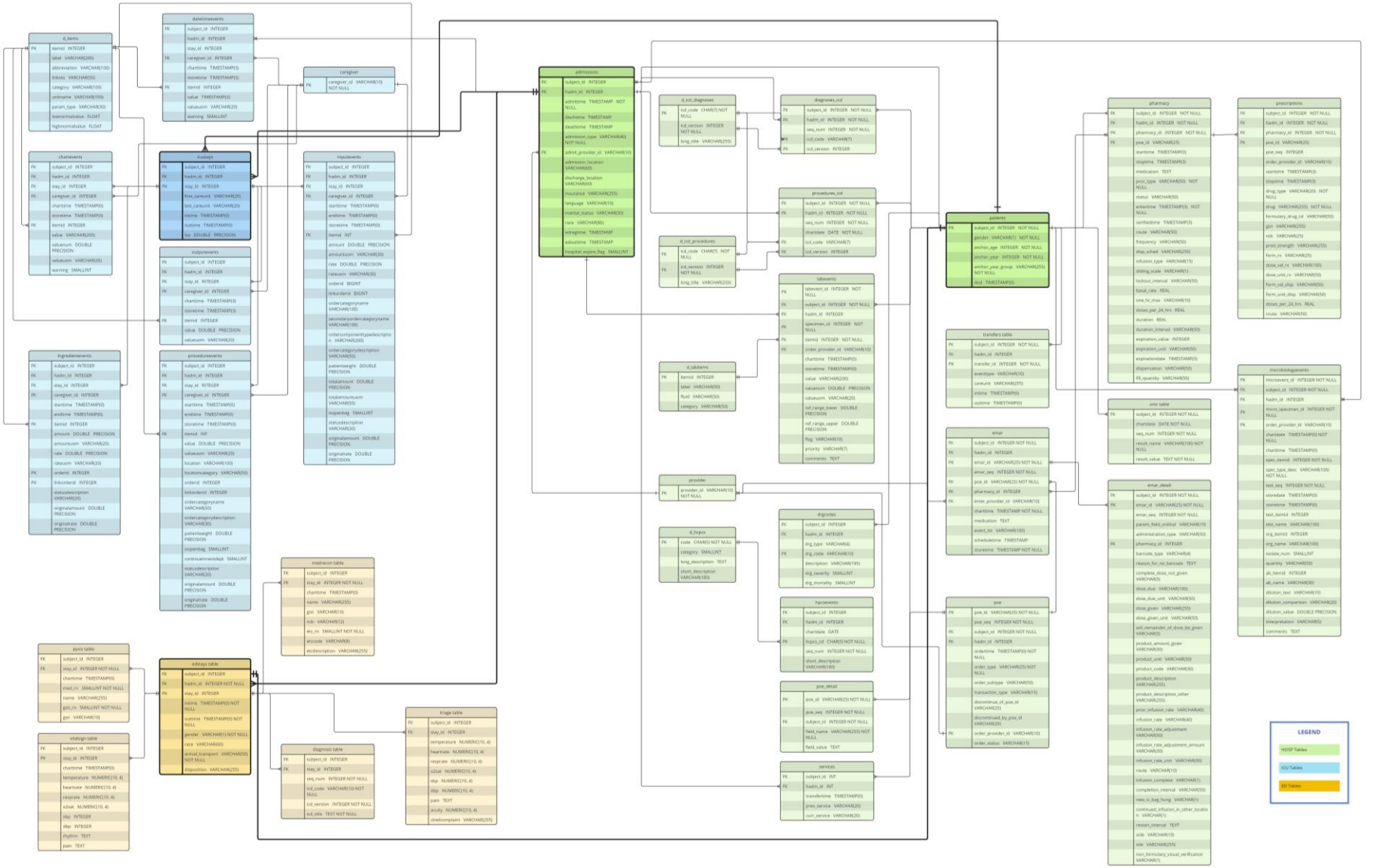

Figure 4 – MIMIC-IV Relational Diagram overview

This diagram was essential to analyzing the connections and decisions on how to make this collection. For example, to verify which tables deal with diagnosis, one could search the string "*diagn*" simply by typing the keyboard command CTRL + F. The research will point to the "diagnosis table" in the ED module and the "diagnoses_icd" and "d_icd_diagnoses" tables in the hospital module.

3.2. Data collection and preparation

This study was applied to the MIMIC-IV database (Johnson et al. 2023; A. L. Goldberger et al. 2000). MIMIC is an abbreviation of Medical Information Mart for Intensive Care and contains a freely available database of health-related data from patients admitted to the Beth Israel Deaconess Medical Center in Boston-USA. Data is divided into three releases; this work deals with the last one available, which comprises the years from 2008 to 2019, named MIMIC-IV. Data is deidentified to protect patients' confidentiality; therefore, each patient received an exclusive ID that allowed analysis of gender, race, age, etc., but all the dates concerned with patient hospitalization were randomly shifted to the future.

MIMIC-IV is divided into four modules: Hosp, ICU, ED, and CXR. The modules contain 37 tables that are connected to each other through data ID; for example, the list of procedures registered during a stay at the ICU can be tracked using the stay_id data that is part of these two tables, procedures, and ICU stays.

Hosp module contains all data from patients' admission to discharge, including laboratory measurements, medication administration and billed diagnosis. This module is composed of 22 tables: omr table, provider table, admissions table, d_hcpcs, d_icd_diagnoses, d_icd_procedures, d_labitems, diagnoses_icd, drgcodes, emar, emar_detail, hpcsevents, labevents, microbiologyevents, patients table, pharmacy, poe, poe_detail, prescriptions, procedures_icd, services, and transfers' table.

The ICU module has the register of all procedures, administrations, and charted items during ICU stay. This module is composed of nine tables: caregiver table, d_items, chartevents, datetimeevents, ICU stays, Ingredientevents, Inputevents, outputevents, and procedureevents.

ED module contains data from the emergency department and includes, for example, the reason for admission and triage assessment. There are six tables available in this module, they are diagnosis table, edstays table, medrecon table, pyxis table, triage table, and vitalsign table.

The CXR module contains information about radiology images from patients' chest X-rays. Data is also deidentified to protect patient confidentiality. This module allows analysis of image and radiology reports linked to clinical data from other modules.

MIMIC-IV contains data on 299,712 patients, 431,231 admissions, and 73,181 ICU stays in the current release 2.2 of Jan. 6, 2023. A set of eligibility criteria was applied to the database to select the sample of interest:

- Adult patients (age ≥18 years old).
- Patients admitted to ICU.
- ICU stays for at least 48 hours.
- Patients with diagnose of sepsis.
- qSOFA score ≥ 2 in the first 48 hours of ICU admission.

The first criterion comprehends all the data since MIMIC-IV only contains adult patients. Therefore, the second criterion comprehends all icustays patients. The third criterion basically consists of a filter at the ICU/icustays table. To select patients who met the fourth criterion, the string "seps" was filtered at d_icd_diagnoses hospital table. Then, the ICD codes (International Classification of Diseases) were used to filter the patients with this diagnosis in the diagnoses_icd table.

Session 3.2.1 describes the method to calculate the fifth criterion.

3.2.1. qSOFA SCORE

qSOFA score comprises three indicators: systolic blood pressure, respiration rate, and mental status. Each indicator points 1 if the measured value is reached or transposed as defined by Evans et al. (2021). Still, according to Sepsis-3, a respiration rate of 22/min or greater, altered mental status, and systolic blood pressure of 100mm Hg or less indicate a critical status if at least two of them are observed in the first 24 hours of ICU admission.

The indicators to calculate qSOFA are contained in the chartevents table from ICU module. ICU/chartevents contains charted lecture items registered during each

patient's stay at the ICU. It includes all electronic chart information like routine vital signs and additional relevant information like mental status, laboratory values, etc.

Each recorded data is identified by a number indicating the record type being made. This number connects with the HOSP/d_items table, a dimension table containing the definition of all events along ICU stays (Johnson et al., 2023). These tables are linked to each other on itemid.

Items related to qSOFA indicators were categorized into BP—blood Pressure, MS—mental Status, and RR—respiratory Rate. Records that did not match any of the categories and qSOFA parameters were omitted; Appendix I presents the list.

To calculate qSOFA score, a filter was applied at the ICU/chartevents table to select events occurred at the first 48 hours of ICU admission, then a new filter selected only the items related to qSOFA indicators. If the reference measure reaches or transposes the parameters, that category (BP, MS, or RR) scores one; otherwise, it is zero. Finally, if at least two categories have scored, the respective combination of patient and hadm_id is considered critical for sepsis diagnoses. The other combinations that scored less than two, i.e., the non-critical, were excluded.

After applying the procedure described in these sections, 7,790 admissions were found diagnosed with sepsis and in a critical condition observed in the first 48 hours. Figure 5 summarizes this procedure.

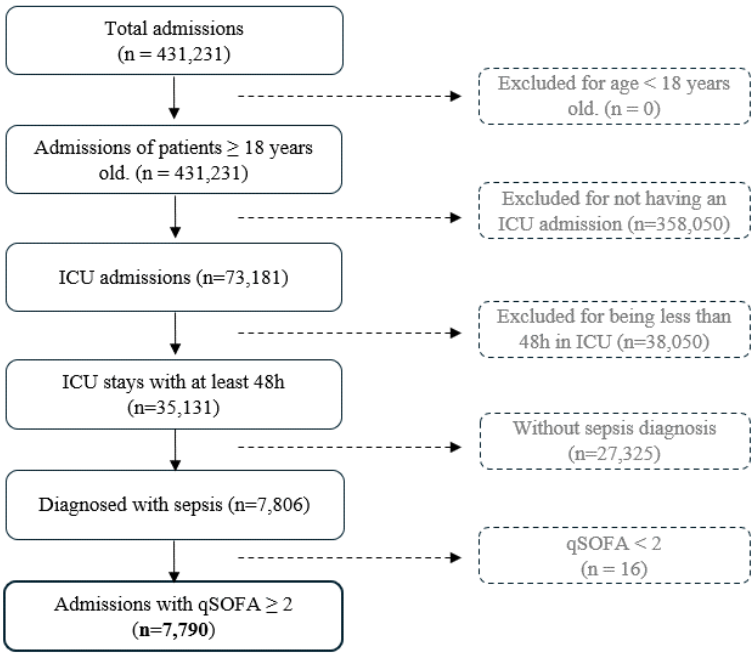

Figure 5 – Inclusion criteria. This figure presents the number of admissions excluded after applying each criterion.

3.3. Descriptive analysis

To better understand the data, a descriptive analysis was made. The necessary data was collected from three tables: ICU/icustays, HOSP/admission, and HOSP/patients. From the ICU/icustays table, intime and outtime columns were used to calculate LOS. From HOSP/admission, the next columns were collected: admission time, discharge time, death time, and race; the death time was used to infer the life status (alive/dead). From the HOSP/patients table, the gender and, initially, the age was collected.

After analyzing the data, an additional data treatment was necessary to determine the patient's age at admission. The HOSP/patients table has unique patient age data, as shown in the column "anchor_age." These columns contain the patient's age at the anchor_year. However, the same patient can have more than one admission. The maximum difference between the ages of the patients in the different admissions was 12 years. Considering this, an additional column was created with the patient's age at the admission.

The descriptive analysis was executed using the R Studio tool; some data will be highlighted below. The dataset is composed mainly of people declared white (68%), followed by not declared or not specified (unknown, 14%) and black (11%); Hispanics, Latinos, Asians, and South Americans had low percentages, so they were grouped as Other (7%). Most patients were male (60%), but the outcome was almost equal between males (72% discharged) and females (71% discharged). The mean age is also almost equal between men (65 years old) and women (66 years old), and in both situations, the mean age of patients with death outcomes was a little bit higher (67 for men and 69 for women). LOS analysis reveals a similar pattern; data shows an increase of LOS among patients with the outcome of death (from 7.5 to 9 days, average). Most patients were first admitted to the emergency room (51.3%) or transferred from the hospital (28.2%); considering the type of admission, 80% of the admissions occurred in an emergency or urgent situation. Generally, the mortality rate is around 30%, consistent with the international average. Table 3 shows the summary data.

Table 3 - Descriptive analysis

Variables	Overall n=7,790	Outcome	
		Discharge n=5,549	Death n=2,241
Gender			
F	3,331	2,360 (71%)	971 (29%)
M	4,459	3,189 (72%)	1,270 (28%)
Age	66 (16)	65 (16)	68 (15)
Race			
White	5,308	3,850 (73%)	1,458 (27%)
Unknown	1,077	680 (63%)	397 (37%)
Black	569	406 (73%)	223 (27%)
Other	569	406 (71%)	163 (29%)
Admission Location			
Emergency room	3998	2,927 (73%)	1,071 (27%)
Transfer from hospital	2199	1,502 (68%)	697 (32%)
Physician Referral	915	643 (70%)	272 (30%)
Skilled Nursing Facility	237	175 (74%)	62 (26%)
Other	441	302 (68%)	139 (32%)
Admission type			
Emergency	4502	3,273 (73%)	1,229 (27%)
Urgent	1778	1218 (69%)	560 (31%)
Observational admit	990	711 (72%)	279 (28%)
Other	520	347 (67%)	173 (33%)
LOS (ICU)	7.9 (8)	7.5 (8)	9.1 (9)
LOS (Hospital)	12.3 (14.8)	11.3 (13.3)	14.8 (17.6)

3.4. Standard process design

Considering the study realized by Evans et al. (2021) and Kalimouttou et al. (2023), the guidelines for sepsis treatment were selected to support this study in the design of a standard process for sepsis treatment. Evans et al. (2021) present 93 guidelines for sepsis treatment. However, most guidelines regard qualitative recommendations; for example, their first guideline concerns the use of a performance improvement program for sepsis. Since this work aims to identify guidelines in the MIMIC-IV database, selecting more quantitative guidelines was necessary. Kalimouttou et al. (2023) prioritized recommendations based on their relative impact on mortality. Based on these two works, an analysis was conducted to identify

the quantitative guidelines that could be used and also consider the adequate identification of the MIMIC-IV database. Guidelines from 1 to 6 came from studies cited above, and guidelines from 7 to 9 were added with the help of a consultant expert:

#01 For adults with sepsis or septic shock who require ICU admission, it is suggested to admit the patients at the ICU within six hours.

#02 For adults suspected of having sepsis, it is suggested that blood lactate be measured within the first hour.

#03 For adults with suspicion of sepsis or septic shock, it is recommended to realize blood culture within one hour.

#04 For adults with possible septic shock or a high likelihood of sepsis, it is recommended to administer antimicrobials immediately, ideally within one hour of recognition.

#05 For adults with sepsis or septic shock, we recommend using crystalloids as first-line fluid for resuscitation.

#06 For adults with sepsis or septic shock, we recommend initiating insulin therapy at a glucose level of > 180 mg/ dL (10 mmol/L).

#07 Administrate corticosteroids.

#08 Administrate fluids medication.

#09 Administrate vasopressors.

Table 4 describes the correspondence of the guidelines with their respective numbers from the documents of origin by Evans et al. (2021) and Kalimouttou et al. (2023).

Table 4 - Guidelines correspondence

Guideline number	Evans et al. 2021	Kalimouttou et al. 2023
#01	10	1
#02	3	2
#03	-	3
#04	12	5
#05	4	4
#05.1	5	7 and 16
#06	69	14
#06.1	Remark of 69	14

From now on, the guideline number above will be used to refer to the respective recommendations.

Some guidelines suggest executing an event within a time interval, such as administering antibiotics, conducting blood cultures, and performing blood lactate checks within the first hour of ICU admission.

From this selection, a BPMN model was developed in the Bizagi® tool to show the standard process of sepsis treatment. Figure 6 represents the reference process for the treatment of sepsis, consolidating the nine selected recommendations in BPMN (Business Process Model and Notation), in which the green and red circles represent the beginning and end of the process, respectively; the rounded edge rectangles represent process activities; an empty diamond represents an XOR-join gateway, which denotes a synchronism point of 2 alternative flows of the process, derived from a previously made decision; Finally, the diamonds with the symbol "O" represent "OR" ("inclusive OR" gateways), which delimit sub-flows of the process that can be executed concurrently. In the case of a gateway "OR" with one input flow and several outputs, each output flow represents a sub-flow of the process that may or may not be run in parallel to the others, and an "OR" gateway with several input flows and 1 output represents a synchronism point, followed by an XOR gateway that indicates the sequence of only one of the streams.

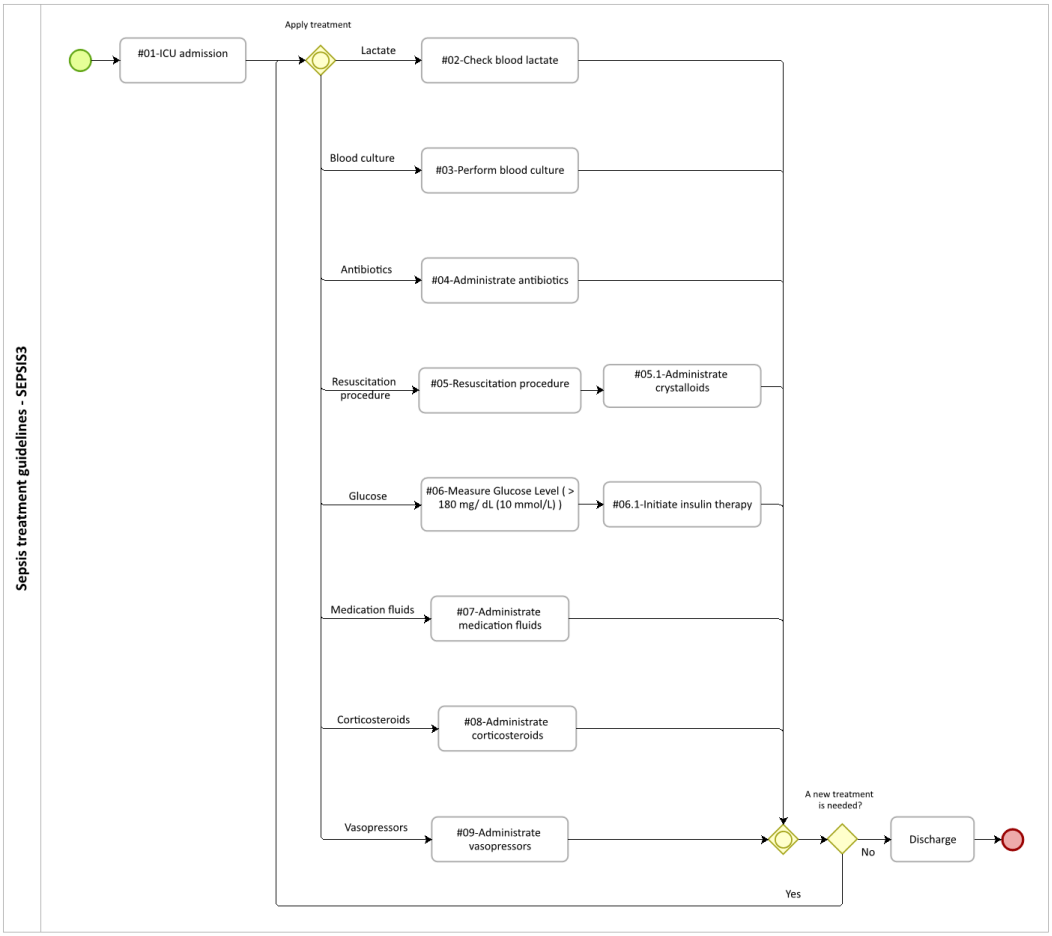

Figure 6 - BPMN model of sepsis treatment guidelines. These guidelines are based on the Sepsis-3 protocol, considering data available on MIMIC-IV

The conformance-checking procedure needs a model to compare in Petri net format, so this structure was also developed in Petri Net using Yasper software.

3.5. Event log

With the help of a medical researcher and specialist in intensive care, correspondences were specified between each guideline and the database fields. The data was searched and selected accordingly, for example, the third guideline concerns to performance of blood lactate, the corresponding data belongs to table procedureevents of ICU module in the itemid column. The event log was created considering seven tables: admissions, labevents, and procedures_icd from the HOSP module; edstays from the ED module; icustays, procedureevents, and chartevents from the ICU module. Table 5 describes the origin and type of data used to create the event log.

Table 5 - Origin of event log data

Guideline number	Event	Module	Tabel	Key column	Type
#01	ICU admission	ICU	icustays	intime	TIMESTAMP(0) NOT NULL
#02	Check blood lactate	HOSP	labevents	itemid	INTEGER NOT NULL
#03	Perform blood culture	ICU	procedureevents	itemid	INTEGER
#04	Administrate antibiotics	ICU	pharmacy/prescriptions	itemid	INTEGER
#05	Register time of resuscitation	HOSP	procedures_icd	chartdate	DATE NOT NULL
#05.1	Administrate crystalloids	ICU	inputevents	ordercategoryname	INTEGER
#06	Measure Glucose Level (> 180 mg/ dL (10 mmol/L))	HOSP	labevents	itemid	INTEGER
#06.1	IF Glucose Level > 180 mg/ dL (10 mmol/L), Initiate insulin therapy	ICU	inputevents	itemid	INTEGER
#07	Administrate medication fluids	ICU	pharmacy/prescriptions	itemid	INTEGER
#08	Administrate corticosteroids	ICU	pharmacy/prescriptions	itemid	INTEGER
#09	Administrate vasopressors	ICU	pharmacy/prescriptions	itemid	INTEGER
-	ICU discharge	ICU	icustays	outtime	TIMESTAMP(0) NOT NULL

The event log was created using R Studio and the libraries `dyplr`, `tidyverse` and `lubridate`. This key is called case_id and was included in all tables. The tables that did not have these two columns were checked using HOSP/transfers table.

Some tables, such as HOSP/procedures_icd, did not have the time data of the event. In these cases, it was assumed that the event had occurred at "00:00:00". The procedures to find and process each guideline and to create the event log are described in Appendix II.

After applying this procedure 167,474 events were mapped from the 7,790 cases.

3.6. Process mining discovery

The process mining discovery was executed using Disco 4.0.8. This choice was made considering the interactive design, which allows for easy adjustment of

some parameters, such as the percentage of activities or paths and visualization types. The process discovered will be presented in Chapter 4.

3.7. Conformance analysis

Conformance analysis was performed using PM4Py, a Python library, and the `token_based_replay` a fitness algorithm. This algorithm verifies whether a trace matches a Petri net model by replaying the event log. Diagnostics points to the percentage of the event log matching (or fitting) the model; deviations are related to executions out of order or unexpected events. The algorithm assumes that tokens are inserted at the start to achieve this. After each transition, the algorithm searches for a correspondence between the event and the model; if the expected activity is not found, an additional token is added to enable that execution. The trace fits the model if, during the replay, the transitions can be fired without the need to insert any missing token. At the end of the replay, the conformance rate is calculated based on the missing and remaining tokens (Berti and van der Aalst, 2020). Missing tokens are tokens that were produced in the replay, while remaining tokens are the tokens that were not consumed (Berti and Van Der Aalst 2019).

For each trace, four variables must be determined: produced tokens (p), remaining tokens (r), missing tokens (m), and consumed tokens (c) (Berti and Van Der Aalst 2019). Considering this, the fitness can be described as:

$$fitness_{\sigma} = \frac{1}{2}\left(1 - \frac{r}{p}\right) + \frac{1}{2}\left(1 - \frac{m}{c}\right) \quad (3)$$

To apply the formula on the whole event log, p, r, m, and c are calculated for each trace, summed up, and placed into (3).

Algorithm 1 describes this process.

Algorithm 1: Conformance analysis

pn: Petri net
mi: initial mark
mf: final mark
dataframe: event log

```
pn, mi, mf ← petri_net.importer("petrinet.pnml");
i = 1;
list_conform ← [];
while i <= 7,790 do
    dataframe = pm4py.format_dataframe(("dataframe.csv", sep=','), ),
    case_id = 'case_id', activity_key = 'activity', timestamp_key =
    'timestamp');
    conformance = token_based_replay (dataframe, pn, im, fm)
    lista_conform[i] = conformance
    i = i + 1
fim
Return list_conform;
```

The authors.

The aim was to register each case's conformance, so the event log was partitioned into 7,790 subsets, and this algorithm was played for each subset. The results were registered and extracted in a list.

3.8. Sensitivity analysis using severity-adjusted measures

The patients' outcomes assessing was developed in three parts:

- SAPS3 calculation
- SRU calculation
- SMR calculation

The procedures were performed using the R Studio and MS Power BI tools. To calculate the SAPS3 score, the 21 items described by Moreno et al. (2005) were scrutinized through the MIMIC-IV database and carefully calculated. An auxiliary of an expert consultant was important to define the corresponding items in the MIMIC-IV database. Table 6 presents the SAPS3 item, and the module, table, and column used to calculate the score.

Table 6 - SAPS3 variables

#	Variable	Description	Module	Table	Column
1	ICU admission	Every patient gets an offset of 16 points for being admitted (to avoid negative SAPS3 scores)	ICU	icustays	stay_id
2	Age, years		HOSP	patients	anchor_age
3	Comorbidities	Chemotherapy, immunosuppression, radiotherapy, steroid treatment	HOSP	procedures_icd / d_icd_procedures diagnoses_icd / d_icd_diagnoses	icd_code
12	Glasgow Coma Scale/Score	Lowest within 1 hr of ICU admission	HOSP	diagnoses_icd / d_icd_diagnoses	icd_code
13	Total bilirubin, mg/dL (µmol/L)	Highest within 1 hr of ICU admission	HOSP	labevents / d_labevents	itemid / value
14	Body temperature, °C (°F)	Highest within 1 hr of ICU admission	ICU	chartevents / d_items	itemid / value
15	Creatinine, mg/dL (µmol/L)	Highest within 1 hr of ICU admission	HOSP	labevents / d_labevents	itemid / value
16	Heart rate, beats/min	Highest within 1 hr of ICU admission	ICU	chartevents / d_items	itemid / value
17	Leukocytes, G/L	Highest within 1 hr of ICU admission	HOSP	labevents / d_labevents	itemid / value
18	Hydrogen ion concentration (lowest), pH	Lowest within 1 hr of ICU admission	ICU	chartevents / d_items	itemid / value
19	Platelets, G/L	Lowest within 1 hr of ICU admission	HOSP	labevents / d_labevents	itemid / value
20	Systolic blood pressure, mm Hg	Lowest within 1 hr of ICU admission	ICU	chartevents / d_items	itemid / value
21	Oxygenation	PaO2 and FiO2 refer to arterial oxygen pressure (lowest) and inspiratory oxygen concentration. MV			

SRU and SMR were calculated according to Rothen et al. (2007) and Moreno et al. (2005).

SRU is evaluated from the quotient of observed LOS to expected LOS. The expected resource use is the total LOS of all patients divided by the number of surviving patients (Rothen et al. 2007).

SMR is defined as the quotient of observed to predicted mortality, using SAPS3 score as an adjustment of criticality (Rothen et al. 2007). The probability of death is obtained from the relationship of the SAPS3(Moreno et al. 2005):

$$probability\ of\ death = \frac{e^x}{1 + e^x} \quad (4)$$

with,

$$x = -32.6659 + \ln(SAPS3\ score + 20.5958) \times 7.3068 \quad (5)$$

.

4 Results and discussion

This chapter will present and discuss the results. They were split into three groups: the first discussed the process discovery perspective, the second the conformance checking perspective, and the third the SMR and SRU perspectives.

a. Process discovery

Process mining was executed on the event log using the Disco tool (version 4.0.8) to understand the real process behavior. The process discovered is presented in Figure 7, which has the 20% highest occurrences. The dark-colored elements represent the events with more absolute frequencies in this sample. For example, the administration of antibiotics was the event that happened most times (50,308 times in 7,335 cases), followed by the administration of vasopressors (31,026 times) and insulin therapy (21,030 times). The density of the arrows indicates the number of times this path was traveled; thicker arrows represent paths traveled more often.

Table 7 presents the absolute and relative frequencies of the events in this dataset by quantity of executions. This event log is composed of 167,474 events, distributed into 7,790 cases. The administration of antibiotics was the event most frequently executed, applied 50,308 times, and present in 7,335 cases (94%). The second one was insulin therapy, which was applied 31,026 times but was only present in 506 cases (6,5%). Blood lactate was in third place, with 27,030 executions in 634 cases (8%). This corroborated with the specialist consultant, who indicated that the administration of antibiotics is one of the most important activities in sepsis treatment.

Table 7 - Absolute and relative frequencies of events

Event	Frequency	Relative frequency
#04-Administrate antibiotics	50.308	30,0%
#06.1-Initiate insulin therapy	31.026	18,5%
#02-Check blood lactate	27.030	16,1%
#07-Administrate medication fluids	11.588	6,9%
#09-Administrate vasopressors	11.493	6,9%
#03-Perform blood culture	8.360	5,0%
#06-Measure Glucose Level (> 180 mg/ dL (10 mmol/L))	7.476	4,5%
#08-Administrate corticosteroids	4.529	2,7%
#05.1-Administrate crystalloids	46	0,0%
#05-Resuscitation procedure	38	0,0%

The variants differ by order of activities and the number of times each activity was performed; for example, one variant could be composed of <ICU Admission, G1#04-Administrate antibiotics, ICU discharge>, and a second one could be <ICU Admission, G1#04-Administrate antibiotics, G1#04-Administrate antibiotics, ICU discharge>, although these two traces have the same activities, one has one occurrence of "G1#04-Administrate antibiotics" and the other has two occurrences of the same event, thus, these two similar sequences are set as two different variants.

This analysis was made on the Disco tool and showed that the ten first variants with the major case coverage, which comprehends 12% of the cases, present a large number of events related to antibiotics administration happening repeatedly. For example, Variant 1 comprises an ICU admission followed by three events of antibiotics administration and ICU discharge. Variant 2 has the same structure with two events of antibiotics administration. The same behavior is observed in variants from three to seven.

To explore these, an activity position analysis was performed in PM4Py. This analysis investigates the frequency of an event occurring in a specific order and shows that the most frequent activity executed after admission was the administration of antibiotics, occurring in this position 4,032 times (51.6%). The administration of vasopressors was executed 1,613 times (20.7%), and medication fluids were in this position 815 times (10.5%), followed by a performance of blood culture (450; 5.8%) and blood lactate check (302; 3.9%). This result corroborates with the consultant expert analysis of the importance of antibiotics in sepsis treatment.

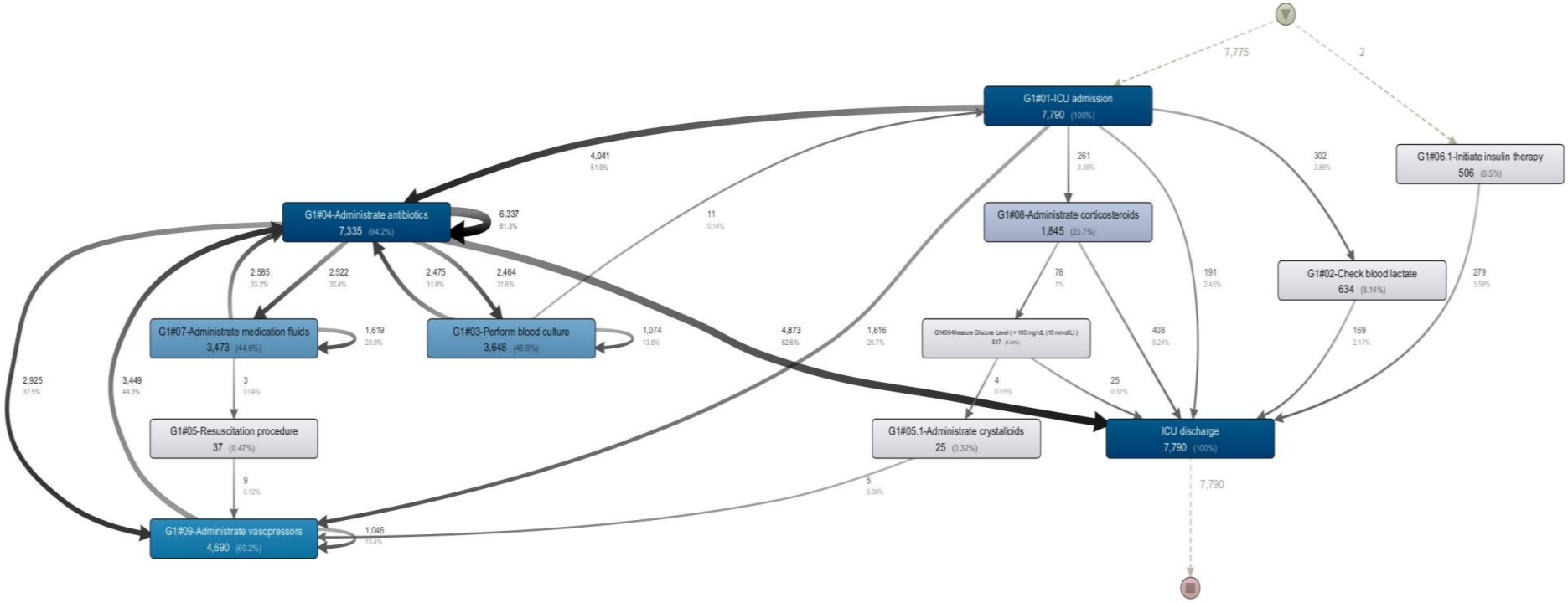

Figure 7 - Process discovered - Complete event log

Considering this difference between the frequency of executions and case coverage, a path analysis was made. The dataset presented 5,476 variants. Figure 8 presents the distribution of variants per number of cases; the total of 80.5% of cases is reached with almost four thousand variants; this highlights how scattered the paths are.

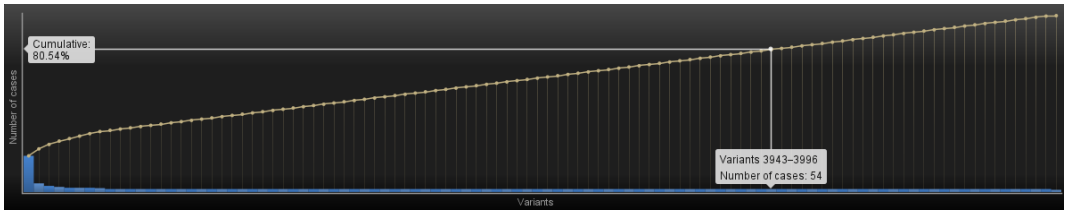

Figure 8 - Distribution of variants per number of cases

Clustering was used to identify the combination of treatments and their results. The 15 most common combinations were analyzed and corresponded to 86% of the event log. Antibiotics were present in all combinations, and the lower mortality rate was observed in groups with antibiotics and medication fluids combined with blood culture (Table 8).

Table 8 – Mostly used guideline combinations– 15 mostly used guideline combinations under the perspective of LOS, Conformance, mortality rate, and SAPS3.

Componentes	Qty	LOS	Conformance	Mortality	SAPS3
antibiotics+med. fluid+vasopressors	936	5.37	0.96	0.21	43.69
antibiotics	886	4.11	0.92	0.13	40.61
blood culture+antibiotics+med. fluid+vasopressors	823	8.45	0.97	0.26	42.69
antibiotics+vasopressors	676	5.38	0.95	0.26	45.5
blood culture+antibiotics	645	6.79	0.95	0.19	40.17
blood culture+antibiotics+vasopressors	604	8.19	0.96	0.32	44.31
antibiotics+med. fluid	373	3.97	0.94	0.09	38.78
blood culture+antibiotics+med. fluid+corticosteroids+vasopressors	323	9.97	0.98	0.47	43.06
antibiotics+med. fluid+corticosteroids+vasopressors	295	6.49	0.97	0.39	43.68
antibiotics+corticosteroids+vasopressors	220	6.03	0.96	0.37	43.82
blood culture+antibiotics+corticosteroids+vasopressors	219	9.57	0.97	0.49	44.81
antibiotics+corticosteroids	209	4.99	0.94	0.23	39.09
blood culture+antibiotics+med. fluid	193	5.59	0.96	0.11	38.89
blood culture+antibiotics+corticosteroids	187	8.56	0.96	0.34	41.29
blood lactate+blood culture+antibiotics+insulin+glucose+med. fluid+vasopressors	117	32.02	0.59	0.32	43.35

A conformance-checking analysis was performed to understand how the process discovered aligns with the pattern designed from the guidelines' observation. This analysis will be presented in the next section.

b. Conformance checking

The conformance checking aims to answer how the log fits the model. To reach this, a token-based replay analysis was performed using PM4Py. The minimum conformance found was 2.55%, and the maximum conformance was 99.8%, as shown in Table 9. On average, the dataset presents a conformance of 92.4% (standard deviation of 11.2%) and a median of 95.5%, considering that the first quartile was 92.9% and the third quartile was 96.9%; this suggests a concentration of high conformance results through the log, this will be explored below.

Table 9 - Conformance analysis of basic statistics

N	Mean	StDev	Min	Quartile 1	Median	Quartile 3	Max
7790	0.92	0.11	0.025	0.93	0.95	0.97	0.99

From an age range perspective, 25% of the patients were 60 to 70 years old, and 82% were over 50 (Figure 9, a). Regarding conformance, the numbers were similar among all age ranges, between 92% and 94% (Figure 9, b), suggesting that the patient's age did not influence the conformance. Despite the results relative to conformance, Figure 9 (c) shows a potential influence of age on mortality rate, as the group of younger patients (18 – 30 years old) corresponded to less than half of the Rate relative to older patients (70 years old or more), respectively of 16% and 34%.

Figure 9 - Conformance analysis through age ranges. (a) Number of cases x age range, (b) Conformance percentage x age range, and (c) mortality rate x age range.

Regarding ICU LOS, 76.5% of the cases had been discharged from the ICU within ten days; if considered up to twenty days, the percentage is 92.8% (Figure 10, (a)). The conformance presented a considerable difference among the groups; patients up to twenty days had 94% conformance, on average; after that, the conformance was 70%, almost 25% less conformance, suggesting that the longer the LOS, the lower the conformance (Figure 10 (b)). Regarding mortality, the behavior was similar; the group with LOS up to ten days had a lower mortality rate than the others, and the group with LOS higher than 50 days had an almost 43% mortality rate. Comparing the group up to ten days and the others, respectively 26,.4%, and 36.6%, on average (Figure 10 (c)).

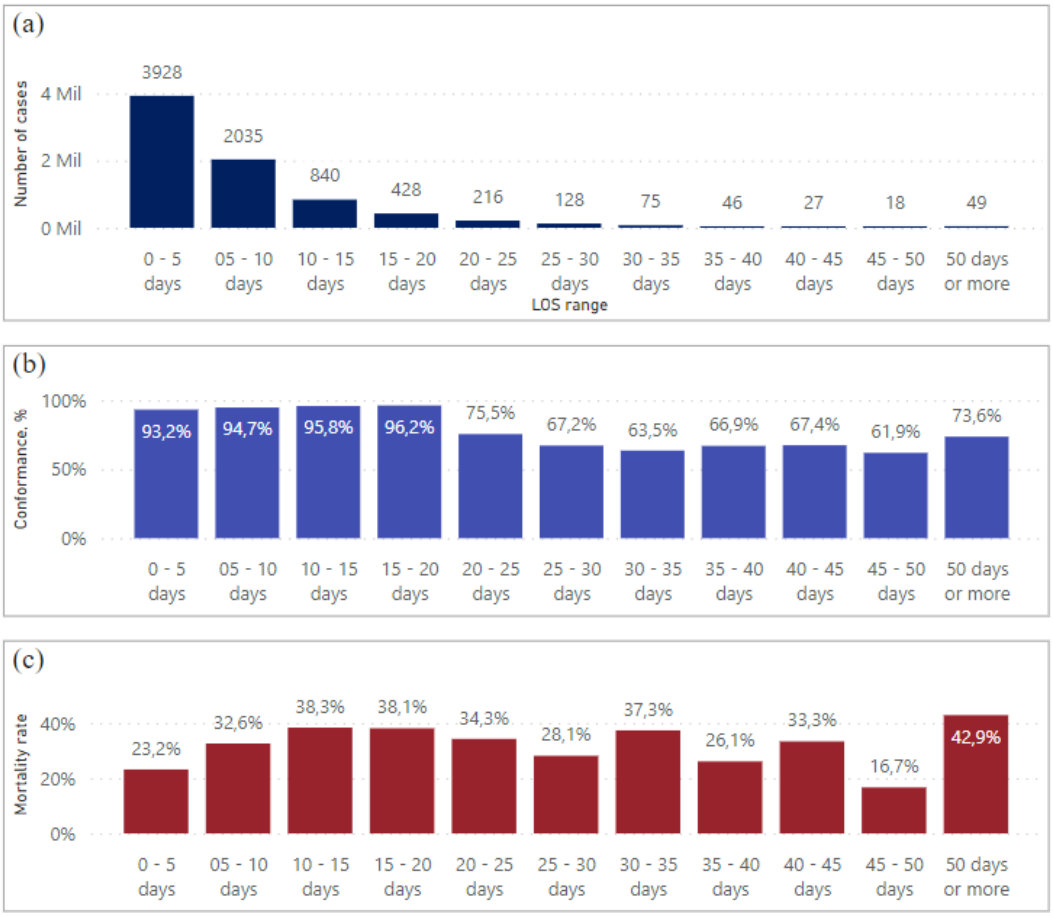

Figure 10 - LOS analysis. (a) Number of cases x LOS range, (b) Conformance percentage x LOS range, and (c) mortality rate x LOS range.

c. SAPS3, SMR and SRU

SAPS3 is an indicator that supports the estimate of SMR, and its distribution score is presented in Figure 11. The minimum value observed was 22, and the maximum value was 89, considering that the sample comprises only patients admitted to the ICU; all scores start from 16. The average was 42.3, with a standard deviation of 8.79.

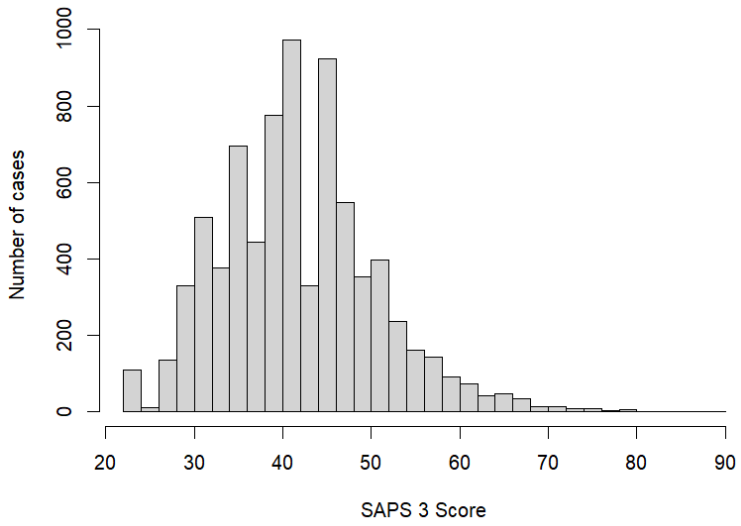

Figure 11 - SAPS3 score

Figure 12 describes the relationship between the SAPS3 score and the probability of death; the curve is similar to that published by Moreno et al. (2005) but with a more acute inclination, suggesting an accelerated behavior. This behavior is compatible with mortality results above expectations.

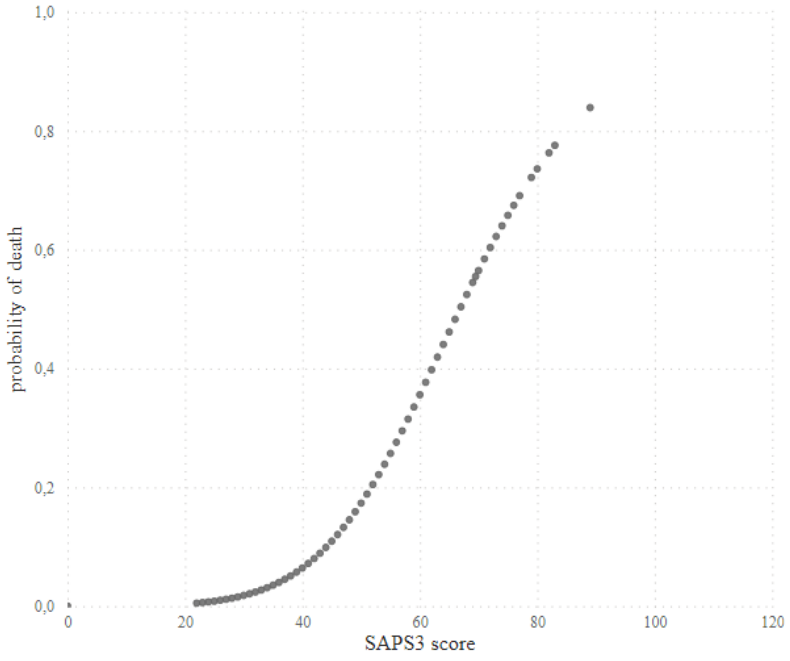

Figure 12 - SAPS3 score x probability of death

Table 10 presents SMR and SRU results. This analysis considers that a number equal to one indicates that reality is aligned with expectations, a number lower than one indicates that the real process has fewer deaths or less LOS than expected, and a number higher than one indicates the opposite. The results were clustered into quartiles of conformance.

Table 10 - SMR and SRU. Q# = quartiles of conformance, Obs. = Observed, Exp. = Expected.

Group	Quartile range	Conformance	Number of cases		SAPS3 Mean	Mortality Rate		LOS		SMR	SRU
			Total	Surviving		Obs.	Exp.	Obs.	Exp.		
Q1	0 - 0.92	0.82	2,021	1,663	41.7	0.18	0.078	9.15	11.1	2.28	0.82
Q2	0.93 - 0.96	0.95	2,168	1,765	41.9	0.19	0.079	4.72	5.8	2.34	0.81
Q3	0.96 - 0.97	0.96	1,810	1,362	42.8	0.25	0.087	6.59	8.75	2.85	0.75
Q4	0.97 – 1.00	0.98	1,791	1,099	43	0.39	0.09	12.07	19.67	4.32	0.61
Total	-		7,790	5,889	42.3	0.24	0.083	7.99	10.6	2.94	0.75

SMR was concerned with the mortality rate; the results showed that the log had more deaths than expected, respectively 24% and 8%. Regarding SRU, which verifies LOS, all the groups presented a lower length of stay than expected; on average, the patients were admitted for 75% of the time expected. These two data could suggest that the patients needed more time to recover, combined with the mortality rate being higher than expected.

The guidelines presented in section 3.4 were also analyzed under the perspective of SRU and SMR indicators, with two perspectives: the first one regards the recommendations to execute the action within a certain interval of time, and the third guidelines refer to the first hour of ICU admission. The second perspective concerns a combination of guidelines independent of order, as shown before in Table 8.

Regarding guidelines that suggest the execution of an event within the first hour of ICU admission, the combination of antibiotics administration (#04), check of blood lactate (#02), and blood culture (#03) had no deaths, and an SRU equal to one, i.e., the LOS was equal to the expected. The cases with guidelines #04 and #02 within the first hour had an SMR of 0.88 and SRU of 0.91, presenting results of superior efficiency (less mortality and less use of the resources than expected).

Cases that had only one of these guidelines in the first hour and the combination of (#03) and (#04) had SMR results further away the target, 2.37 and 3.14, and SRU results were from 0.56 and 0.76, representing low real LOS in comparison with expected LOS (Table 11).

Table 11 - Guidelines executed in the first hour

Guidelines	SMR	SRU
(#04) Antibiotics + (#03) BloodCulture + (#02) BloodLactate	0,00	1,00
(#04) Antibiotics + (#02) BloodLactate	0,88	0,91
(#03) BloodCulture + (#02) BloodLactate	0,93	0,89
(#04) Antibiotics	3,01	0,76
(#02) BloodLactate	2,37	0,74
(#03) BloodCulture	2,71	0,69
(#04) Antibiotics + (#03) BloodCulture	3,14	0,56

A similar analysis was conducted considering the combination of guidelines independent of order. The ten most recurring combinations were selected and are shown in Table 12, ranked by the number of case occurrences.

Table 12 - Guidelines combinations independent of sequence

Nº	Componentes	SMR	SRU
1	(#04) Antibiotics + (#07) Med. Fluid+(#09) Vasopressors	2.21	0.79
2	(#04) Antibiotics	1.95	0.87
3	(#03) Blood culture + (#04) Antibiotics + (#07) Med. Fluid + (#09) Vasopressors	3.00	0.74
4	(#04) Antibiotics + (#09) Vasopressors	2.23	0.74
5	(#03) Blood culture + (#04) Antibiotics	2.86	0.81
6	(#03) Blood culture + (#04) Antibiotics + (#09) Vasopressors	3.10	0.68
7	(#04) Antibiotics + (#07) Med. Fluid	1.68	0.91
8	(#03) Blood culture + (#04) Antibiotics + (#07) Med. Fluid + (#08) Corticoster-oids + (#09) Vasopressors	5.21	0.53
9	(#04) Antibiotics + (#07) Med. Fluid + (#08) Corticosteroids+ (#09) Vasopressors	4.08	0.61
10	(#04) Antibiotics + (#08) Corticosteroids + (#09) Vasopressors	3.79	0.63

Antibiotics (#04) were used in all the combinations, and the SRU indicator was less than one in all of them, varying from 0.53 to 0.91; this means that observed LOS was always less than expected in this sample. The most common combination of guidelines was “(#04) Antibiotics + (#07) Med. Fluid+(#09) Vasopressors”, with SMR of 2.21 and SRU of 0.79, followed by “(#04) Antibiotics”, with SMR of 1.95 and SRU of 0.87. Comparing the results, the second and the seventh combinations had SMR and SRU closest to one; this suggests that the combination of these events

contributed to better results in terms of patient outcomes. On the other hand, combinations eight and nine had the least compliant results, combination 8 with SMR of 5.21 and SRU of 0.53, and combination 9 with SMR of 4.08 and SRU of 0.61.

5 Conclusions

This chapter aims to present the conclusions and highlight the main contributions of this work. The purpose of the present work was to evaluate whether the process conformance of an ICU during a sepsis treatment was aligned with the Sepsis-3 guidelines. The guidelines were selected with the help of a medical researcher and specialist in intensive care, and their correspondence was searched in the MIMIC-IV database. A process mapping was designed based on guidelines and used to verify the conformance, replaying the event log using a PM4Py fitness algorithm. We evaluated the results regarding SAPS3 SMR and SRU, further discussions were presented in Chapter 4.

The relational diagram developed expands comprehension of the MIMIC-IV database, allowing developers to quickly understand the connection between the modules and tables and supporting developers in understanding existing data types and formats and key columns for connections between tables, for example.

As an extra contribution, SAPS3 was not available in the MIMIC-IV database, so it was determined in this work, the script is freely available at GitHub, as mentioned before.

Regarding indicators and analysis, the mortality rate was considerably higher than expected, with an expected mean of 8.3% and an observed mean of 24%, confirmed by the SMR, which led to 2.98. The observed LOS in the database was lower than the expected LOS, leading to a mean SRU of 0.75. Data showed that groups of patients with LOS over 20 days had 25% less conformance in their treatment pathways and a mortality rate of 32.7%, compared with 28.5% of the group with LOS less than 20 days. When analyzing the conformance quartiles, the ones with a lower mortality rate had better SMR and SRU results. Furthermore, the mortality rate was found to be slightly higher for older patients, 31.7% for patients over 60 years old compared with 24% for younger patients; a similar characteristic was also observed by Bao, Deng, and Zhao (2023).

The guidelines that recommend checking blood culture and blood lactate and administering antibiotics in the first hour of admission combined had no fatal outcomes and an SRU of 1, reinforcing the importance of these procedures as early as possible.

Finally, conformance checking proved not to be an attractive mechanism for the analysis in this study once the model tolerates a large number of paths and has few restrictions, which was similarly verified by Mannhardt and Blinde (2017). These conditions create a scenario of high conformance results, reducing the possibilities that this analysis could bring to the context.

Regarding the MIMIC-IV database, some lessons learned are presented:

- MIMIC-IV is a very structured database and well organized in tables, allowing the connection easily
- Preexistent conditions are only available through free-text clinical notes, which makes their potential influence on the analysis difficult.
- The age of the patients is described based on a specific year, not at admission.
- SAPS3 and qSOFA scores are not available.
- The HOSP/diagnoses_icd and HOSP/procedures_icd tables do not have the time of the event; they only show the date. This prejudices the time analysis, for example.

For future research, we recommend developing a more defined standard process, considering, with the help of a specialist, some critical conditions and events according to the patient's premises and the literature guidelines. With this, a declarative analysis will also be feasible. Our study also highlights the importance of considering expert knowledge in diary decisions. Therefore, another opportunity for research would be relating sepsis treatment and knowledge-intensive process analysis.

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APPENDIX I – Items selected to compose the qSOFA index

Table 13 - Blood pressure (BP) and respiratory rate (RR) items

Category	itemid	Label
BP	223752	Non-Invasive Blood Pressure Alarm - Low
	220056	Arterial Blood Pressure Alarm - Low
	220058	Arterial Blood Pressure Alarm - High
	220179	Non-Invasive Blood Pressure systolic
	223751	Non-Invasive Blood Pressure Alarm - High
	220050	Arterial Blood Pressure systolic
	224167	Manual Blood Pressure Systolic Left
	227243	Manual Blood Pressure Systolic Right
	227537	ART Blood Pressure Alarm - High
	227538	ART Blood Pressure Alarm - Low
RR	220210	Respiratory Rate
	224161	Resp Alarm - High
	224162	Resp Alarm - Low
	224688	Respiratory Rate (Set)
	224689	Respiratory Rate (spontaneous)
	224690	Respiratory Rate (Total)
	224745	Respiratory Quotient

Table 14 - Mental status (MS)

icd_code	long_title
R4024	Glasgow coma scale, total score

APPENDIX II – Eventlog creation procedure

Subset of ICU admissions (Guideline #01 and discharge event)

The ICU/icustays table was used to collect data on the date and time of ICU admission and discharge. The steps described were similarly used to develop each subset:

1. Selection of the columns case_id and:
    a. ICU/icustays/intime to create the subset of ICU admissions.
    b. ICU/icustays/outtime to create the subset of ICU discharge.
2. Filtering the table with the sample of interest using the `merge` function and the case_id key.
3. Renaming the columns intime and outtime as “timestamp”.
4. Create the column "event" and insert the description of the proper event (“#01-ICU admission” and “ICU discharge”).

Subset of prescriptions (Guidelines #04, #07, #08 and #09)

With the help of a consulting expert, medications were selected, considering their importance in the sepsis treatment. These medications were grouped into four categories: Antibiotics, Fluids, Vasopressors, and Corticosteroids, as can be checked in Appendix III. With this information, prescriptions and pharmacy tables had some treatments applied as described below:

1. Merging the tables of prescriptions and pharmacy and creating a new table named medication_table, selecting the columns case_id and starttime.
2. Identify the drug group according to the specialist's data, merging medication_table with medication_group by the "drug" key.
3. Renaming the column starttime as “timestamp”.
4. Create the column "event" and insert the description of the proper event.

Subset of resuscitation (Guideline #05)

The resuscitation procedure was identified at HOSP/d_icd_procedures by the icd_code = "9393" and "9960". The d_icd_procedures is a dimension table that links to the fact table HOSP/procedures_icd by the icd_code, so the first step was to apply this filter.

1. Filtering the icd_code at procedures_icd table.
2. Selection of case_id and chartdate columns.
3. Create the column "event" and insert the description "Resuscitation procedure."
4. Renaming the column chartdate as “timestamp”.
5. The procedures_icd table has a date pattern different from the other tables, informing only the procedure date without the time. So, to put the data in the pattern and avoid problems with the reading of the event log, an additional treatment was made:
   Inclusion of time "00:00:00" in the column "timestamp."

Subset of blood culture (Guideline #03)

Blood culture is a procedure registered at ICU/procedureevents table and linked with ICU/itemid, a dimension table that describes the events of the ICU module. The correspondent ID for blood culture was found as "225401" and a similar procedure was executed to create the subset.

1. Filtering the itemid at procedureevents.
2. Selection of case_id and starttime columns.
3. Create the column "event" and insert the description "G1#03-Perform blood culture”.
4. Renaming the column starttime as “timestamp”.

Subset of blood lactate and glucose (Guidelines #02 and #06.1)

Blood lactate and glucose data are registered in the HOSP/labevents table and connected with a dimension table named HOSP/d_labitems.

2. Filtering the correspondent IDs at labevents:
   a. To filter blood lactate: "52442", "50813", "53154" and "50954".

   b. To filter glucose: "51478", "51981", "51084", "51034", "51941", "51790", "51053", "51022", "50842", "52027", "50809", "52569", "50931".
3. The glucose measurements of interest are the ones above 180mg/dL, so this was also filtered.
4. Selection of case_id and charttime columns.
5. Creation of the column "event" and insertion of the proper description
   a. “#02-Check blood lactate”.
   b. “#06-Measure Glucose Level (> 180 mg/ dL (10 mmol/L))”.
6. Renaming the column charttime as “timestamp”.

A subset of insulin therapy (Guideline #06.1)

Information about insulin therapy can be found in ICU/inputevents table connected with a dimension table named ICU/d_items through the key itemid.

7. Filtering the correspondent itemids: "229619", "229299", "223262", "223261", "223260", "223259", "223258", "223257" and "228236".
8. Selection of hadm_id and starttime columns.
9. Creation of the column “event” and insertion of the description " #06.1-Initiate insulin therapy".
10. Renaming the column starttime to “timestamp”.

Subset of crystalloids (Guideline #05.1)

Crystalloid administration is registered at the ICU/input events table. The procedure to create this dataset was:

11. Filtering the correspondent itemid " 226364".
12. Selection of case_id and starttime columns.
13. Create the column "event" and insert the description " #05.1-Administrate crystalloids".
14. Renaming the column starttime to “timestamp”.

The event log was created from the join of the subsets described above (blood culture, blood lactate, ICU admission, ICU discharge, resuscitation procedure, insulin therapy, medication table groups, and glucose) using an R function named `bind_rows`. This function combines multiple data frames into a new one. After that, a CSV file was created and converted into an XES file using the ProM tool "Convert CSV to XES" (Version 6.12 – Revision 45684).

APPENDIX III – Groups of drugs

drug	generic_name	event
Amikacin	Amikacin	Administrate antibiotic
Amikacin Inhalation	Amikacin	Administrate antibiotic
Amoxicillin	Amoxicillin	Administrate antibiotic
AMOXicillin 250mg CAP	Amoxicillin	Administrate antibiotic
AMOXicillin Oral Susp.	Amoxicillin	Administrate antibiotic
Amoxicillin-Clavulanate Susp.	Amoxicillin/clavulanate	Administrate antibiotic
Amoxicillin-Clavulanic 875mg TAB	Amoxicillin/clavulanate	Administrate antibiotic
Amoxicillin-Clavulanic Acid	Amoxicillin/clavulana te	Administrate antibiotic
Ampicillin	Ampicillin	Administrate antibiotic
Ampicillin Desensitization	Ampicillin	Administrate antibiotic
Ampicillin Sodium	Ampicillin	Administrate antibiotic
Ampicillin-Su 3g/100mL 100mL BAG	Ampicillin	Administrate antibiotic
Ampicillin-Sulbact Graded Challenge	Ampicillin/sulbactam	Administrate antibiotic
Ampicillin-Sulbactam	Ampicillin/sulbactam	Administrate antibiotic
Ampicillin-Sulbactam 3g VIAL	Ampicillin/sulbactam	Administrate antibiotic
Azithromy	Azithromycin	Administrate antibiotic
Azithromyc 500mg/250mL 250mL BAG	Azithromycin	Administrate antibiotic
Azithromyci	Azithromycin	Administrate antibiotic
Azithromycin	Azithromycin	Administrate antibiotic
Azithromycin	Azithromycin	Administrate antibiotic
Azithromycin (in NS)	Azithromycin	Administrate antibiotic
Azithromycin 250mg TAB	Azithromycin	Administrate antibiotic
Azithromycin 500mg VIAL	Azithromycin	Administrate antibiotic
Aztreonam	Aztreonam	Administrate antibiotic

drug	generic_name	event
Hydrocortisone Oint 2.5%	Hydrocortisone	Administrate corticosteroids
Hydrocortisone Val. Cream 0.2%	Hydrocortisone	Administrate corticosteroids
hydrocortisone-acetic acid	Hydrocortisone	Administrate corticosteroids
Imipenem-Cilastatin	Imipenem/Cilastatin	Administrate antibiotic
INV-Hydrocortisone	Hydrocortisone	Administrate corticosteroids
Lactated Ringers	Ringers lactate	Administrate fluids
Levofloxac 500mg/100mL 100mL BAG	Levofloxacin	Administrate antibiotic
Levofloxac 750mg/150mL 150mL BAG	Levofloxacin	Administrate antibiotic
Levofloxacin	Levofloxacin	Administrate antibiotic
Levofloxacin 250mg TAB	Levofloxacin	Administrate antibiotic
Levofloxacin 500mg TAB	Levofloxacin	Administrate antibiotic
Linezolid	Linezolid	Administrate antibiotic
Linezolid Antibiotic Lock	Linezolid	Administrate antibiotic
mafenide acetate	Mafenide	Administrate antibiotic
Meropenem	Meropenem	Administrate antibiotic
Meropenem Desensitization	Meropenem	Administrate antibiotic
Meropenem Graded Challenge	Meropenem	Administrate antibiotic
Methylprednisolone	Methylprednisolone	Administrate corticosteroids
Methylprednisolone ACETATE	Methylprednisolone	Administrate corticosteroids
MethylPREDNISolone Na Suc	Methylprednisolone	Administrate corticosteroids
Methylprednisolone Na Succ	Methylprednisolone	Administrate corticosteroids
MethylPREDNISolone S 1000mg VIAL	Methylprednisolone	Administrate corticosteroids
MethylPREDNISolone So 125mg VIAL	Methylprednisolone	Administrate corticosteroids
MethylPREDNISolone Sod 40mg VIAL	Methylprednisolone	Administrate corticosteroids

Bacitracin	Bacitracin	Administrate antibiotic
Bacitracin Ointment	Bacitracin	Administrate antibiotic
Bacitracin Ophthalmic Oint	Bacitracin	Administrate antibiotic
Betamethasone Dipro 0.05% Augmented Gel	Dexamethasone	Administrate corticosteroids
Betamethasone Dipro 0.05% Cream	Dexamethasone	Administrate corticosteroids
Betamethasone Dipro 0.05% Lot.	Dexamethasone	Administrate corticosteroids
Betamethasone Dipro 0.05% Oint	Dexamethasone	Administrate corticosteroids
Betamethasone Sodium Phos/Acet	Dexamethasone	Administrate corticosteroids
Betamethasone Valerate 0.1% Cream	Dexamethasone	Administrate corticosteroids
Betamethasone Valerate 0.1% Ointment	Dexamethasone	Administrate corticosteroids
Bleomycin	Neomycin	Administrate antibiotic
Bleomycin - Test Dose	Neomycin	Administrate antibiotic
CefazoLIN	Cefazolin	Administrate antibiotic
CeFAZolin 1g VIAL	Cefazolin	Administrate antibiotic
CeFAZolin 1g/50mL 50mL BAG	Cefazolin	Administrate antibiotic
CeFAZolin Desensitization	Cefazolin	Administrate antibiotic
CeFAZolin Duple 2g/50mL 50mL BAG	Cefazolin	Administrate antibiotic
CeFAZolin in Dextrose (iso-os)	Cefazolin	Administrate antibiotic
CefePIME	Cefepime	Administrate antibiotic
CefePIME (Fro 2g/100mL 100mL Bag	Cefepime	Administrate antibiotic
CefePIME (Min 2g/100mL 100mL BAG	Cefepime	Administrate antibiotic
CefePIME 2g VIAL	Cefepime	Administrate antibiotic
CefePIME 2g/100mL 100mL BAG	Cefepime	Administrate antibiotic
MethylPREDNISolone Sod Succ	Methylprednisolone	Administrate corticosteroids
MethylPREDNISolone Sodium Succ	Methylprednisolone	Administrate corticosteroids
MetroNIDAZ 500mg/100mL 100mL BAG	Metronidazole	Administrate antibiotic
MetroNIDAZOLE	Metronidazole	Administrate antibiotic
MetRONIDAZOLE (FLagyl)	Metronidazole	Administrate antibiotic
MetroNIDAZOLE (Flagyl) 250mg TAB	Metronidazole	Administrate antibiotic
MetroNIDAZOLE (Flagyl) 500mg TAB	Metronidazole	Administrate antibiotic
Metronidazole Gel 0.75%-Vaginal	Metronidazole	Administrate antibiotic
MetronidAZOLE Topical 1 % Gel	Metronidazole	Administrate antibiotic
Minocycline	Minocycline	Administrate antibiotic
Moxifloxacin	Moxifloxacin	Administrate antibiotic
Mupirocin	Mupirocin	Administrate antibiotic
Mupirocin Cream 2%	Mupirocin	Administrate antibiotic
Mupirocin Nasal Ointment 2%	Mupirocin	Administrate antibiotic
Mupirocin Ointment 2%	Mupirocin	Administrate antibiotic
Nafcillin	Nafcillin	Administrate antibiotic
Nafcillin Desensitization	Nafcillin	Administrate antibiotic
Nafcillin Graded Challenge	Nafcillin	Administrate antibiotic
Neomycin Sulfate	Neomycin	Administrate antibiotic
Nitrofurantoin (Macrodantin)	Nitrofurantoin(Bs)	Administrate antibiotic
Nitrofurantoin Monohy (Macro-BID)	Nitrofurantoin(Bs)	Administrate antibiotic
Nitrofurantoin Monohy 100mg CAP	Nitrofurantoin(Bs)	Administrate antibiotic
Nitrofurantoin Monohyd (Macro-BID)	Nitrofurantoin(Bs)	Administrate antibiotic

Cefepime Graded Challenge	Cefepime	Administrate antibiotic
Cefoxitin	Cefoxitin	Administrate antibiotic
Cefpodoxime Proxetil	Cefpodoxime	Administrate antibiotic
Cefpodoxime Proxetil 100mg TAB	Cefpodoxime	Administrate antibiotic
Ceftaroline	Cefazolin	Administrate antibiotic
Cephalexin	Cefalexin	Administrate antibiotic
Cephalexin 250mg CAP	Cefalexin	Administrate antibiotic
Ciprofloxa 400mg/200mL 200mL BAG	Ciprofloxacin	Administrate antibiotic
Ciprofloxacin	Ciprofloxacin	Administrate antibiotic
Ciprofloxacin 0.3% Oph 2.5mL BTL	Ciprofloxacin	Administrate antibiotic
Ciprofloxacin 0.3% Ophth Soln	Ciprofloxacin	Administrate antibiotic
Ciprofloxacin 250mg TAB	Ciprofloxacin	Administrate antibiotic
Ciprofloxacin 500mg TAB	Ciprofloxacin	Administrate antibiotic
Ciprofloxacin HCl	Ciprofloxacin	Administrate antibiotic
Ciprofloxacin IV	Ciprofloxacin	Administrate antibiotic
Clarithromycin	Clarithromycin	Administrate antibiotic
Clarithromycin 250mg TAB	Clarithromycin	Administrate antibiotic
Clindamycin	Clindamycin	Administrate antibiotic
Clindamycin 1% Solution	Clindamycin	Administrate antibiotic
Clindamycin 150mg CAP	Clindamycin	Administrate antibiotic
Clindamycin 600mg BAG	Clindamycin	Administrate antibiotic
Clindamycin 600mg/50mL 50mL BAG	Clindamycin	Administrate antibiotic
Clindamycin P 600mg/4mL 4mL VIAL	Clindamycin	Administrate antibiotic
Clindamycin Phosphate	Clindamycin	Administrate antibiotic
Clindamycin Solution	Clindamycin	Administrate antibiotic
Colistin	Colistin	Administrate antibiotic
Daptomycin	Daptomycin	Administrate antibiotic
NORepinephri 8mg/250mL 250mL BAG	Noradrenaline/Norepinephrine	Administrate vasopressors
NORepinephrine	Noradrenaline/Norepinephrine	Administrate vasopressors
NORepinephrine ((for dil 8mg KIT	Noradrenaline/Norepinephrine	Administrate vasopressors
NORepinephrine ((for dilution)	Noradrenaline/Norepinephrine	Administrate vasopressors
NORepinephrine (in NS)	Noradrenaline/Norepinephrine	Administrate vasopressors
Norepinephrine Bitartrate	Noradrenaline/Norepinephrine	Administrate vasopressors
ofloxacin	Ofloxacin	Administrate antibiotic
ofloxacin otic solution	Ofloxacin	Administrate antibiotic
Oxacillin	Oxacillin	Administrate antibiotic
Penicillamine	Penicillin G	Administrate antibiotic
Penicillin G Benzathine	Penicillin G	Administrate antibiotic
Penicillin G Potassium	Penicillin G	Administrate antibiotic
Penicillin V Potassium	Penicillin G	Administrate antibiotic
Penicillin V Potassium 250mg TAB	Penicillin G	Administrate antibiotic
PHENYLEPHrin 100mcg/1mL 10mL SYR	Phenylephrine	Administrate vasopressors
PHENYLEPHrin 50mg/250mL 250mL NS	Phenylephrine	Administrate vasopressors
PHENYLEPHrin 60mg/250mL 250mL NS	Phenylephrine	Administrate vasopressors
PHENYLEPHrine	Phenylephrine	Administrate vasopressors
Phenylephrine 0.5% Nasal Spray	Phenylephrine	Administrate vasopressors
PHENYLEPHrine (for 50mg/5mL VIAL	Phenylephrine	Administrate vasopressors
PHENYLEPHrine (for dilute 60mg/6mL	Phenylephrine	Administrate vasopressors
PHENYLEPHrine (for dilution)	Phenylephrine	Administrate vasopressors
PHENYLEPHrine (QuVa)	Phenylephrine	Administrate vasopressors
Phenylephrine 10 % Ophth Soln	Phenylephrine	Administrate vasopressors
Phenylephrine 2.5 % Ophth Soln	Phenylephrine	Administrate vasopressors
PHENYLEPHrine 50mg/5mL 5mL VIAL	Phenylephrine	Administrate vasopressors
Piperacilli 4,5g/100mL 100mL Bag	Piperacillin	Administrate antibiotic

Daptomycin Desensitization	Daptomycin	Administrate antibiotic
Dexamethasone	Dexamethasone	Administrate corticosteroids
Dexamethasone 10mg/1mL 1mL VIAL	Dexamethasone	Administrate corticosteroids
Dexamethasone 4mg TAB	Dexamethasone	Administrate corticosteroids
Dexamethasone Ophthalmic Soln 0.1%	Dexamethasone	Administrate corticosteroids
Dexamethasone Ophthalmic Susp 0.1%	Dexamethasone	Administrate corticosteroids
Dexamethasone Oral Soln (0.1mg/1mL)	Dexamethasone	Administrate corticosteroids
Dexamethasone Sod Phosphate	Dexamethasone	Administrate corticosteroids
DiCLOXacillin	Dicloxacillin	Administrate antibiotic
DOBUTamine	Dobutamine	Administrate vasopressors
DOBUTamine 250mg BAG	Dobutamine	Administrate vasopressors
DOPamine	Dopamine	Administrate vasopressors
DOPamine 400mg BAG	Dopamine	Administrate vasopressors
Doxycycline	Doxycycline	Administrate antibiotic
Doxycycline Hyclate	Doxycycline	Administrate antibiotic
Doxycycline Hyclate 100mg CAP	Doxycycline	Administrate antibiotic
ertapenem	Ertapenem	Administrate antibiotic
Ertapenem Sodium	Ertapenem	Administrate antibiotic
Erythromycin	Erythromycin	Administrate antibiotic
Erythromycin 0.5% Ophth 1g TUBE	Erythromycin	Administrate antibiotic
Erythromycin 0.5% Ophth Oint	Erythromycin	Administrate antibiotic
Erythromycin 250mg TAB	Erythromycin	Administrate antibiotic
Erythromycin Ethylsuccinate Suspension	Erythromycin	Administrate antibiotic
Fidaxomicin	Fidaxomicin	Administrate antibiotic
Fludrocortisone Acetate	Hydrocortisone	Administrate corticosteroids

Piperacilli 4.5g/100mL 100mL BAG	Piperacillin	Administrate antibiotic
Piperacillin-4.5g/50mL 50mL BAG	Piperacillin	Administrate antibiotic
Piperacillin-Tazo Graded Challenge	Piperacillin	Administrate antibiotic
Piperacillin-Tazob	Piperacillin/tazobacta m	Administrate antibiotic
Piperacillin-Tazob (Mini Bag +)	Piperacillin/tazobacta m	Administrate antibiotic
Piperacillin-Tazob premix	Piperacillin/tazobacta m	Administrate antibiotic
Piperacillin-Tazobactam	Piperacillin/tazobacta m	Administrate antibiotic
Piperacillin-Tazobactam Na	Piperacillin/tazobacta m	Administrate antibiotic
Piperacillin-Tazobactam Na (RX Compound)	Piperacillin/tazobacta m	Administrate antibiotic
Piperacillin-Tazobactam Na***	Piperacillin/tazobacta m	Administrate antibiotic
Plasma-Lyte A (pH 7.4)	plasma-lyte	Administrate fluids
Polymyxin B -Trimethoprim Ophth Soln	Polymyxin B	Administrate antibiotic
prednisoLONE	Methylprednisolone	Administrate corticosteroids
PrednisoLONE Acetate 0.12% Ophth. Susp.	Methylprednisolone	Administrate corticosteroids
PrednisoLONE Acetate 1% Oph DBTL	Methylprednisolone	Administrate corticosteroids
PrednisoLONE Acetate 1% Ophth. S	Methylprednisolone	Administrate corticosteroids
PrednisoLONE Acetate 1% Ophth. Susp.	Methylprednisolone	Administrate corticosteroids
Sulfacetamide 10% Ophth Soln.	Sulfacetamide	Administrate antibiotic
SulfADIAZINE	Sulfadiazine	Administrate antibiotic
SulfaSALAzine DR	Sulfasalazine	Administrate antibiotic
SulfaSALAzine_	Sulfasalazine	Administrate antibiotic
Tetracaine 0.5% (******Ophth)	Tetracycline	Administrate antibiotic
Tetracaine 0.5% (Ophth)	Tetracycline	Administrate antibiotic
Tetracaine 0.5% (Ophth) 2mL DBTL	Tetracycline	Administrate antibiotic
Tetracaine 0.5% (Ophth) 4mL DBTL	Tetracycline	Administrate antibiotic

Fosfomycin Tromethamine	Fosfomycin	Administrate antibiotic
gatifloxacin	Gatifloxacin	Administrate antibiotic
Gentamicin	Gentamicin	Administrate antibiotic
Gentamicin (Premix)	Gentamicin	Administrate antibiotic
Gentamicin (Premix) 80mg BAG	Gentamicin	Administrate antibiotic
Gentamicin 0.1% Cream	Gentamicin	Administrate antibiotic
Gentamicin Sulfate	Gentamicin	Administrate antibiotic
Hydrocortison 100mg/2mL 2mL VIAL	Hydrocortisone	Administrate corticosteroids
Hydrocortisone	Hydrocortisone	Administrate corticosteroids
Hydrocortisone (Rectal) 2.5% Cream	Hydrocortisone	Administrate corticosteroids
Hydrocortisone Acetate 10% Foam	Hydrocortisone	Administrate corticosteroids
Hydrocortisone Acetate Suppository	Hydrocortisone	Administrate corticosteroids
Hydrocortisone Cream 0.5%	Hydrocortisone	Administrate corticosteroids
Hydrocortisone Cream 1%	Hydrocortisone	Administrate corticosteroids
Hydrocortisone Cream 2.5%	Hydrocortisone	Administrate corticosteroids
Hydrocortisone Enema	Hydrocortisone	Administrate corticosteroids
Hydrocortisone Na Succ	Hydrocortisone	Administrate corticosteroids
Hydrocortisone Na Succ.	Hydrocortisone	Administrate corticosteroids
Hydrocortisone Na Succinate	Hydrocortisone	Administrate corticosteroids
Hydrocortisone Oint 0.5%	Hydrocortisone	Administrate corticosteroids
Hydrocortisone Oint 1%	Hydrocortisone	Administrate corticosteroids

Tetracaine 0.5% Ophth 15mL DBTL	Tetracycline	Administrate antibiotic
Tetracaine 0.5% Ophth Soln	Tetracycline	Administrate antibiotic
Tetracycline	Tetracycline	Administrate antibiotic
Tigecycline	Tigecycline(Bs)	Administrate antibiotic
Tobramycin 0.3% Ophth Ointment	Tobramycin	Administrate antibiotic
Tobramycin 0.3% Ophth Soln	Tobramycin	Administrate antibiotic
Tobramycin Fortified Ophth. Soln.	Tobramycin	Administrate antibiotic
Tobramycin Inhalation Soln	Tobramycin	Administrate antibiotic
Tobramycin Sulfate	Tobramycin	Administrate antibiotic
Trimethoprim	Trimethoprim(Bs)	Administrate antibiotic
Vancomycin 1000mg/200mL 200mL BAG	Vancomycin	Administrate antibiotic
Vancomycin	Vancomycin	Administrate antibiotic
vancomycin	Vancomycin	Administrate antibiotic
Vancomycin ****	Vancomycin	Administrate antibiotic
Vancomycin 14mg/mL Ophth Soln	Vancomycin	Administrate antibiotic
Vancomycin 25mg/mL Ophth Soln	Vancomycin	Administrate antibiotic
Vancomycin Antibiotic Lock	Vancomycin	Administrate antibiotic
Vancomycin Enema	Vancomycin	Administrate antibiotic
Vancomycin Intraventricular	Vancomycin	Administrate antibiotic
Vancomycin Oral Liquid	Vancomycin	Administrate antibiotic