Pontifícia Universidade Católica
do Rio de Janeiro

Raphaela Gasparini François Diehl de Souza

Method proposal to transform medical guidelines to a conceptual process model: A case study for Sepsis

DISSERTAÇÃO DE MESTRADO

Dissertation presented to the Programa de Pós-Graduação em Engenharia de Produção of the Departamento de Engenharia Industrial, PUC-Rio as partial fulfillment of the requirements for the degree of Mestre em Engenharia de Produção – Opção Profissional.

Advisor: Prof. Silvio Hamacher

Rio de Janeiro
November 2016

Pontifícia Universidade Católica
do Rio de Janeiro

Raphaela Gasparini François Diehl de Souza

Method proposal to transform medical guidelines to a conceptual process model: A case study for Sepsis

Dissertation presented to the Programa de Pós-Graduação em Engenharia de Produção of the Departamento de Engenharia Industrial do Centro Técnico Científico da PUC-Rio, as partial fulfillment of the requirements for the degree of Mestre. – Opção Profissional.

Prof. Silvio Hamacher
Orientador
Departamento de Engenharia Industrial - PUC-Rio

Erin Streton
Philips Research

André Miguel Japiassu
Fundação Oswaldo Cruz

Prof. Márcio da Silveira Carvalho
Coordinator of the Centro Técnico Científico da PUC-Rio

Rio de Janeiro, November 24rd, 2016.

Raphaela Gasparini François Diehl de Souza

Graduated in Industrial Engineering form Pontifical Catholic University of Rio de Janeiro – PUC-Rio in 2005.

Bibliographic data

Souza, Raphaela Gasparini François Diehl de

Method proposal to transform medical guidelines to a conceptual process model : a case study for Sepsis / Raphaela Gasparini François Diehl de Souza ; advisor: Silvio Hamacher. – 2016.

113 f. : il. ; 30 cm

Dissertação (mestrado)–Pontifícia Universidade Católica do Rio de Janeiro, Departamento de Engenharia Industrial, 2016.

Inclui bibliografia

1. Engenharia Industrial – Teses. 2. Assistência médica. 3. Implementação de diretrizes clínicas. 4. Caminhos clínicos. 5. Modelagem de processos. I. Hamacher, Silvio. II. Pontifícia Universidade Católica do Rio de Janeiro. Departamento de Engenharia Industrial. III. Título.

CDD: 658.5

Acknowledgments

I would like to thank my supervisor, Silvio Hamacher, for introducing me to this interesting research and for his good advices throughout my Master program.

I would like to express my sincere appreciation to Erin Streton, at Philips Research. I am gratefully indebted to her for her very valuable comments and all the support through the development of this thesis.

I would like to thank the team at Philips Research and at Tecgraf for their collaboration in the project.

I would also like to offer my special thanks to Ricardo Quintano and Giulia Paruolo for their support and friendship throughout the project development. Without them, it would not be as joyful.

I am grateful for all my colleagues and teachers of PUC-Rio for creating such a great learning environment.

I would like to thank CNPq for the financial support.

Above all, I want to express my profound gratitude to my husband and children for their love, support and encouragement throughout my years of study. This accomplishment would not have been possible without them. Thank you.

Abstract

Souza, Raphaela Gasparini François Diehl de; Hamacher, Silvio (Advisor). **Method proposal to transform medical guidelines to a conceptual process model: A case study for Sepsis.** Rio de Janeiro, 2016. 113p. MSc. Dissertation – Departamento de Engenharia Industrial, Pontifícia Universidade Católica do Rio de Janeiro.

One of the main issues for health professionals is how to improve the quality of care offered to patients. Problems related to healthcare quality and high costs are observed not only in Brazil but also in developed countries. The wide variation in a particular disease treatment process can lead to medical errors, overuse of resources and unnecessary patient suffering. Therefore, nowadays many institutions around the world are developing clinical evidence-based guidelines with recommendations for the treatment of several diseases. However, there is a great difficulty to implement these guidelines. Usually written by doctors, these documents are difficult to read by non-physicians, who play an important role in its implementation, such as system developers and administrators. This master thesis proposes a method to transform clinical guidelines in a conceptual process model that can be implemented in a software. The method facilitates the reading and understanding of these guidelines recommendations. The transformation of guidelines recommendations in process information facilitates its implementation in any hospital department. The proposed method was applied for the Sepsis diagnosis and treatment process. The conceptual process model designed in this Master Thesis will be used in the development of a Clinical Pathway technological solution for Sepsis treatment. Sepsis is a serious medical condition that affects millions of people worldwide each year, with high mortality rates. The early recognition of its symptoms and proper treatment significantly increases the survival probability. The intent behind the proposed method in this thesis is to increase the use of clinical guidelines for Sepsis in hospitals.

Keywords

Healthcare; Clinical Practice Guidelines Implementation; Clinical Pathways; Process Modelling.

Resumo

Souza, Raphaela Gasparini François Diehl de; Hamacher, Silvio. **Proposta de método para converter de diretrizes clínicas a um modelo de processo conceitual: Um estudo de caso para Sepsis.** Rio de Janeiro, 2016. 113p. Dissertação de Mestrado – Departamento de Engenharia Industrial, Pontifícia Universidade Católica do Rio de Janeiro.

Uma das principais questões dos profissionais de saúde é como aprimorar a qualidade do tratamento oferecido aos pacientes. Problemas relacionados à qualidade e altos custos nos serviços de saúde são observados não somente no Brasil, mas também em países desenvolvidos. A grande variação no processo de tratamento de uma determinada doença pode gerar erros médicos, uso excessivo de recursos e sofrimento desnecessário aos pacientes. Por esse motivo, atualmente muitas instituições ao redor do mundo desenvolvem diretrizes clínicas baseadas em evidências, com recomendações para o tratamento de diversas doenças. A utilização de diretrizes clínicas pode reduzir a variabilidade no processo de tratamento e trazer benefícios como redução da mortalidade e redução de custos. No entanto, existe uma grande dificuldade para implementação destas diretrizes. Normalmente escritas por médicos, estes documentos são de difícil leitura para não-médicos, que tem um papel importante em sua implementação, como desenvolvedores de sistema e administradores. Esta dissertação propõe um método para transformar diretrizes clínicas em um modelo de processo conceitual que possa ser implementado num software. O método proposto facilita a leitura e entendimento das recomendações presentes nestas diretrizes. A transformação das recomendações em informações de processo facilita a implantação das diretrizes em qualquer departamento hospitalar. Além disto, o método permite a comparação de recomendações propostas em diferentes publicações de diretrizes clínicas. O método proposto foi aplicado no processo de diagnóstico e tratamento da Sepse. A Sepse é uma condição grave que acomete milhões de pessoas por ano no mundo, com altos índices de mortalidade. A rapidez na identificação dos sintomas e início do tratamento adequado aumenta significativamente a probabilidade de sobrevivência. A intenção do método proposto nesta dissertação é aumentar a utilização de diretrizes clinicas de Sepse em hospitais. O modelo de processo conceitual apresentado no método será utilizado no desenvolvimento de

uma solução tecnológica real para suportar o processo de identificação e tratamento da Sepse em hospitais. Este modelo foi construído com base na revisão da literatura de Sepse e no estudo de caso realizado em um hospital de grande porte no Brasil. O modelo desenvolvido foi validado por médicos durante o estudo de caso e por uma equipe de especialistas em desenvolvimento de sistemas hospitalares.

Palavras-chave

Assistência médica; Implementação de diretrizes clínicas; Caminhos clínicos; Modelagem de processos.

Table of Contents

List of Figures

List of Tables

1
Introduction

Quality problems in medical care are not a new issue. Variations in medical practice as well as actual medical errors have been pointed out for many decades (Gross et al., 2001). Studies have estimated that between 30 to 40% of patients do not receive treatments that follow recommended best practice. Yet, research suggests that 20% to 25% of patients have treatments that are unnecessary or potentially harmful and 30% to 40% of patients do not receive treatments of proven effectiveness (Grol and Grimshaw, 2003; Elshaug et al., 2009). One of the most persistent problems in providing high-quality health care is the gap between research evidence and clinical practice (Grol and Grimshaw, 2003).

Therefore, there is an increasing pressure in healthcare professionals to standardize their clinical practice in order to prevent undesired variations. Clinical practice guidelines (CPGs) are developed in order to achieve this purpose. In fact, CPGs are, currently, the best way to convey information to healthcare professionals to ensure that their clinical practice follows the rules of medical procedures (Oliveira et al., 2014).

The worldwide interest over the past 10–15 years in clinical guideline development and implementation has grown, reflected by an increasing body of primary and secondary research in this area (Prior et al., 2008).

The noticed benefits of guideline implementation include reducing healthcare variations, improving diagnostic accuracy, promoting effective therapy, and discouraging ineffective – or potentially harmful – interventions (Rosenfeld et al., 2013).

Nevertheless, effective and timely transfer of guidelines into clinical practice remains fragmented and inconsistent (Ploeg et al., 2007). Researchers have noticed many barriers to the successful implementation of clinical practice guidelines (Grol, 2001).

The format of CPGs documents is not standardized and shows variations according to the organization producing the guideline and the clinical area it addresses (Oliveira et al., 2014). In addition, these documents have a structure that makes them difficult to consult. Usually they are long texts and the clinical recommendations are contained in the body of that text. This aspect interferes with the retrieval of relevant information by healthcare professionals and makes the consultation for real time application rather complicated. Moreover, these long documents are difficult to update, which is a drawback in the evolution of a guideline. They should accompany the development of clinical knowledge in a specific medical area (Rosenbrand et al., 2008).

The vocabulary used in CPGs may also denote vagueness (Codish and Shiffman, 2005). Sometimes the boundaries of a term are not completely understood by healthcare professionals.

Therefore, there is a need to create methodologies to transform the information contained in clinical practice guidelines into information that are necessary to implement them. This master thesis aims to create a method that will facilitate the understanding of clinical practice guidelines and translate their recommendations as process information. The secondary objectives are to apply the proposed method for existing Sepsis guidelines and to verify its adherence to a real Sepsis treatment process in a case study hospital.

Sepsis is one of the leading causes of death worldwide (Fei et al., 2016). Despite advances in medicine (i.e. vaccinations, antibiotics, acute care hospitals, and evidence-based guidelines), sepsis remains the primary cause of death from infection and is one of the most expensive ailments to treat (Doolen et al., 2015). Patients with sepsis have higher hospital bills and longer lengths of stay compared to patients with other illnesses (Doolen et al., 2015).

The alarming rise in sepsis rates during the last two decades has sparked global efforts to improve awareness, early recognition, diagnosis, and management (Gohil et al., 2016).

Therefore, the proposed method developed in this master thesis was applied for Sepsis guidelines. The case study was the modelling of a real Sepsis identification and treatment process from a Brazilian large private hospital.

In Chapter 2, it is presented the literature review performed to form the basis for this Master Thesis. In Chapter 3, the methodology steps to develop the proposed method are presented. In Chapter 4, the proposed method is presented and in Chapter 5, the application of the method for three different selected guidelines is presented. In Chapter 6, a conclusion and suggestion for future work is presented.

2
Literature Review

The research objective of the Literature Review is to describe the four different subjects that influence the study and development of the proposed method to read and classify clinical practice guidelines as a conceptual process model.

The first subject is related to clinical practice guidelines, protocols and pathways. Clinical practice guidelines are written to give medical staff date and evidence-based recommendation on medical best practices to handle a specific patient disease or condition. Protocols and Pathways are tools to implement guidelines in a specific hospital. They differ in the level of information abstraction and in their objectives.

The second subject aims to different business process management and modelling considerations to relate business process to healthcare processes. The modeling language, tools selected, and reasons for the selection are also described.

The third subject is the Diagnostic Reasoning Process, which presents a process view for the steps between a patient admission in a hospital and the treatment for a medical condition.

The fourth subject aims to describe the Sepsis condition, its characteristics, impacts and treatment guidelines developed to reduce the mortality rate in affected patients.

These four subjects and their relation form the basis for the development of the method proposed in this master thesis, as represented in Figure 1:

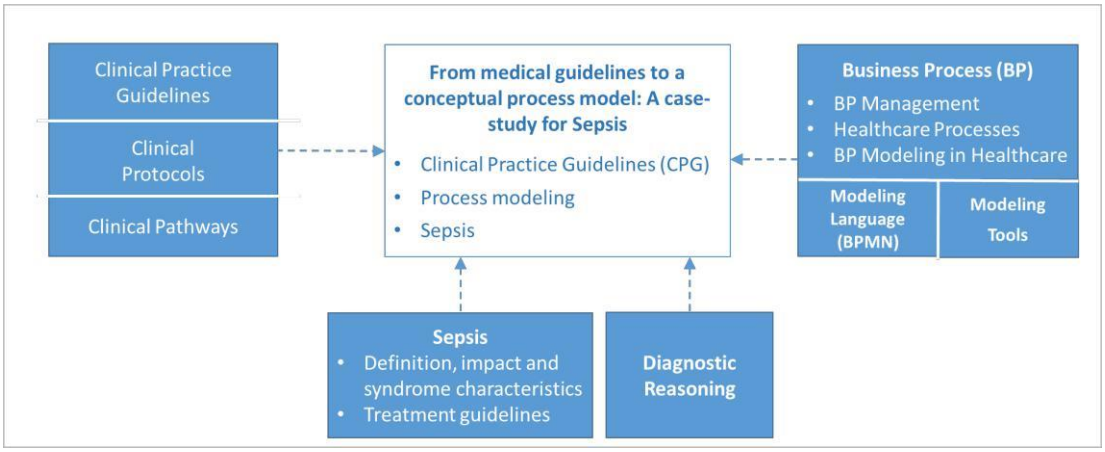

Figure 1 – Literature Review Structure. Source: Prepared by author.

2.1.
Clinical Practice Guidelines

Clinical practice guidelines, CPGs, are defined as systematically formulated documents that assist practitioners to make clinical decisions informed by best available evidence (Prior et al., 2008).

Although the term "Clinical Practice Guidelines" is widely used and its importance is recognized, there is still confusion regarding its definition. According to Gooch and Roudsari (2011), the term clinical guidelines is often used interchangeably with clinical pathways and protocols, although each may be considered a distinct type of workflow with a different scope:

> A **clinical practice guideline** provides recommendations for best practice for the clinical domain addressed by the guideline, but does not provide implementation details, such as determining which role should perform a specific task. Instead, it details which task should be done in a specific time frame (Gooch and Roudsari, 2011);
>
> A **clinical protocol** provides a local, consensus view of a guideline or routine with explicit steps for implementation (Gooch and Roudsari, 2011);

> A **clinical pathway** is defined by the European Pathway Association as ‘A complex intervention for the mutual decision making and organization of predictable care for a well-defined group of patients during a well-defined period’ (Vanhaecht et al., 2010).

In 2007, Lenz and Reichert classified the influence of different levels of explicit medical knowledge on the patient care process and related it with guidelines and pathways. According to Lenz and Reichert (2007), CPGs are domain-specific medical knowledge available in medical literature that require consensus among medical experts (and scientific evidence) and Clinical Pathways are site-specific knowledge that require consensus among cooperating healthcare professionals (Lenz and Reichert, 2007).

It is important to say that guideline recommendations may not be applied under all circumstances. It rests with the clinician to decide whether a certain recommendation should be adopted or not, taking into consideration the unique set of clinical facts presented in connection with each individual patient as well as the available resources (Reinhart et al., 2010).

The potential benefits from the implementation of CPGs include the reduction of morbidity and mortality, efficiency improvement and cost containment. They also provide their users with a reference by which they guide their clinical practice, and measurable criteria to assess their performance. The evidence contained in CPGs is used, at the same time, to inform healthcare professionals of the latest developments in scientific knowledge and to justify their decisions during the clinical process (Thomson, 2000).

Medical practitioners, overloaded with information, do not always have the time, or the computational means, to use the valuable knowledge encoded in clinical practice guidelines during actual patient treatment. Although there are thousands of text-based CPGs, there is usually no automated support for their specification and application, even though clinicians at the point of care would obviously benefit from such support (Shalom et al., 2008).

In order for CPGs to be effective, they need to be integrated with the care flow and provide patient-specific advice when and where needed. Hence, their formalization as computer-interpretable guidelines makes it possible to develop a decision-support system, which have a better chance of impacting clinician behavior than narrative guidelines (Patel et al., 2001).

Studies have shown that computer-based clinical decision support systems, when developed to provide patient-specific assistances in decision-making and integrated with clinical workflow, can improve clinicians' compliance with CPGs and patient outcomes. However, there exist several obstacles to the implementation of computer-based guideline systems. For example, translation of CPGs into computer algorithms from their published formats, which are typically not computer interpretable, is not an easy task (Wang et al., 2002).

In the field of Medical Informatics, one can find several modeling methodologies and tools for translation of CPGs into computer interpretable guidelines. Several research groups have suggested various ways for conducting the collaboration between clinical experts and knowledge engineers. A good overview of methods for formalizing clinical practice guidelines can be found in Peleg (2013).

The method proposed in this Master Thesis can be used as a tool to the design the Sepsis identification and treatment process, based in any Sepsis guideline. It differs from the existing modeling methodologies because it is focused in the Sepsis condition and it is intended to support the system developer to better understand the guidelines recommendations as process information, to create a high quality computer interpretable guideline.

2.2.
Clinical Protocols

Clinical protocols are agreed statements about a specific issue, with explicit steps based on clinical guidelines and/or organizational consensus. A protocol is not specific to a named patient (Fox et al., 2006). They are practice-area specific and specify details concerning the treatment and / or procedure endorsed by the employing agency (Gallery et al., 2016).

By definition, a protocol is seen as a local version of a guideline, meant to be useful as a guide for daily clinical care (Hommersom et al., 2006).

While guidelines are usually extensive and detailed documents, they do not contain detailed recommendations about drug duration, dose (drug formularies) or how to accomplish an actual procedure. The information specified in a clinical protocol builds on that provided in the clinical guideline and directs the care provider on specific elements of the recommended care (Gallery et al., 2016).

2.3.
Clinical Pathways

Clinical pathways can be seen as a methodology to organize the care process. Although there is no single, widely accepted definition of a clinical pathway (De Bleser et al., 2006), in general they represent a sequence of activities to be executed by a multidisciplinary team composed of doctors, nurses and other healthcare professionals for the treatment of a specific disease/patient condition. There are also many different terms related to the meaning of clinical pathways, including (amongst others) care map, care pathway, critical pathway, integrated care pathway, protocol and guidelines (Kinsman et al., 2010).

A clinical pathway is defined by the European Pathway Association as ‘A complex intervention for the mutual decision making and organization of predictable care for a well-defined group of patients during a well-defined period’.

Defining characteristics of pathways include: an explicit statement of the goals and key elements of care based on evidence, best practice and patient expectations; the facilitations of the communication and coordination of roles, and sequencing the activities of the multidisciplinary care team, patients and their relatives; the documentation, monitoring, and evaluation of variances and outcomes; and the identification of relevant resources (Vanhaecht et al., 2010).

Clinical pathways have been implemented internationally since the 1980s (Kinsman et al., 2010). They originated in nursing practice when the application of a business process management approach to the organization of clinical practice was used to improve the quality and efficiency of patient care (Seethamraju, 2012).

In 2003, it was reported that clinical pathways had been implemented in more than 80% of hospitals in the USA. This represents an enormous resource commitment both in the development of pathways, the training of staff, and in the ongoing implementation of pathways in the hospital setting (Kinsman et al., 2010).

In 2006, De Bleser et al. conducted a study to survey the definitions used in describing the concept and to derive key characteristics of clinical pathways. They concluded that clinical pathway explicitly states the goals and key elements of care based on Evidence Based Medicine (EBM) guidelines, best practice and patient expectations. It achieves that by facilitating the communication, coordinating roles and sequencing the activities of the multidisciplinary care team, patients and their relatives; by documenting, monitoring and evaluating variances; and by providing the necessary resources and outcomes.

Based on 84 different definitions founded, De Bleser et al. (2006) listed the main characteristics, aims and outcomes of a clinical pathway, as shown in Table 1:

Characteristics:	Aims and outcomes:
Homogeneous patient group	Efficiency of care
Multidisciplinary team	Evaluation
Time scale	Quality of care
Inventory of actions	Decreasing variance
Management of patient care	Clinical outcome
Efficiency of care	Change of processes
Sequencing	Compliance
Variance analysis	Patient satisfaction
Evidence based medicine (EBM)	Data collection
Improving quality of care	Best practice
Part of patient record	Accountability
Guidelines	
Education	
Communication	
Data collection	

Table 1 - Analysis of the definitions of clinical pathways. Source: Adapted from De Bleser et al. (2006).

They also observed that most often, clinical pathways are strictly limited to tasks, whereas time was limited to the hospitalization period. They observed that tasks were used in clinical pathways to describe goals, problems and various key elements pertaining to the care of patients, whereas time was used more to describe patient time than to describe professional time. (De Bleser et al., 2006).

When developing a clinical pathway, one needs to take into account the evidence based key interventions through the treatment process, the interdisciplinary teamwork, the patient involvement and the available resources (Gooch and Roudsari, 2011).

According to Gesme and Wiseman (2011), the available options and treatment costs for any given disease can vary widely simply depending on the facility where the treatment is delivered and the exact nature of the treatment regimen itself. Thus, most clinical pathways are developed and defined at the local or institutional level by the providers who are expected to implement then. This approach takes into account variations in the ways providers practice medicine within their local ecosystem to ensure that the needs of their patients are met. Some clinical pathways, however, are intended to standardize treatment protocols at a national, state, or regional scale to further reduce variations in the

delivery of evidence-based care across sites, particularly in the absence of scientific merit for regional or local variability in treatment regimens.

2.4.
Business Process Modeling and Analysis in Healthcare

2.4.1.
Healthcare Processes

Healthcare Processes can be classified as medical processes, administrative, and support processes. Medical processes are those directly related to providing health services to patients and include activities such as diagnosis tests or treatment processes. Administrative processes support hospital organization management, for example, Billing and Patient admission. Support processes support the provision of medical/hospital services (Cleaning, Laundry and Kitchen) (Levy et al., 2003).

According to Rebuge and Ferreira (2012), medical treatment processes are directly linked to the patient and are executed according to a diagnostic– therapeutic cycle, comprising observation, reasoning and action. The diagnostic– therapeutic cycle heavily depends on medical knowledge to deal with case-specific decisions that are made by interpreting patient-specific information. On the other hand, administrative and support processes are generic process patterns that support medical treatment processes in general.

According to Lenz and Reichert (2007), healthcare processes are not trivial. They are executed under an environment that is continually changing and that is commonly accepted to be one of the most complex when compared to other environments. The healthcare environment and its underlying processes have peculiar characteristics with respect to their degree of dynamism, complexity and multi-disciplinary nature. In general, healthcare processes are recognized to have the following characteristics: are highly dynamic, highly complex, multi-disciplinary, highly depends on distributed human collaboration, and participants

have the expertise and autonomy to decide their own working procedures (Lenz and Reichert, 2007).

In this study, first we create a method to transform clinical practice guidelines into a high level conceptual process. This process is generic enough to be site-independent. That means that in this process the details required from specific site demands (like roles and responsibilities in the process, individual tasks and site-specific variables and decision rules) are not considered.

2.4.2. Business Process Management (BPM)

Business processes have been a subject of formal study from multiple perspectives since the start of industrial age and is an evolving paradigm. Starting from scientific management to the current business process management (BPM) many perspectives of processes exist in the literature. Several initiatives and approaches such as systems thinking, operations research, data processing, socio-technical systems, systems modeling, process reengineering, Total Quality Management, Lean and Six Sigma systems and process models have all processes as their underlying theme (Møller et al., 2009).

BPM blends paradigms and methodologies from different disciplines. It is neither a new management theory nor another form of automation. It manages the lifecycle of improvement and optimization (Møller et al., 2009).

Recently, BPM has come to be considered a valuable asset in the healthcare domain. BPM heavily relies on process models to identify, review, validate, represent, and communicate process knowledge (Müller and Rogge-Solti, 2011).

From the perspective of Business Process Management, a Clinical Pathway can be seen as a predefined process model to develop and implement well-organized care. Apart from the medical content, it is important to analyze the treatment as a process, in order to continuously improve quality and efficiency and to benefit from the BPM methodologies.

Usually hospitals protocols are a predefined list of sequential activities. Once one is able to model protocols as business processes, the hospital can benefit from the advantages of having structured business processes operating.

According to Vanhaecht et al. (2010), recent research describes that during the pathway development, even before the implementation of the pathway, the organization of the care process can be improved. Over time the team will improve the quality and efficiency of the care process by analyzing the actual organization and performance of the care process. Based on the bottlenecks, the team will improve the process by using the plan–do–study–act cycle for continuous improvement with respect to patient characteristics and expectations.

2.4.3. Process Modeling in Healthcare

The importance of the process point of view is not restricted to a specific enterprise sector. In the field of health, as a result of the nature of the service offered, health institutions' processes are also the basis for decision making which is focused on achieving their objective of providing quality medical assistance (Barbagallo et al., 2015).

According to Ruiz et al. (2012), the main challenges of business process modelling in healthcare are the definition of healthcare processes, the multi-disciplinary nature of healthcare, the flexibility and variability of the activities involved in health care processes, the need of interoperability between multiple information systems, and the continuous updating of scientific knowledge in healthcare.

Clinical practice guidelines provides the most recent information on the best and evidence-based clinical practices. Being able to relate the knowledge available in the guidelines with process information is crucial to keep the process model up to date and aligned with the latest guidelines recommendations.

2.4.4.
Business Process Model and Notation (BPMN 2.0)

Any system development process covering the system's lifecycle form analysis through design, specification, implementation, testing, certification, and maintenance must be started from the business needs to be met by running an appropriate business process. For describing that business process in a way understandable by both humans and machines, business process modeling is widely used in any kind of enterprises. This also holds for the medical domain. The objectives driving these processes range from the economic aspects of process optimization through the increase of transparency and exchangeability of data and knowledge even including the assurance and certification of quality. The development and standardization of meta-languages to formally describe and model business processes as well as solutions for the execution of model files enables the reuse of those models for different purposes with theoretical and practical implications (Ruiz et al., 2012).

Various modeling languages have been developed to cover different aspects of business processes and organizations. In that context, the Business Process Modeling and Notation (BPMN) standardized by the Object Management Group (OMG) plays a pivotal role. Some of the models and notations (e.g. organigram, value added chains) are used to describe structures and processes on a very high abstract level and cannot be executed. In contrast BPMN and the Business Process Execution Language (BPEL) facilitate execution and re-usage modeling problems (Ruiz et al., 2012).

BPMN is comprehensible by different kinds of specialists: such as computer scientists, IT staff, healthcare workers, and management personnel (Barbagallo et al., 2015).

In 2011, the OMG release a new standard called BPMN 2.0. The main characteristic of BPMN 2.0 is that this modeling technique simplifies and

facilitates future software implementation, which will be needed to manage and optimize the process. BPMN is essentially a derivative of the formalism of a flow chart, but with some additions and modifications, which overcome certain limitations in modeling business processes, and enable process adaptation, flexibility, and evolution. It allows one to construct business process diagrams representing graphs, or networks made of "objects" exhibited by the process activities, connected by control flows, which define the logical relationship, the dependencies, and the order of execution of the activities. The use of the BPMN standard can also define a specific workflow, for the process under investigation, and its subsequent development including computerization, with resource management, and the definition of the actors involved (Barbagallo et al., 2015).

When modelling the conceptual process model the BPMN 2.0 standard will be used.

In this study, the Bizagi Modeler software is used for the design of the conceptual process model. This process modeler is a free tool that is easy to use and compatible with BPMN 2.0 standard, designed to map, model and diagram all types of workflows. It is available at http://www.bizagi.com/en/bpm-suite/bpm-products/modeler.

2.5. The Diagnostic Reasoning Process

Diagnostic reasoning is the process of thinking about a clinical problem to form a diagnosis (Rendon et al., 2015). Clinicians solve diagnostic problems using both nonanalytic and analytic reasoning processes. Although evidence is inconclusive, some clinical reasoning experts suggest the use of reflective strategies to enhance diagnostic accuracy, especially in a complicated case (Mamede et al., 2008).

In literature, various models have been proposed for Diagnostic Reasoning in clinical practice. For this study, we analyzed five different models (Balogh et al., 2016; Rendon et al., 2015; Nendaz and Perrier, 2012; Bowen, 2006; Rothstein and Echternach, 1986) to identify the key elements in the diagnostic reasoning process and use them, combined with the Sepsis evolution stages, to create a generic sepsis identification and treatment process.

In its 2016 "Improving Diagnosis in Health Care" report, Balogh et al. have developed the framework presented in Figure 2 to define the diagnostic process.

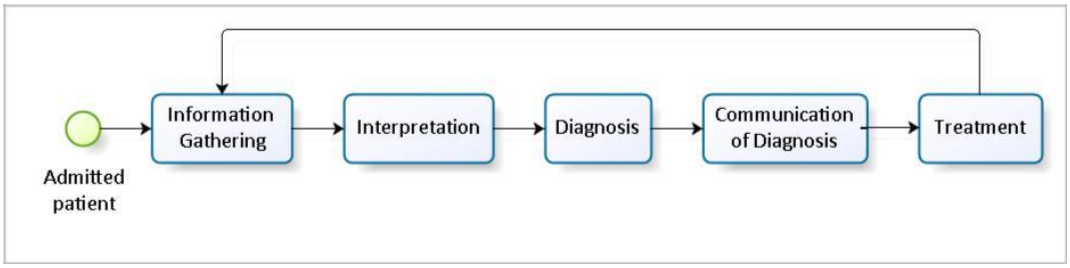

Figure 2 – Institute of Medicine Committee's conceptual model of the diagnostic process. Source: Adapted from Balogh et al. (2016).

According to Rendon et al. (2015), the literature describes five steps in the reasoning process (Figure 3). In the early stages of data collection, hypotheses emerge that feed back into data collection behaviors as the clinician seeks confirmatory evidence. This complex interplay between data collection and hypothesis generation/elimination leads to a more clearly defined understanding of the patient's presentation. The synthesis of the patient's presentation, including epidemiologic risk factors, symptoms, signs, laboratory, and radiologic studies is called the "problem representation." After a clinician conceives the problem representation, he or she reviews the mental representations of diseases (i.e., illness scripts) to determine a hypotheses by finding the disease presentations that best match the formulated problem representation.

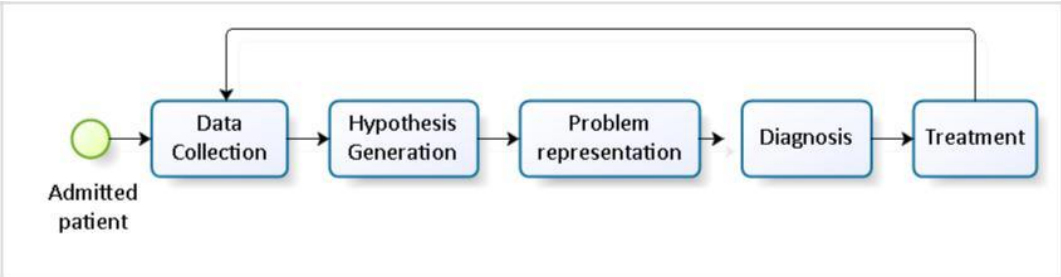

Figure 3 – Demonstration of the non-linear nature of clinical reasoning. Source: Adapted from Rendon et al. (2015).

In 2012, Nendaz and Perrier presented the dual process of reasoning including immediate recognition of clinical picture (non-analytic process) and hypothetico-deductive process (analytic process), shown in Figure 4.

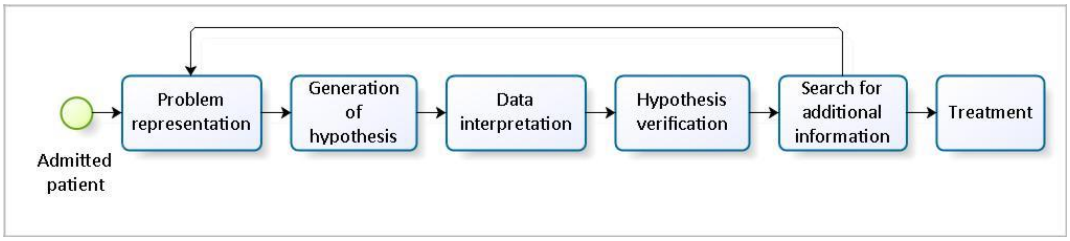

Figure 4 - Schematic representation of the dual process of reasoning. Source: Adapted from Nendaz and Perrier (2012).

In 2006, Bowen presented key elements of clinical diagnostic reasoning, as shown in Figure 5

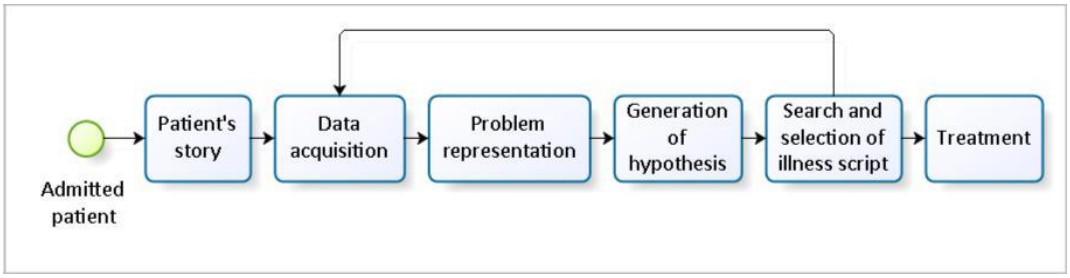

Figure 5 – Key elements of the clinical diagnostic reasoning process. Source: Adapted from Bowen (2006).

In 1986, Rothstein and Echternach presented a hypothesis-oriented algorithm for clinicians (HOAC), which is designed to aid physical therapists in clinical decision making and patient management (Figure 6).

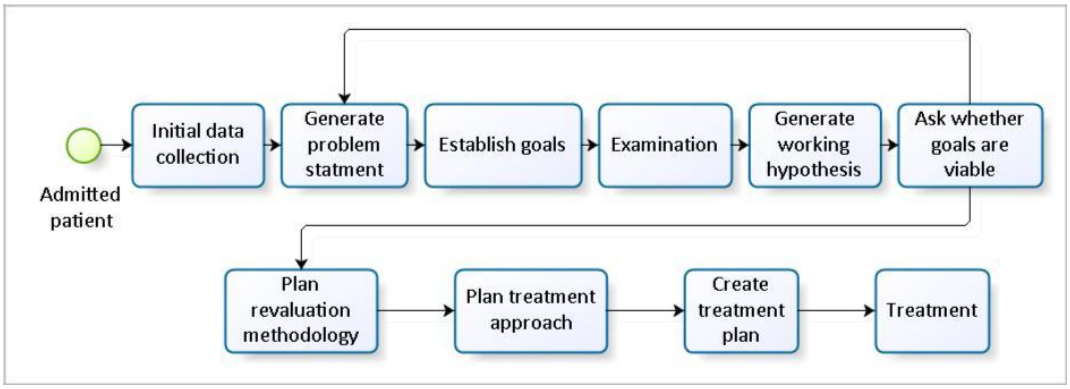

Figure 6 – Diagnostic Reasoning algorithm. Source: Adapted from Rothstein and Echternach (1986).

All these models present elements that represent the first steps from patient admission in a hospital to the start of a treatment and apply from simple to more complex diseases.

All the models present steps followed to stablish treatment after a patient is admitted. From the selected model is possible to identify the key elements in the process. These key elements will be used as basis for the development of the conceptual process model presented in the proposed method.

2.6. Sepsis

Sepsis is a serious medical condition caused by an overwhelming immune response to an infection. Sepsis is unpredictable and can progress rapidly, possibly leading to death (NIH, 2015).

The condition is defined by the presence of both infection and a systemic inflammatory response (NCEC, 2014), which can lead to severe sepsis (acute organ dysfunction secondary to documented or suspected infection) and septic shock (severe sepsis plus hypotension not reversed with fluid resuscitation). Severe sepsis and septic shock are major healthcare problems, affecting millions

of people around the world each year, killing one in four patient diagnosed with Sepsis, and increasing in incidences (Dellinger et al., 2013).

Sepsis is a common and time-dependent medical emergency. It can affect a person of any age, from any social background and can strike irrespective of underlying good health or concurrent medical conditions. International sepsis campaigns that have introduced and promoted an approach to sepsis care based on early recognition of sepsis with resuscitation and timely referral to critical care have reported reductions in mortality from severe sepsis/septic shock in the order of 20-30% (NCEC, 2014).

Sepsis is a leading global health and financial burden and is expected to increase further with an aging population. Fixed direct costs associated with the spectrum of sepsis, such as increased Intensive Care Unit, Length of Stay, ICU staffing, medications and new technologies are significant. Equally concerning are the indirect costs associated with sepsis, such as loss of earnings, productivity and mortality. In fact, indirect costs may account for up to 70% of the total costs of sepsis. European studies estimate that a typical episode of severe sepsis will cost a healthcare institution around €25,000. In addition, long-term mortality in previously healthy patients with severe sepsis/septic shock has been shown to be worse than that of those patients with non-septic critical illness and of the underlying general population. (NCEC, 2014).

In Brazil, a study conducted in 2015 by the Latin American Sepsis Institute (ILAS) considering data from 116 health centers across the country showed that mortality rates reached 30.8 % for patients with severe sepsis and 64.3% for patients with septic shock (ILAS, 2015).

As with most diseases and syndromes, sepsis is a progressive disorder and includes several stages (Bone et al., 1992). These stages, describing the inflammatory response to infection, include systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock. The evolution of these stages is related with an increase in the mortality rate. Figure 7 shows the main

symptoms presented along the syndrome's progression and the Brazilian mortality rates associated with each stage.

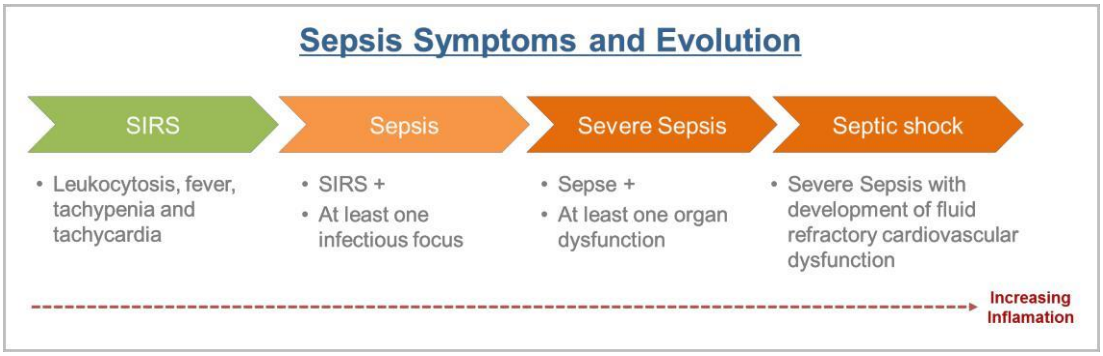

Figure 7 – Sepsis Symptoms and Evolution. Source: Adapted from Dellinger et al. (2013) and Bone et al. (1992).

One important characteristic noted is there is also an accumulative aspect in the relationship between the three stages of Sepsis. If a patient is diagnosed with Severe Sepsis, it means the patient has the symptoms of Sepsis plus at least one organic dysfunction. A patient that presents Septic Shock is also with Severe Sepsis, but with a severe hypotension. The interrelationship between these stages is show in Figure 8.

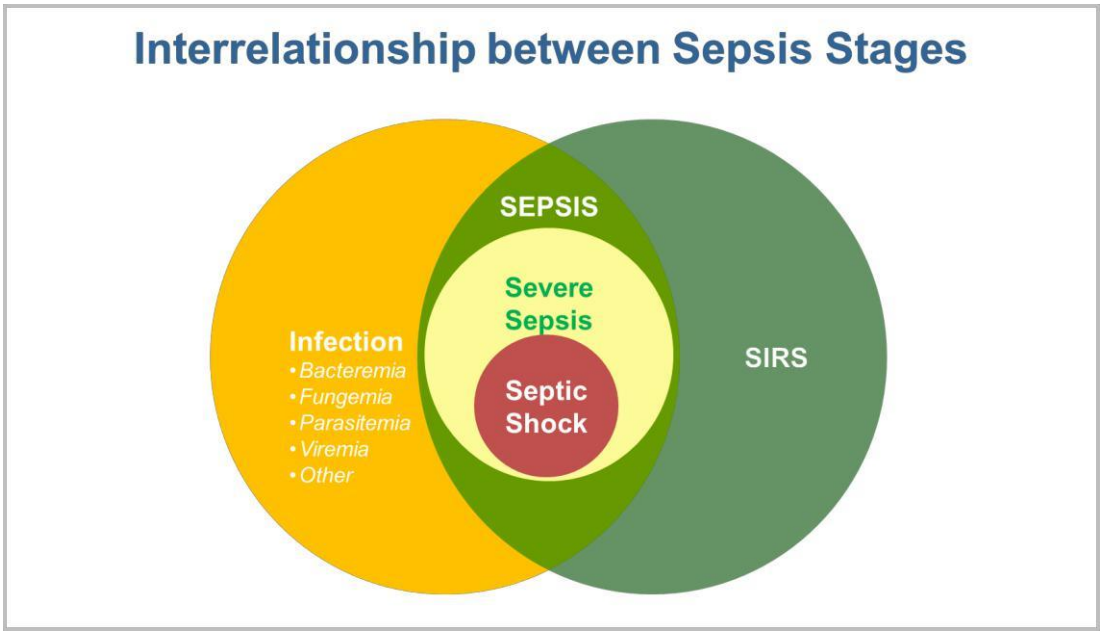

Figure 8 – Interrelationship between Sepsis Stages. Source: Adapted from Bone et al. (1992) and Hodgin and Moss (2008).

This accumulative aspect is also observed in treatment recommendations. That means that a patient with Septic Shock must receive the specific treatment for Septic Shock, Sepsis and Severe Sepsis. In Figure 8 is possible to observe the overlap between SIRS, Sepsis, Severe Sepsis and Septic Shock.

The management of the septic patient in the first hour is a time critical emergency and requires a team based approach involving relevant healthcare staff members. This will have to be adapted for the local context depending on the composition of the team. A patient may present in an emergency department (ED) or other healthcare setting (e.g. a General Practice or specialty department such as an oncology ward) with sepsis or may develop sepsis during hospital admission. There are essentially 4 steps in the management of patients with sepsis, detection, communication, recognition (and diagnosis), and treatment (resuscitation and referral), as shown in Figure 9 (NCEC, 2014).

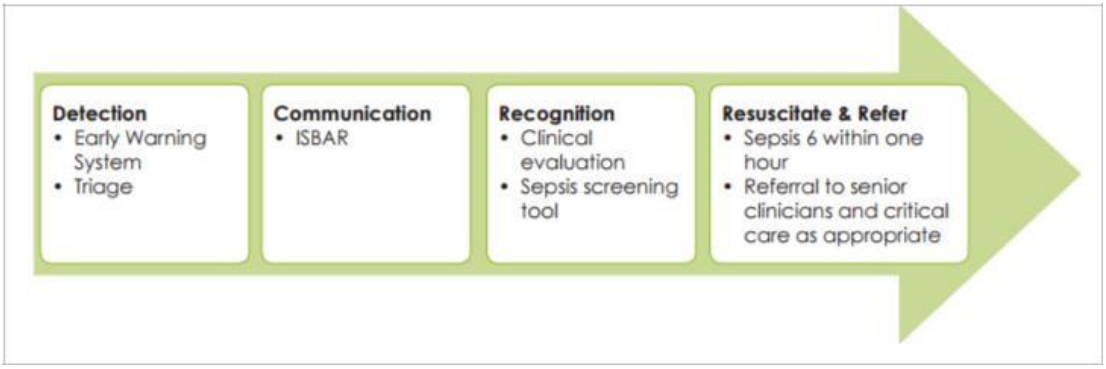

Figure 9 – Summary of Pathway of care for patients presenting with sepsis. Source: NCEC, 2014.

Sepsis 6 is a bundle developed by the Surviving Sepsis Campaign for the initial six hour management of all patients diagnosed with sepsis.

The subjects studied in Chapter 2 formed a basis for the proposed method development.

The method aims to facilitate the reading of clinical practice guidelines and extract the process information from it. That is necessary to successfully implement clinical pathways and take advantage of its benefits.

The method was developed for the Sepsis condition, based on its specific characteristics. To develop the conceptual process model, the key elements from the Diagnostic Reasoning process were considered, along with these Sepsis specific characteristics.

3
Methodology

In this chapter, the research design is presented. In section 3.1 the research questions and objectives are defined. Next, the steps followed to derive the proposed method to transform Sepsis guidelines into a conceptual process model are described.

3.1.
Research question and objectives

Medical guidelines represent a good source of evidence-based recommendations and up-to-date knowledge about best healthcare practices. Unfortunately, a gap exists between the information contained in published guidelines and the knowledge and information that are necessary to implement them (Lobach, 1995).

A successful implementation requires an accurate process design and to create process models it is fundamental to understand the sequencing of the activities and the business rules applied to it. Medical guidelines tend to be unstructured documents with complex medical information and a high level of abstraction, which make it difficult for non-doctors to understand and extract the information necessary to model process to support the implementation of the guidelines (Lobach, 1995). In that way, it is hard to extract process information from the guidelines, especially the sequencing of activities.

The research objective of this study is to develop a method to read and classify Sepsis guidelines recommendations and transform into a conceptual process model, in order to answer the following Research Question***:*** **How can Sepsis medical guidelines be transformed in a conceptual process model in a structured and reproducible way?**

The use of this method will facilitate the implementation of the guidelines recommendations in a hospital environment and, with that, increase the usability of and the compliance with the guidelines by medical staff. As discussed in Chapter 2, increasing the usability and compliance with clinical guidelines and pathways may lead to an improvement in quality of care and cost reduction.

Business analysts and IT developers can use this proposed method as a link between medical content and process information, and as an input for developing clinical pathways workflow and systems.

3.2. Methodology Steps

In this section, the research steps used to develop the proposed method are introduced.

The aim of this study was to create a method to facilitate the understanding of Sepsis medical guidelines and the translation of its recommendations into process information. To develop a conceptual process model for Sepsis, one must understand the Sepsis condition and the characteristics of its evolution in a patient. That understanding was achieved through the analysis of primary data (literature review) and secondary data (case study in a hospital). After that, the conceptual model for the Sepsis identification and treatment process was developed and validated. The steps followed to develop the method are shown in Figure 10.

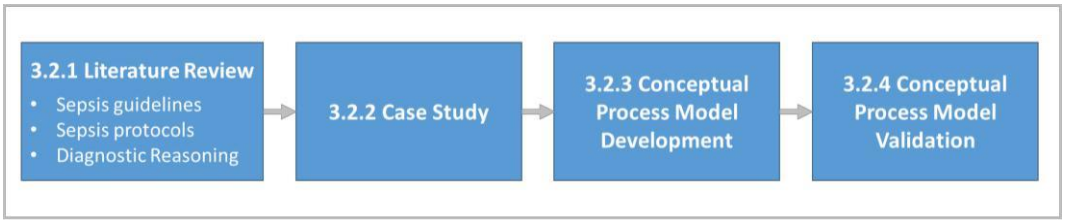

Figure 10 – Methodology steps. Source: Prepared by the author.

The chosen object of study for this Master Thesis was Sepsis, due to its relevance for the Brazilian Heath Care System. As mentioned before, Sepsis is a leading global health and financial burden. According to the Latin American Sepsis Institute (ILAS, 2015), the syndrome is responsible for 25% of bed occupation in Brazilian Intensive Care Units and is the main cause of death in Intensive Care Unit (ICU) patients. In addition, it is the main source of costs in both public and private sector due to the demand of sophisticated equipment, expensive medications and many workhours from the medical staff. In Brazil, the rate of mortality is in 65%, while the world rate is around 30-40% (ILAS, 2015).

3.2.1. Literature Review

The literature review first step was to understand Sepsis and what are the standards guidelines and protocols available for the initial treatment of this syndrome. The main objective of this step was to understand the behavior and characteristics of the syndrome progression in a patient, and which are the medical recommendations in every stage of its progression. The source of information for this step was public available guidelines, protocols and articles on Sepsis and interviews with medical staff in a Brazilian large private hospital.

3.2.1.1. Sepsis Guidelines

This step started with the study of the following guidelines for the care of Sepsis:

Surviving Sepsis Campaign (SSC): International Guidelines for Management of Severe Sepsis and Septic Shock, 2012 (Dellinger et al., 2013);

Sepsis Management - National Clinical Guideline (NCEC, 2014);

Prevention, diagnosis, therapy and follow-up care of sepsis (Reinhart et al., 2010).

The selection of these guidelines for this study took in consideration the suggestion from the case study hospital physician involved in the project. To be included in the study the guidelines had to be available in English and be develop for national or international use.

3.2.1.2. Sepsis Protocols

After that, a research for Sepsis Protocols made public available online from different hospitals across the world was performed. The Google search engine was used for this research with the key words "sepsis protocol" and "hospital". The Surviving Sepsis Campaign also makes available in their website a list of locally created protocols from their colleagues. It was also used protocols suggested by the doctors in the study case hospital.

To be selected, the protocol had to be written in English or Portuguese and present a flowchart, algorithm or information regarding the sequence of activities to identify and treat Sepsis or Severe Sepsis. Four protocols were selected, along with the case study sepsis protocol as basis for the development of the first model during the visit preparation.

The following protocols were selected: St Joseph Mercy Hospital (2015); Albert Einstein Hospital (2015)[1]; ILAS (2012); British Columbia (2012).

The aim of this research was to understand how real hospitals translate guidelines into protocols and to have a better idea of the treatment process and the sequencing of activities. This step provided valuable information on the syndrome and the main recommended interventions around the world to timely respond to its identification, with the aim to increase patient survival probability.

The protocols provide not only information on how the recommended activities are sequenced in real practice, but also the business rules applied to it

[1] This document is private and confidential.

and the parameters to be considered in each activity. With that knowledge, it was easier to understand the Sepsis care management protocol of the case study hospital.

3.2.1.3.
Diagnostic Reasoning

In order to create a conceptual process model for Sepsis, it was important to understand the key elements in a generic disease identification and treatment process. That helped defining the sequencing of activities in each stage of process. Therefore, this step consisted in researching generic disease identification and treatment process models in the academic literature in order to identify their key elements.

As explained in Chapter 2, Diagnostic Reasoning is the process of thinking about a clinical problem to form a diagnosis.

It was hard to find in literature one single standard model that describes the activities in a disease identification and treatment process in a hospital. However, during the research, different models and researches on the Diagnostic Reasoning Process were identified, which can describe this process in a high level and was used as a reference in this study.

For this study, the five different models presented in Section 2.5 were used to identify the key elements in the diagnostic reasoning process. Based in these key elements and in the Sepsis evolution stages described in Section 2.6, it was possible to create a conceptual sepsis identification and treatment process.

3.2.2.
Case Study

For the case study of a real Sepsis identification and treatment process, the choice was a large private Brazilian hospital, which has over 5,000 credentialed

physicians, in addition to over 2,000 medical staff team. Its infrastructure counts with over 300 ward beds and over 70 intensive care beds.

The hospital has over 200 cases of Sepsis suspicion per month and has a specific protocol for Sepsis management to handle these cases.

A team formed by three researchers from PUC-Rio and a physician from Philips Research visited the hospital in two different occasions. The objective of the visit was to map the Sepsis Identification and Treatment Process and design a process model to represent it. Figure 11 represents the steps followed to achieve this goal.

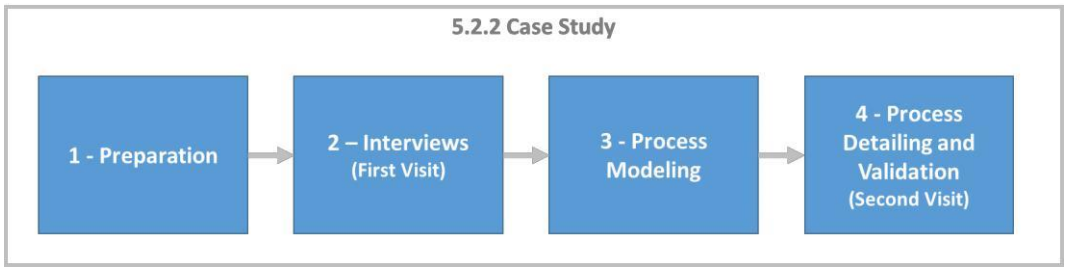

Figure 11– Case study steps. Source: Prepared by author.

Step 1 – Preparation

Based on the guidelines, the selected protocols and the case study hospital protocol, a process skeleton was created to facilitate the work. To understand the Sepsis Diagnosis and Treatment Process at the chosen hospital the team counted with the support from a doctor. This doctor was responsible for the first contacts with the hospital about the Sepsis Protocol.

With the information gathered up to this point it was possible to construct the first general Sepsis treatment process skeleton and to list related questions to be asked during the first visit. In addition, the team created a template for each activity in the process with the following fields: description, person responsible for the activity, other participants, main inputs, checklist for this activity, main outputs, communication/alerts, system interactions, and risks. This template for the activities helped to define the necessary information to design the process. By

filling the template, the team could determine the missing information that should be requested to the hospital staff. A physician from Philips Research helped in this step.

With that, it was possible to define the roles involved in the process, to formulate the questions and organize them according to its place in the process and the person responsible for executing the activity.

To prepare for the hospital visit the team organized a list of questions for the medical staff, prepared a work plan with the proposed agenda and the visit goals, and prepared a presentation to the hospital intensive care unit's chief to present the objective and requirements of the study. That was important so that the hospital administration could arrange the time to receive the team and allocate the appropriate professionals to participate in the interviews.

The list of question to the medical staff is in Appendix 8.1.

Step 2 – First visit to the hospital – Interviews

The visits to the hospital allowed us to map the Sepsis Diagnosis and Treatment Process and to have a deep understand of the factors that affect the outcomes of the treatment.

In the first visit, the team had the opportunity to interview the ICU coordinator, the ICU nurse supervisor, the Emergency Department (ED) coordinator, the ED nurse supervisor, and the hospital quality manager, who is responsible for controlling the sepsis key indicators in the hospital. The team also had the opportunity to visit the Emergency Department and the Intensive Care Unit facilities. This visit lasted three days and after that, it was possible to map and validate the Sepsis Identification and Treatment Process for the ICU and Emergency Department. The team found it helpful to interview the department's chiefs and supervisors that had a complete view of the end-to-end process. The agenda for this visit is shown in Figure 12.

	Day 1	Day 2	Day 3
Morning	Introduction meeting (Intensive Care Unit's Chief)	ICU Interviews and process observation	Closing meeting (Intensive Care Unit's Chief)
	ED Interviews and process observation		
Afternoon	ED Interviews and process observation	ICU Interviews and process observation	
		Data Quality Mgt and IT Interviews	

Figure 12 – First visit proposed agenda. Source: Prepared by the author.

The introduction meeting with the Intensive Care Unit's Chief was planned to present the team, the visit work plan and ask general questions about the Sepsis protocol. In the interviews with the ED Professionals, the team should meet separately with a nurse responsible for triage and for opening the Sepsis protocol and the ED Doctor responsible for Sepsis protocol. In the interviews with the ICU Professionals, the team should meet separately with at least one ICU Nurse and one ICU. An interview with the Data Quality Management manager was also scheduled to understand the hospital's Sepsis indicators. There was also planned an interview with the IT department analyst. A spot in the agenda was reserved for process observation in ICU and in the ED (respecting patient's privacy) to observe the following activities: symptoms measurement, open protocol, communication, exams request, transfer requests, etc.), and how the protocol is opened. To conclude the visit, a closing meeting with the Intensive Care Unit's
Chief was planned to validate the information gathered and to ask final questions.

Although a structured list of questions (presented in Appendix 8.1) was prepared for the interviews, the team decided to conduct non-structured interviews in order to not limit the discussion with the real experts in the process. The questions were used as key point to remind what the team needed to know from the process and to avoid digressions.

According to Jacka and Keller (2009), interviewing, in the context of process mapping, is not reading a list of questions and recording the answers. It is maintaining an active conversation with people - an exchange of ideas. It is taking a true interest in what they are saying.

This step was important to understand how the Sepsis guidelines and protocols are implemented in different departments in a real hospital.

Step 3 – Process modeling

The team took notes on every interview. To organize all the information listened during the day, at the end of each day the team adjusted the skeleton process created in the preparation step and wrote the notes into a report. As mentioned before, the BPMN notation was used to model the processes.

At the end of the visit, the team had reports describing the sepsis process care in the ICU and the ED and process models for both the ICU and ED, based on the data collected in the interviews. In the last day of the visit, the team had the opportunity to validate the models designed with the ICU coordinator.

Step 4 – Process model detailing and validation

In order to validate the processes mapped in the first visit and to gather detailed information about it, a second visit to the hospital was scheduled. The second visit lasted four days. The team also had the objective of identifying the main issues and points of improvement in the Sepsis Identification and Treatment processes.

To prepare for the visit, the team created a template with types of information needed to detail the process activities. For each activity, the template required the following items: activity description, checklists of tasks to perform during activity, time limit to finish it, necessity of communication to start activity, necessity of communication for starting next activity, documentation, tools and inputs needed to execute activity, systems used during activity, throughput time,

process time, decisions made, interviewee satisfaction with activity, problems and its probability of occurrence, work around and preferred solution.

Professionals with different roles that participate in the process (that could be doctor, nurse, nurse technician, laboratory technician and pharmacist) were interviewed. Participants were not expected to prepare in any special manner for the interviews. The team was divided to conduct the interviews separately for each department (ED, ICU and Wards).

Since this time the objective was to detail and validate the model designed, the team performed structured interviews, with questions based on the templates created for each process activity. In each interview, one or two participants with the same role were asked to validate the model presented and to fill the templates on the activities performed by their role. In this step, the process model was adjusted, a few activities were created and other eliminated, and the sequencing have changed. Special attention was given to the issues reported and its probability of occurrence.

After the interviews, the team compiled the information of the templates and adjusted the process with the inputs from the participants.

3.2.3. Conceptual Process Model Development

In order to develop the method, it was necessary to create a conceptual process model for the Sepsis identification and treatment process. This conceptual model should be generic enough to represent the process in any department in any hospital.

The level of abstraction of the conceptual model is higher than the level of abstraction of the process models for the ICU and ED of the case study hospital. The case study modeled processes were used as a proof of concept for the conceptual process model.

The conceptual process model was created based on the key elements in the Diagnostic Reasoning Process and the specific characteristics of the Sepsis progression.

The proposed method consists of three templates, listed below, that are used together to generate a Sepsis identification and treatment process report based on any selected Sepsis medical guideline.

1. Conceptual Sepsis Identification and Treatment Process Model, presented in Figure 15 – Conceptual Sepsis Identification and Treatment Process Model. Source: Prepared by author.Figure 15.
2. Template table for classification of the guidelines recommendations, presented in Table 2.
3. Process Activities Description Report Template, presented in Appendix 8.2.

The first proposed template is the *Sepsis Identification and Treatment Conceptual Process Model*. This template was empirically created based on the knowledge of the studied Sepsis guidelines, the characteristics of the Sepsis evolution in a patient and the key elements in the Diagnostic Reasoning process. This model was constructed using the BPMN 2.0 notation.

The second proposed template is a table to classify the recommendations of one or more selected Sepsis guidelines. This table was created based on the *Sepsis Identification and Treatment Conceptual Process Model* elements. We have empirically defined classification fields for the guidelines recommendations that could be related with the elements in the process model. In this step, it was essential the participation of a specialist doctor to validate the adequacy of the classification fields for the recommendations from the chosen guidelines.

Third and last template is the *Process Activities Description Report Template*. This document describes in detail each element in the *Sepsis Identification and Treatment Conceptual Process Model*.

3.2.4.
Conceptual Proces Model Validation

A group of researchers from PUC-Rio and from Philips Research was formed to design models in three different levels of abstraction for the Sepsis Identification and Treatment Process, as shown in Figure 13. This group was formed by three biomedical engineers, three computer scientists and two industrial engineers.

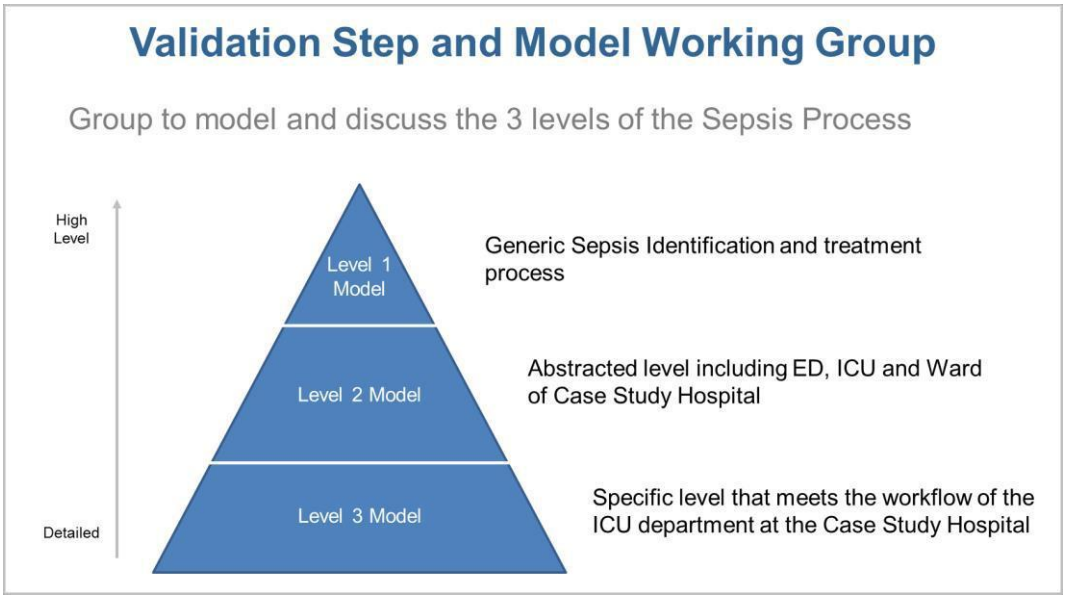

Figure 13 – Three levels of the Sepsis Identification and Treatment Process. Source: Prepared by the author.

Abstraction is generalization that reduces the undesired details in order to retain only information relevant for a particular task. Process model abstraction goal is to produce a model containing significant information based on the detailed model specification (Polyvyanyy et al., 2008).

The aim of the abstraction was to create a generic sepsis identification and treatment process that would serve for any department in any hospital. This process would not consider the specific characteristics of a hospital or a department in the hospital neither the roles assigned to the activities.

In terms of software development, the higher abstraction level model allows the design of a system structure. The lower level models would then represent the customization necessary to attend specific requirements of a hospital or a department in a hospital.

Level 1 was derived from the conceptual model proposed in this Master Thesis and represents a generic process for a Sepsis Identification and treatment process that should fit any hospital operation. It does not consider the specifics characteristics from the case study hospital.

Level 2 derived from level 1 and was detailed to meet the specifications of both the ICU and the ED department Sepsis processes. It reflects the current Sepsis protocol in the hospital but does not consider the specifics characteristics from these departments. In this level, some of the activities may be group in subprocesses to represent an idea of the tasks that should be performed. It does not necessarily specifies all activities in the processes or the roles that should execute them.

Level 3 was the most detailed process and should be consistent with the Sepsis process designed in the case study for the ICU department. It consider the roles that execute each activity and the same sequencing of activities that is observed in this department.

During three months, the group met weekly to discuss the process models, detailing its activities, creating a list of assumptions and exclusions and mapping communication activities. The ICU process model designed in the case study was used as the Level 3 model. The Conceptual Process Model proposed in this Master Thesis was used as an input for the development of the Level 1 model.

A specialist doctor and a group of researchers from Philips validated the proposed method and its templates.

The doctor helped in the medical content validation, especially in reviewing the proposed classification fields for the guidelines recommendations and in the activity of classifying the recommendations, i.e. the application of the method for the selected guidelines.

4
The proposed method

In this section the method to read and classify any sepsis guidelines recommendations is presented. Through this method, the user can create a Process Activities Report for the Conceptual Sepis Identification and Treatment Process Model based in one or more Sepsis guidelines. The user can also integrate and compare the recommendations presented in different Sepsis guidelines.

The method consists of the following three templates:

1. Conceptual Sepsis Identification and Treatment Process Model (Figure 15) – A generic model for the sepsis identification and treatment process.
2. Template table for classification of the guidelines recommendations (Table 2) – The columns of this table are the classification fields that can be related to the elements in the conceptual process model.
3. Process Activities Description Report Template (Appendix 8.2) – This report is the final output of the method and describes in detail the elements of the conceptual process model, according to the recommendations of the guidelines selected.

The *Conceptual Sepsis Identification and Treatment Process Model* was created based on the key elements in the Diagnostic Reasoning process and the specific characteristics of the Sepsis evolution.

From five different models presented in literature for the diagnostic reasoning process (Balogh et al., 2016; Rendon et al., 2015; Nendaz and Perrier, 2012; Bowen, 2006; Rothstein and Echternach, 1986), we were able to identify the following key elements:

- Symptoms Identification (can be performed by any medical staff);
- Medical Evaluation (performed by a doctor):
  - Clinical Evaluation (Patient's clinical history, interview, physical exam);

  - Data Collection and interpretation;
  - Hypothesis generation.
- Diagnosis;
- Treatment.

From those elements, it is possible to create a high-level model for a generic identification and treatment process, shown in Figure 14 that flows from left to right although it can present loops in the middle of the process.

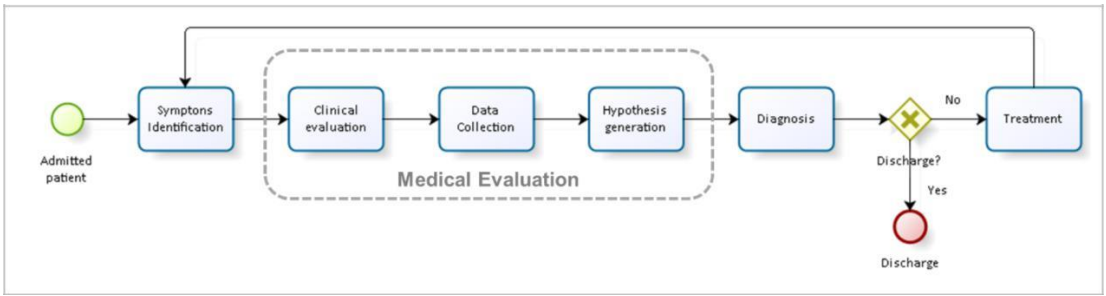

Figure 14 – Generic identification and treatment process. Source: Prepare by the author.

Based on this high-level model and the characteristics of Sepsis evolution, we can start mapping the Sepsis Identification and Treatment Process Model.

For each stage of the evolution of the syndrome, we can associate the steps in the generic process, creating the process model proposed in Figure 15.

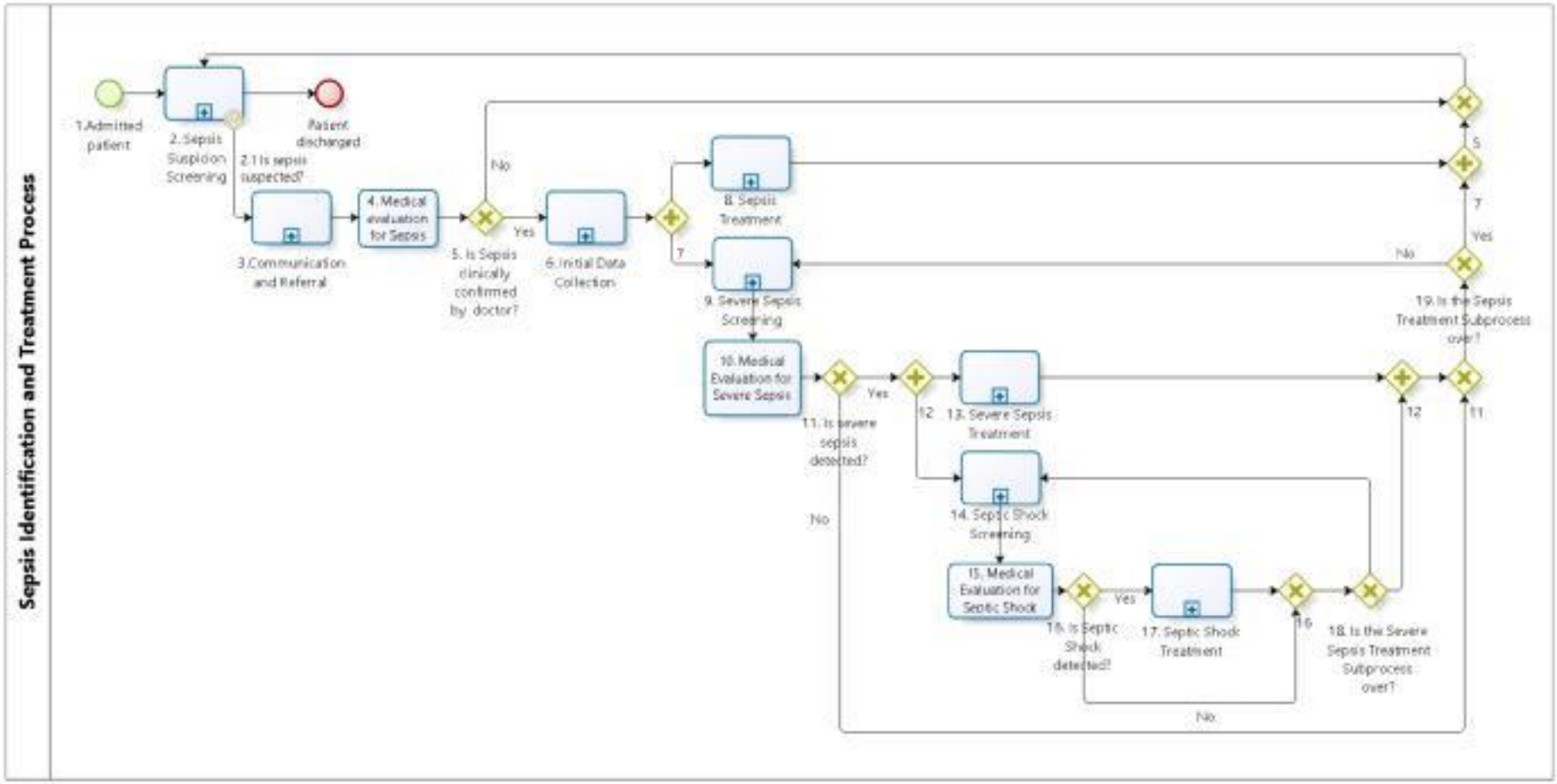

Figure 15 – Conceptual Sepsis Identification and Treatment Process Model. Source: Prepared by author.

Summarizing, for every stage of Sepsis evolution (SIRS, Sepsis, Severe Sepsis and Septic Shock) the key elements from the generic identification and treatment process are performed. There are monitoring activities to identify the symptoms of Sepsis or its progression, a medical evaluation to confirm the suspicion raised by the presence of the symptoms, a confirmation of the suspected diagnosis, and a treatment plan based on the diagnosis.

Sepsis evolution in a patient can happen fast and medical staff may not perceived it gradually. For example, patients can arrive in the Emergency Department already presenting Septic Shock symptoms, which demands rapid treatment with the activities that are present in the "Septic Shock Treatment" sub process. In this case, due to the overlapping characteristic of the Sepsis syndrome, the process will start the three different treatment sub processes (Sepsis Treatment, Severe Sepsis Treatment and Septic Shock Treatment) in parallel.

In the studied guidelines, the Sepsis treatment recommendations include elements like "Communication and Referral" and "Initial Data Collection".
Therefore, this recommendations were included as subprocesses in the process model. The "Communication and Referral" was included in the model after the intermediate event that represents that there is a Sepsis suspicion for that patient. Any professional in the hospital (doctor, nurse, nurse technicians, nutritionists, etc.) may notice SIRS signs that raise a Sepsis suspicion but once the signs are noticed a doctor must evaluate the patient to confirm the suspicion. The "Initial Data Collection" sub process was included after the physician clinically confirms
Sepsis and before the beginning of the treatment. Every Sepsis guideline studied recommended collecting blood cultures before administering any antimicrobial therapy.

We can notice it from the model that for every stage of the syndrome's progression there are evaluation and monitoring activities to identify the symptoms, a set of symptoms parameters to consider, a rule to guide the doctors decision about the diagnosis and the treatment plan according to the diagnosis.

This process model was then used to identify the classification fields that are necessary to classify the medical recommendations presented in the guidelines. From this model and from the guidelines studied, we have empirically defined classification fields for the guidelines recommendations that could be related with the elements in the process, to help understand the time and sequencing of them. These classification fields are shown in Figure 16 in the gray boxes close to the process elements they are related to.

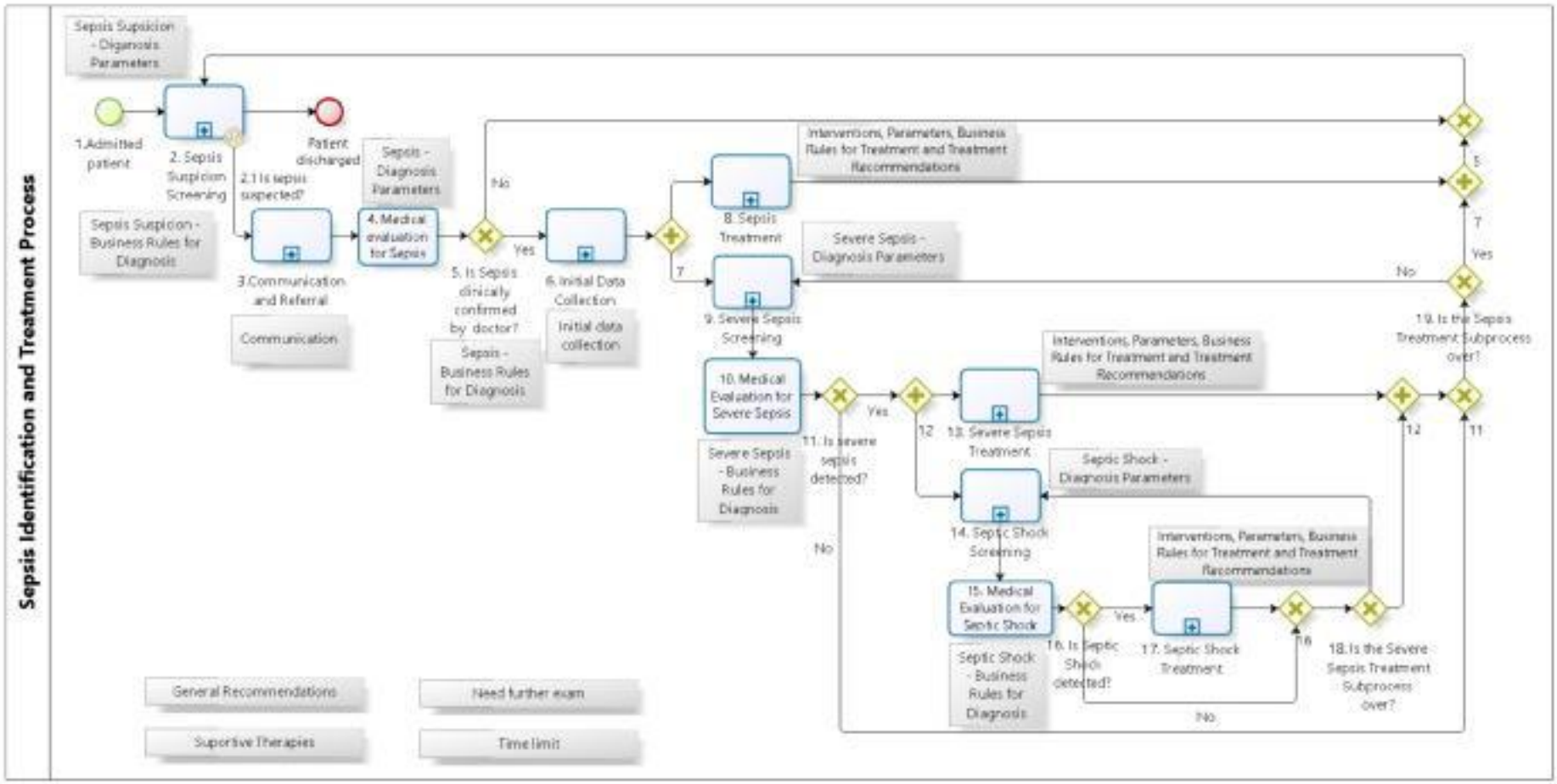

Figure 16 – Sepsis Identification and Treatment Process Model with the proposed recommendations classification fields. Source: Prepared by author.

Figure 17 shows the necessary steps to implement the method.

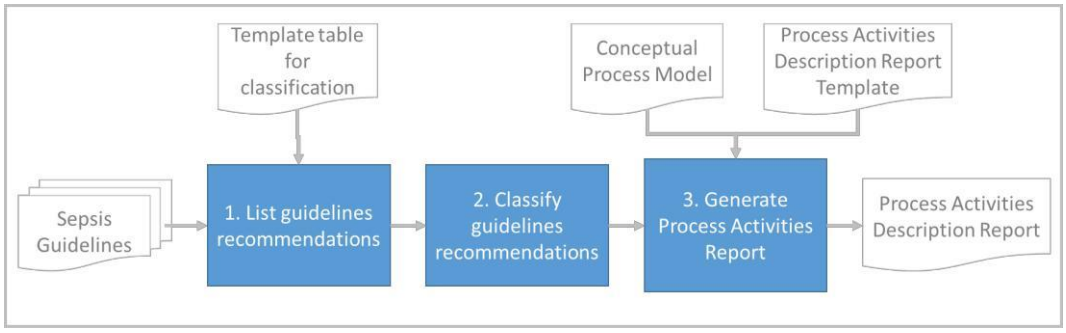

Figure 17 – Method for translating guidelines into process information. Source: Prepared by the author.

In essence, the method presents a conceptual process model for the Sepsis identification and treatment process, a table for the user to classify the recommendations of the selected Sepsis guidelines texts according to the elements of this process, and a template to generate a detailed process report according to the recommendations of the selected guidelines and the conceptual process model. This framework was created to allow the user to classify the recommendations of any Sepsis guidelines into groups of information that could be related to the elements in a sepsis identification and treatment process model, in order to understand the sequencing of the guidelines recommendations in a process.

The main input for the method are the selected Sepsis guidelines and the output is the Process Activities Report for the Sepsis Identification and Treatment process, according to the selected guidelines recommendations. This report will help the reader to understand the guidelines recommendations according to its related elements in the Conceptual Process model.

The application of this method will help the modeler to gain or improve his/her knowledge about the disease he/she is studying and wants to model and to build a detailed conceptual process model report according to the selected guidelines recommendations.

The user should review all the templates before starting the classification of the selected guidelines recommendations and make necessary adjustments according to his/her objectives. As mentioned before, it is crucial to have the support of a specialist doctor.

Step 1 – List guidelines recommendations

The first step is to list all the recommendations presented in the selected guidelines. The method can be applied to one or more guidelines. If more than one guideline is used, it is possible to compare the differences between these guidelines.

The guideline selection is based on the user or corporative objectives. In this selection, it is important to consider who developed the guidelines and where the guideline does apply (local coverage). In addition, some guidelines texts may be simpler and better structured than others and, in that way, it would be easier to identify process elements (triggers events, activities and decision points) in the text.

Once the user has chosen which guidelines will be used, the first step is to fill the *template table for the classification of the recommendations* (Table 2). Each recommendation of the guideline have to be placed as a new line in the spreadsheet. If the user is using more than one guideline, he/she should first list all the recommendations of the first guideline studied and then, for the second guideline, list only the recommendations that are different from the ones in the first guideline. The user should record in the table were the recommendation was extracted from. For that, for every guideline studied, the user should create a new column in the table, and mark with an "x" in every line respective to a recommendation that was extract from that guideline. Table 3 shows an example of a list of recommendations extracted from more than one guideline.

Guideline Recommendations	Guideline 1	Guideline 2	Guideline 3	Sepsis Suspicion		Sepsis						Severe Sepsis						Septic Shock or Hyperlactemia						Need further exam Communication	Initial Data Collection	Time limit	General Recommendations
				Diagnosis Parameters	Business Rules for Diagnosis	Diagnosis Parameters	Business Rules for Diagnosis	Treatment Intervention	Treatment Parameters	Business Rules for Treatment	Treatment Recommendations	Diagnosis Parameters	Business Rules for Diagnosis	Treatment Intervention	Treatment Parameters	Business Rules for Treatment	Treatment Recommendations	Diagnosis Parameters	Business Rules for Diagnosis	Treatment Intervention	Treatment Parameters	Business Rules for Treatment	Treatment Recommendations				

Table 2 – Template table for classification of guidelines recommendations. Source: Prepared by the author.

Guideline Recommendations	SSC	Irish	German
General variables for Sepsis Suspicion:			
Fever (> 38.3°C)	x	x	x
Hypothermia (core temperature < 36°C)	x	x	x
Heart rate > 90/min–1 or more than two sd above the normal value for age	x	x	x
Tachypnea	x	x	
Altered mental status	x	x	
Significant edema or positive fluid balance (> 20mL/kg over 24hr	x	x	
Hyperglycemia (plasma glucose > 140mg/dL or 7.7 mmol/L) in the absence of diabetes	x	x	

Table 3 – Example of filled template for recommendation from more than one guideline. Source: Prepared by author.

After this step, the user will have a list of the recommendations, from the selected guidelines, ready to be classified according to the template columns.

Step 2 - Classify the recommendations listed in the template table using the recommended columns

In this step, the modeler will have to understand and classify all the recommendations (listed in the template table in the previous step) according to the template's classification fields. The better the modeler knows the subject, the more realistic the process will become.

Table 4 shows the full list of the classifications fields in the template table and their description.

Classification Field		Description
Sepsis Suspicion	Diagnosis Parameters	Refers to variables that must be collected by exams or observed in a physical evaluation. These variables will be analyzed to set the diagnosis.

Classification Field		Description
	Business Rules for Diagnosis	Rule to define a diagnosis, usually based on a combination of observed/measured diagnosis parameters.
Sepsis	Diagnosis Parameters	idem
	Business Rules for Diagnosis	idem
	Treatment Intervention	Recommendations that explicitly indicates an action of a nurse/doctor.
	Treatment Parameters	Refers to variables that must be collected by exams or observed in a physical evaluation during treatment execution. These variables will be analyzed to monitor and guide the treatment.
	Business Rules for Treatment	Rule to define the course of the treatment, usually based on a combination of observed/measured treatment parameters.
	Treatment Recommendations	Recommendation related to a treatment procedure.
Severe Sepsis	Diagnosis Parameters	idem
	Business Rules for Diagnosis	idem
	Treatment Intervention	idem
	Treatment Parameters	idem
	Business Rules for Treatment	idem
	Treatment Recommendations	idem
Septic Shock or Hyperlactemia	Diagnosis Parameters	idem
	Business Rules for Diagnosis	idem
	Treatment Intervention	idem
	Treatment Parameters	idem
	Business Rules for Treatment	idem
	Treatment Recommendations	idem

Classification Field	Description
Need further exam	Refers to the parameters that cannot be measure in the clinical evaluation, requires further exams like lab or imaging exams.
Initial Data Collection	Parameters that have to be collected before the beginning of the treatment.
Time limit	Recommendations that explicitly indicates a time limit for an activity to be performed.
General Recommendations	Recommendation on the Sepsis Identification and Treatment process that are not necessarily related to a specific step in the process.
Supportive therapies	Adjunctive therapies used together with the primary treatment (ancillary to the care needed short term to stabilize a patient). Also related to recommendationson comorbidities therapies.

Table 4 – List of possible classification for the guidelines recommendations and its description. Source: Prepared by author.

For example, we know that the first step is screening for the presence of symptoms that may lead to a suspicion of Sepsis. For this screening, no matter in which department of the hospital, the medical staff have to be aware of the diagnosis parameters they have to monitor and the business rule that will trigger this suspicion. In some guidelines, for example, we have the recommendation that every patient that presents two or more SIRS symptoms should be evaluated for the presence of Sepsis by a physician. The guidelines also present a list of those symptoms (for example, fever > 38^{o} C). This recommendation can be classified as "*Business Rule for Diagnosis*" and later be used as a decision rule in the process model. The list of symptoms monitored can be classified as "Diagnosis Parameters".

For this specific task it is mandatory to have a subject's expert support (in this case a doctor with Sepsis knowledge). As mentioned before, guidelines are usually written by physicians and present many medical terms that can be difficult for a non-doctor to read and understand. In addition, there is a lot of medical information that is not explicit in the guidelines, for example, if the doctor can

observe a specific criterion in a physical evaluation or if it needs further exams (blood or imaging, for example) to be measured.

Step 4 – Fill the Process Activities Description Report template according to the classification of the recommendations

After all the recommendations are properly classified, step 3 is to fill *the Process Activities Description Report* (Appendix 8.2).

The template already provides the user with a text description for each element in the process, but the user can put his/her experience on a specific hospital or local practice to enrich any description. The template also gives instructions on how to use the filters in the *Template table for classification of the guidelines recommendations* (Table 2) *to* fill the tables of recommendations for each element.

After going through those three steps, the user will have:

1. A Conceptual Process Model for the Sepsis Identification and Treatment Process (Figure 15);
2. A table with the recommendations studied and classified according to the elements in the process (Table 2);
3. A Process Activities Description Report for the Conceptual Process Model (Appendix 8.2).

These documents can help the user and his/her team to understand the process in any Sepsis guidelines implementation project.

The Conceptual Process Model describes the process in a generic and high-level manner. To implement the guidelines recommendation in practice it might be necessary to detail the sub processes in a lower level. That will depend on the specific hospital the process will be implemented. Many specific local factors can affect the model such as hospital infrastructure, organizational structure of the medical staff, resources availability and point of detection (Emergency Department, Wards, Intensive Care Units, etc.).

5
Method application for three different selected Guidelines

This section will exemplify the method application based on three different guidelines chosen for this study: The Surviving Sepsis Campaign guideline (Dellinger et al., 2013), The Irish National Clinical Guideline (NCEC, 2014) and the guidelines from the German Sepsis Society (Reinhart et al., 2010).

The Irish National Clinical Guideline is supported by the National Clinical Effectiveness Committee (NCEC), which is a Ministerial committee established as part of the Patient Safety First Initiative. The NCEC role is to prioritize and quality assure National Clinical Guidelines and National Clinical Audit to recommend them to the Minister for Health to become part of a suite of National Clinical Guidelines and National Clinical Audit. The Irish guideline provide guidance and standards for improving the quality, safety and cost-effectiveness of healthcare in Ireland. Therefore, they have no ambition in crossing borders.

According to NCEC "The purpose of the National Sepsis Workstream is to guide the implementation process of the National Clinical Guideline No. 6 Sepsis Management with the aim that every person in the Republic of Ireland who develops sepsis has a pathway to access appropriate care as outlined in the guidelines" (NCEC, 2014).

The German sepsis guideline was developed by the German Sepsis Society, in association with the German Interdisciplinary Association of Intensive Care and Emergency Medicine. The aim of the German guideline is, like the Irish, a local objective. As all guidelines, the German guideline does not oblige the physician to follow the recommendations. The doctor is free and responsible to decide any treatment for a specific patient. To emphasize that, is written in the guideline: "The guideline recommendations may not be applied under all circumstances. It rests with the clinician to decide whether a certain recommendation should be adopted or not, taking into consideration the unique set of clinical facts presented in connection with each individual patient as well as the available resources".

The Surviving Sepsis Campaign is an international campaign that since its inception, in 2002, has been raising awareness to sepsis and trying to reduce mortality. Different from the other guidelines studied, the SSC guideline has goals that are more global. For example, one of the SSC milestones is to reduce the world mortality from sepsis by 25% in five years. From what we can see, is very different from the Irish guideline, which has a local ambition. The SSC executive committee is international, with people from USA, Belgium, England and Italy, Spain and France. This characteristic strengthens the idea of an international guideline. Moreover, innumerous organizations sponsored the SSC guideline, like Brazilian Society of critical Care, Latin America Sepsis Institute and the German sepsis Society- that is responsible for the German guideline.

Two people participated in the method application. The author and an industrial engineer research student from PUC-Rio.

In the step 1, from the three guidelines selected, more than 500 recommendations were extracted and then listed in the template spreadsheet. After that, the team analyzed them to remove duplicate recommendations and marked with an "x" to signalize from which guideline the recommendation came from. Table 5 shows an extract of the resultant table from this step.

Step 2 was performed with the help of a physician. All the listed recommendations were classified according to the classification fields in the *Template table for classification of the Guidelines recommendations* columns. Table 6 shows an extract of the resultant table from this step.

Guideline Recommendations				Sepsis Suspic		Sepsis					Severe Sepsis						Septic Shock or Hyperlactemia									
	SSC	Irish guideline	German guideline	Diagnosis Parameters	Business Rules for Diagnosis	Diagnosis Parameters	Business Rules for Diagnosis	Treatment Intervention	Treatment Parameters	Business Rules for Treatment	Treatment Recommendations	Diagnosis Parameters	Business Rules for Diagnosis	Treatment Intervention	Treatment Parameters	Business Rules for Treatment	Treatment Recommendations	Diagnosis Parameters	Business Rules for Diagnosis	Treatment Intervention	Treatment Parameters	Business Rules for Treatment	Treatment Recommendations	Need further exam	Communication	Initial Data Collection	Time limit	General Recommendations	Supportive therapies
General variables for Sepsis Suspicion: Infection, documented or suspected, and some of the following: Fever (> 38.3°C) Hypothermia (core																												
temperature < 36°C) Heart rate > 90/min–1 or more than two sd above	x	x	x																									
the normal value for age Tachypnea Altered mental status Significant	x	x	x																									
edema or positive fluid balance (> 20mL/kg over 24hr Hyperglycemia (plasma glucose > 140mg/dL or 7.7 mmol/L) in the absence of diabetes	x	x	x																									
Inflammatory variables: Leukocytosis (WBC count > 12,000 µL–1)	x	x																										
Leukopenia (WBC count < 4000 µL–1) Normal WBC count with greater	x	x																										
than 10% immature forms Plasma C-reactive protein more than two sd	x	x																										
above the normal value Plasma procalcitonin more than two sd above the normal value	x	x																										
	x	x	x																									
	x	x	x																									
	x	x	x																									
	x	x																										
	x	x																										

Table 5 – Extract of listed recommendations from the selected guidelines. Source: Prepared by author.

Guideline Recommendations	SSC	Irishguideline	Germanguideline	Sepsis Suspic		Sepsis						Severe Sepsis						Septic Shock or Hyperlactemia						Needfurtherexam	Communication	InitialDataCollection	Timelimit	GeneralRecommendations	Supportivetherapies
				DiagnosisParameters	BusinessRulesforDiagnosis	DiagnosisParameters	BusinessRulesforDiagnosis	TreatmentIntervention	TreatmentParameters	BusinessRulesforTreatment	TreatmentRecommendations	DiagnosisParameters	BusinessRulesforDiagnosis	TreatmentIntervention	TreatmentParameters	BusinessRulesforTreatment	TreatmentRecommendations	DiagnosisParameters	BusinessRulesforDiagnosis	TreatmentIntervention	TreatmentParameters	BusinessRulesforTreatment	TreatmentRecommendations						
General variables for Sepsis Suspicion: Infection, documented or suspected, and some of the following:																													
Fever (> 38.3°C)	x	x	x	x																									
Hypothermia (core temperature < 36°C)	x	x	x	x																									
Heart rate > 90/min–1 or more than two sd above the normal value for Age	x	x	x	x																									
Tachypnea	x	x		x																									
Altered mental status	x	x										x																	
Significant edema or positive fluid balance (> 20mL/kg over 24hr	x	x																											
Hyperglycemia (plasma glucose > 140mg/dL or 7.7 mmol/L) in the absence of diabetes	x	x																											
Inflammatory variables:	x	x		x		x																							
Leukocytosis (WBC count > 12,000 µL–1)	x	x	x	x																				x					
Leukopenia (WBC count < 4000 µL–1)	x	x	x	x																				x					
Normal WBC count with greater than 10% immature forms	x	x	x	x																				x					
Plasma C-reactive protein more than two sd above the normal value	x	x																						x					
Plasma procalcitonin more than two sd above the normal value	x	x																						x					

Table 6 – Extract of listed and classified recommendations from the selected guidelines. Source: Prepared by author.

The resultant table from steps 1 and 2 was too long to be shown in this document. This table can be found online, at < http://bit.ly/2e3UIzw >. However, the Process Activities Report generated in step 3 shows the recommendations organized according to its classification and related to the elements in the Conceptual Sepsis Identification and Treatment Process Model (Figure 15).

After the recommendations from the selected guidelines were listed and classified, the *Process Activities Description Report template* was filled. In the template for creating this report, for each element in the conceptual process model there is a text commenting the element and an instruction on how to use the filter in the template table to select the recommendations associated with that process element. Taking into consideration the filters, the classified list recommendations were then copied and pasted in the report according to their relations to the conceptual process elements. The resultant report can be found in Appendix 8.2.

6
Conclusion

The aim of this thesis is to increase the usability of clinical practice guidelines in hospitals. This can be facilitated by the implementation of clinical pathways that are developed based on the clinical guidelines recommendations.

It was shown that one of the barriers to successfully implementing CPGs into clinical practice is the difficulty in extracting information contained in the body of the CPGs documents. This aspect interferes with the retrieval of relevant information by healthcare professionals and makes the consultation for real time application rather complicated.

The use of the proposed method makes it easier to extract process information from the Sepsis CPGs, which is an important step in transforming guidelines into clinical pathways.

The classification fields proposed in the method act as a link to relate medical texts, in form of medical recommendations, to process information. That process information can be used by analysts in many ways to implement guidelines in hospital operation, such as software development or process redesign.

The method application also allows the comparison of recommendation presented in different Sepsis guidelines, which could be beneficial in the analysis for the implementation of solutions or programs developed in different countries.

The proposed method was applied for the Sepsis condition, considering three different Sepsis clinical practice guidelines. It was validated by a group of specialists and applied to a real process through a case study in a large private Brazilian hospital.

The resultant process activities report from the method application and the conceptual process model proposed in the method were used in a real project of

software development, which is being developed to support the execution of Sepsis Clinical Pathways in a hospital.

The main limitation of this research is that it is based on the Sepsis condition characteristics and it is not replicable for any other disease guideline.

Another limitation is that the method was constructed based on three different existing guidelines for Sepsis. It assumes that all guidelines have the same text structure. As guidelines represent up to date clinical knowledge and are constantly being updated, it is important to review the method templates and classification fields before implementing it.

In february 2016, a new definition for Sepsis was published in Singer et al. (2016). Develop by a task force convened by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine. This new definition was not considered in this Master Thesis.

For future research, this method can be applied in different hospitals and countries. It could also apply its structure to a guideline developed for a different disease. One improvement to the method that could be studied is how to reproduce it to consider clinical practice guidelines for any disease.

Another contribution would be to develop a method to automatize the classification of the guidelines.

7

Bibliography

ASSUNÇÃO, M.; AKAMINE, N.; CARDOSO, G. S.; MELLO, P. V.; TELES, J. M. M.; NUNES, A. L. B.; MAIA, M. O.; REA-NETO, A.; MACHADO, F. R. Survey on physicians' knowledge of sepsis: Do they recognize it promptly? **Journal of Critical Care**, v. 25, n. 4, p. 545-552, 2010.

BALOGH, E. P.; MILLER, B. T.; BALL, J. R. **Improving diagnosis in health care**. National Academies Press, 2016.

BARBAGALLO, S.; CORRADI, L.; DE GOYET, J. D. V.; IANNUCCI, M.; PORRO, I.; ROSSO, N.; TANFANI, E.; TESTI, A. Optimization and planning of operating theatre activities: an original definition of pathways and process modeling. **BMC Medical Informatics and Decision Making**, v. 15, n. 1, p. 38, 2015.

BONE, R. C.; BALK, R. A.; CERRA, F. B.; DELLINGER, R. P.; FEIN, A. M.; KNAUS, W. A.; SCHEIN, R. M. H.; SIBBALD, W. J. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. **Chest Journal**, v. 101, n. 6, p. 1644-1655, 1992.

BOWEN, J. L. Educational strategies to promote clinical diagnostic reasoning. **New England Journal of Medicine**, v. 355, n. 21, p. 2217-2225, 2006.

BRITISH COLUMBIA. Emergency department sepsis guidelines as an algorithm, 2012. Available at: <https://bcpsqc.ca/clinical-improvement/sepsis/emergency-department-sepsis/guidelines/>. Accessed: 04/01/2015.

CODISH, S.; SHIFFMAN, R. N. A model of ambiguity and vagueness in clinical practice guideline recommendations. In: **AMIA Annual Symposium Proceedings**. American Medical Informatics Association, p. 146, 2005.

DE BLESER, L.; DEPREITERE, R.; WAELE, K. D.; VANHAECHT, K.; VLAYEN, J.; SERMEUS, W. Defining pathways. **Journal of Nursing Management**, v. 14, n. 7, p. 553-563, 2006.

DELLINGER, R. P.; LEVY, M. M.; CARLET, J. M.; BION, J.; PARKER, M. M.; JAESCHKE, R.; REINHART, K.; ANGUS, D. C.; BRUN-BUISSON, C.; BEALE, R.; CALANDRA, T.; DHAINAUT, J.; GERLACH, H.; HARVEY, M.; MARINI, J. J.; MARSHALL, J.; RANIERI, M.; RAMSAY, G.; SEVRANSKY, J.; THOMPSON, B. T.; TOWNSEND, S.; VENDER, J. S.; ZIMMERMAN, J. L.; VINCENT, J. Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock, 2012. **Intensive Care Medicine**, v. 39, n. 2, p. 165-228, 2013.

DOOLEN, J.; SCHREIBER, M. P.; GREENWAY, J. Sepsis: A call for incorporation of regional data and improved education programs. **Nevada Journal of Public Health**, 2015.

ELSHAUG, A. G.; WATT, A. M.; MOSS, J. R.; HILLER, J. E. Policy perspectives on the obsolescence of health technologies in Canada. **Ottawa: Canadian Agency for Drugs and Technologies in Health**, 2009.

FEI, Y.; CHIU, P. Y.; DIAMOND, B.; SHERRY, B. Dysfunctional expansion of immature granulocytes in sepsis survivors. **The Journal of Immunology**, v. 196, n. 1 Supplement, p. 126.29-126.29, 2016.

FOX, J.; ALABASSI, A.; PATKAR, V.; ROSE, T.; BLACK, E. An ontological approach to modelling tasks and goals. **Computers in Biology and Medicine**, v. 36, n. 7, p. 837-856, 2006.

GALLERY, J. C.; CURTIN, F. M.; VOLUNTEERS, C. Guide to the development of clinical guidelines for nurse practitioners. Available at: <http://wacebnm.curtin.edu.au/guide/index.cfm>. Accessed: 01/15/2016.

GESME, D. H.; WISEMAN, M. Strategic use of clinical pathways. **Journal of Oncology Practice**, v. 7, n. 1, p. 54-56, 2011.

GOHIL, S. K.; CAO, C.; PHELAN, M.; TJOA, T.; RHEE, C.; PLATT, R.; HUANG, S. S. Impact of policies on the rise in sepsis incidence, 2000–2010. **Clinical Infectious Diseases**, v. 62, n. 6, p. 695-703, 2016.

GOOCH, P.; ROUDSARI, A. Computerization of workflows, guidelines, and care pathways: a review of implementation challenges for process-oriented health information systems. **JAMIA-Journal of the American Medical Informatics Association**, v. 18, n. 6, p. 738, 2011.

GROL, R. Successes and failures in the implementation of evidence-based guidelines for clinical practice. **Medical Care**, v. 39, n. 8, p. II-46-II-54, 2001.

GROL, R.; GRIMSHAW, J. From best evidence to best practice: effective implementation of change in patients' care. **The Lancet**, v. 362, n. 9391, p. 1225-1230, 2003.

GROSS, P. A.; GREENFIELD, S.; CRETIN, S.; FERGUSON, J.; GRIMSHAW, J.; GROL, R.; KLAZINGA, N.; WILFRIED, L.; MEYER, G.; RICCOBONO, C.; SCHOENBAUM, S. C.; SCHYVE, P.; SHAW, C. Optimal methods for guideline implementation: conclusions from Leeds Castle meeting. **Medical Care**, v. 39, n. 8, p. II-85-II-92, 2001.

HODGIN, K. E.; MOSS, M. The epidemiology of sepsis. **Current Pharmaceutical Design**, v. 14, n. 19, p. 1833-1839, 2008.

HOMMERSOM, A.; GROOT, P.; LUCAS, P.; MARCOS, M.; MARTÍNEZ-SALVADOR, B. A constraint-based approach to medical guidelines and protocols. **Computer-based Medical Guidelines and Protocols: A Primer and Current Trends. Studies in Health Technology and Informatics**, v. 139, p. 213-222, 2006.

ILAS - Latin American Sepsis Institute. Sepsis manual 2012. Available at: <http://www.ilasonlinems.org.br/Pages/Home.aspx>. Accessed: 04/01/2015.

ILAS - Latin American Sepsis Institute. O que é a Sepse. Avalaible at: <http://www.sepsisnet.org/pg.php?v=o-que-e-sepse>. Accessed: 07/11/2015.

JACKA, J. M.; KELLER, P. J. **Business process mapping:** improving customer satisfaction. John Wiley & Sons, 2009.

KINSMAN, L.; ROTTER, T.; JAMES, E.; SNOW, P.; WILLIS, J. What is a clinical pathway? Development of a definition to inform the debate. **BMC Medicine**, v. 8, n. 1, p. 31, 2010.

KUMAR, A.; ROBERTS, D.; WOOD, K. E.; LIGHT, B.; PARRILLO, J. E.; SHARMA, S.; SUPPES, R.; FEINSTEIN, D.; ZANOTTI, S.; TAIBERG, L.; GURKA, D.; KUMAR, A.; CHEANG, M. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock*. **Critical Care Medicine**, v. 34, n. 6, p. 1589-1596, 2006.

LENZ, R.; REICHERT, M. IT support for healthcare processes–premises, challenges, perspectives. **Data & Knowledge Engineering**, v. 61, n. 1, p. 39-58, 2007.

LEVY, M. M.; FINK, M. P.; MARSHALL, J. C.; ABRAHAM, E.; ANGUS, D.; COOK, D.; COHEN, J.; OPAL, S.; VINCENT, J.; RAMSAY, G. 2001 sccm/esicm/accp/ats/sis international sepsis definitions conference. **Intensive Care Medicine**, v. 29, n. 4, p. 530-538, 2003.

LOBACH, D. F. A model for adapting clinical guidelines for electronic implementation in primary care. In: **Proceedings of the Annual Symposium on Computer Application in Medical Care**. American Medical Informatics Association, 1995. p. 581-585.

MAMEDE, S.; SCHMIDT, H. G.; PENAFORTE, J. C. Effects of reflective practice on the accuracy of medical diagnoses. **Medical Education**, v. 42, n. 5, p. 468-475, 2008.

MØLLER, C.; TAN, R.; MAACK, C. J. What is business process management? A two stage literature review of an emerging field'. **Management Stream**, v. 1, n. 10, p. 9-13, 2009.

MÜLLER, R.; ROGGE-SOLTI, A. BPMN for healthcare processes. In: **Proceedings of the 3rd Central-European Workshop on Services and their Composition (ZEUS 2011),** Karlsruhe, Germany. 2011.

NCEC - National Clinical Effectiveness Committee. Sepsis management - national clinical guideline No. 6. ISSN 2009-6259, November 2014.

NENDAZ, M.; PERRIER, A. Diagnostic errors and aflaws in clinical reasoning: mechanisms and prevention in practice. **Swiss Medical Weekly**, v. 142, p. w13706, 2012.

NIH - National Institute Of General Medical Sciences. Available at: <https://www.nigms.nih.gov/Education/pages/factsheet_sepsis.aspx>. Accessed: 07/02/2015.

OLIVEIRA, T.; NOVAIS, P.; NEVES, J. Development and implementation of clinical guidelines: An artificial intelligence perspective. **Artificial Intelligence Review**, v. 42, n. 4, p. 999-1027, 2014.

PATEL, V. L.; AROCHA, J. F.; DIERMEIER, M.; GREENES, R. A.; SHORTLIFFE, E. H. Methods of cognitive analysis to support the design and evaluation of biomedical systems: the case of clinical practice guidelines. **Journal of Biomedical Informatics**, v. 34, n. 1, p. 52-66, 2001.

PELEG, M. Computer-interpretable clinical guidelines: a methodological review. **Journal of Biomedical Informatics**, v. 46, n. 4, p. 744-763, 2013.

PLOEG, J.; DAVIES, B.; EDWARDS, N.; GIFFORD, W.; MILLER, P. E. Factors influencing best-practice guideline implementation: Lessons learned from administrators, nursing staff, and project leaders. **Worldviews on Evidence-Based Nursing**, v. 4, n. 4, p. 210-219, 2007.

POEZE, M.; RAMSAY, G.; GERLACH, H.; RUBULOTTA, F.; LEVY, M. An international sepsis survey: a study of doctors' knowledge and perception about sepsis. **Critical Care**, v. 8, n. 6, p. R409-413, 2004.

POLYVYANYY, A.; SMIRNOV, S.; WESKE, M. Process model abstraction: A slider approach. In: **Enterprise Distributed Object Computing Conference, 2008. EDOC'08. 12th International IEEE**. p. 325-331. 2008.

PRIOR, M.; GUERIN, M.; GRIMMER-SOMERS, K. The effectiveness of clinical guideline implementation strategies–a synthesis of systematic review findings. **Journal of Evaluation in Clinical Practice**, v. 14, n. 5, p. 888-897, 2008.

REBUGE, A.; FERREIRA, D. R. Business process analysis in healthcare environments: A methodology based on process mining. **Information Systems**, v. 37, n. 2, p. 99-116, 2012.

REINHART, K.; BRUNKHORST, F. M.; BONE, H.-G.; BARDUTZKY, J.; DEMPFLE, C.-E.; FORST, H.; GASTMEIER, P.; GERLACH, H.; GRÜNDLING, M.; JOHN, S.; KERN, W.; KREYMANN, G.; KRÜGER, W.; KUJATH, P.; MARGGRAF, G.; MARTIN, J.; MAYER, K.; MEIER-HELLMANN, A.; OPPERT, M.; PUTENSEN, C.; QUINTEL, M.; RAGALLER, M.; ROSSAINT, R.; SEIFERT, H.; SPIES, C.; STÜBER, F.; WEILER, N.; WEIMANN, A.; WERDAN, K.; WELTE, T. Prevention, diagnosis, therapy and follow-up care of sepsis: 1st revision of S-2k guidelines of the German Sepsis Society (Deutsche Sepsis-Gesellschaft eV (DSG)) and the German Interdisciplinary Association of Intensive Care and Emergency Medicine (Deutsche Interdisziplinäre Vereinigung für Intensiv-und Notfallmedizin (DIVI)). **GMS German Medical Science**, v. 8 , 2010.

RENDON, P.; ROESCH, J.; RAO, D.; RENCIC, J. Tips for hospitalists on improving diagnostic skills. **The Hospitalist**, November 2015 issue. Available at: <http://www.the-hospitalist.org/article/tips-afor-hospitalists-on-improving-diagnostic-skills/>. Accessed: 12/14/15.

ROSENBRAND, K.; VAN CROONENBORG, J.; WITTENBERG, J. Guideline development. **Studies in Health Technology and Informatics**, v. 139, p. 3-21, 2008.

ROSENFELD, R. M.; SHIFFMAN, R. N.; ROBERTSON, P. Clinical practice guideline development manual, a quality-driven approach for translating evidence into action. **Otolaryngology--Head and Neck Surgery**, v. 148, n. 1 suppl, p. S1-S55, 2013.

ROTHSTEIN, J. M.; ECHTERNACH, J. L. Hypothesis-oriented algorithm for clinicians. A method for evaluation and treatment planning. **Physical Therapy**, v. 66, n. 9, p. 1388-1394, 1986.

RUIZ, F.; GARCIA, F.; CALAHORRA, L.; LLORENTE, C.; GONÇALVES, L.; DANIEL, C.; BLOBEL, B. Business process modeling in healthcare. **Studies in Health Technology and Informatics**, v. 179, p. 75-87, 2012.

SEETHAMRAJU, R. Business process management: a missing link in business education. **Business Process Management Journal**, v. 18, n. 3, p. 532-547, 2012.

SHALOM, E.; SHAHAR, Y.; TAIEB-MAIMON, M.; BAR, G.; YARKONI, A.; YOUNG, O.; MARTINS, S. B.; VASZAR, L.; GOLDSTEIN, M. K.; LIEL, Y.; LEIBOWITZ, A.; MAROM, T.; LUNENFELD, E. A quantitative assessment of a methodology for collaborative specification and evaluation of clinical guidelines. **Journal of Biomedical Informatics**, v. 41, n. 6, p. 889-903, 2008.

SINGER, M.; DEUTSHCMAN, C.; SEYMOUR, C.; SHANKAR-HARI, M.; ANNANE, D.; BAUER, M.; BELLOMO, R.; BERNARD, G.; CHICHE, J.; COOPERSMITH, C.; HOTCHKISS, R.; LEVY, M.; MARSHALL, J.; MARTIN, G.; OPAL, S.; RUBBENFELD, G.; POLL, T.; VINCENT, J.; ANGUS, D. The third international consensus definitions for sepsis and septic shock (sepsis-3). **Jama**, v. 315, n. 8, p. 801-810, 2016.

ST JOSEPH MERCY HOSPITAL. Sepsis Pocket Card, 2011. Available at: <http://www.survivingsepsis.org/Resources/Pages/Protocols-and-Checklists.aspx>. Accessed: 04/01/2015.

THOMSON, P. Implementing evidence-based health care: the nurse teachers' role in supporting the dissemination and implementation of SIGN clinical guidelines. **Nurse Education Today**, v. 20, n. 3, p. 207-217, 2000.

VANHAECHT, K.; PANELLA, M.; VAN ZELM, R.; SERMEUS, W. An overview on the history and concept of care pathways as complex interventions. **International Journal of Care Pathways**, v. 14, n. 3, p. 117-123, 2010.

WANG, D.; PELEG, M.,; TU, S. W.; BOXWALA, A. A.; GREENES, R. A.; PATEL, V. L.; SHORTLIFFE, E. H. Representation primitives, process models and patient data in computer-interpretable clinical practice guidelines: A literature review of guideline representation models. **International Journal of Medical Informatics**, v. 68, n. 1, p. 59-70, 2002.

8
Appendix

8.1.
Case Study – List of questions to the medical staff

Questions to the Nurses		
Activity	**Information**	**Questions**
Triage	**Description**	How do you identify the Sepsis symptoms in a patient?
	Main inputs	What are the activities prior to the triage process?
		Which data is gathered in those activities? And what information is needed in the triage process?
	Main outputs	Which data is gathered during triage?
	Communication/Alerts	How do you communicate doctor that the protocol was opened?
	System/paper interactions	How do you register the data (system or paper)?
	Risks	What is the risk of a patient with Sepsis do not present symptoms that can be detected in the triage process? For example, symptoms that can only be detected with further exams.
Open Sepsis protocol	**Description**	What are the rules to open the Sepsis protocol?
	Main outputs	Where is the paper protocol placed?
	Communication/Alerts	Do you need to report a Sepsis case to other departments in the hospital?
	System interactions	Does the nurse read patient information on the patient's electronic record?
Communicate Doctor	**Risks**	Is there a risk of:
		The nurse do not finding the doctor at the moment?
		Doctor is busy and cannot see patient in less than 1 hour?
		The doctor doesn't receive nurse's message?
Collect exams ("Sepsis kit")	**Description**	Nurse collects Sepsis Kit for that patient and send to Lab for analysis
		Who request the exams?
		Can the nurse request the exams?
		Who collect the blood sample?
		How the results are reported from the laboratory to

Questions to the Nurses		
Activity	**Information**	**Questions**
		the doctor?
		What is the procedure after the exams are received from the laboratory?
Doctor evaluation	**Other participants**	Does the nurse participate in this activity?
	Communication/Alerts	How is the communication with the nurse that will administer the antibiotics?
		How is the procedure for requesting and executing the Patient transfer to the ICU?
General Questions	**Responsibilities**	Is there other activities performed by the nurse in the diagnosis and treatment of Sepsis?
	Antibiotics administration	How is the procedure to administrate antibiotics?
		Is there a need to wait for laboratory exams to start antibiotics administration in a patient with sepsis suspicion?
	Transfers procedures	Once a patient is diagnosed with sepsis, how is the transfer requested? What are the business rules to request transfer?
		How is the transfer to the ICU procedure?
		Is there a system where the bed availability in the ICU can be checked?
		How is the communication in the transfer process?
		What happens when there is no bed availability in the ICU?
		What are the formularies that need to be filled?
	Volemic expansion procedures	How is the volemic expansion requested?
		In which activity the doctor determines which liquid will be used in the volemic expansion?

Table 7 – Questions to the Nurses. Source: Prepared by author.

Questions to the Doctors		
Activity	**Information**	**Questions**
Doctor evaluation	**Other participants**	Does the nurse participate in this activity?
	Main inputs	How are you communicated of a Sepsis suspicion case?
		How do you prioritize the evaluation of a patient with sepsis suspicion?
	Checklist for this activity	For a patient with Sepsis or Sepsis suspicion, is there a procedure for the medical evaluation?
	Main outputs	Do you have access to a list of antibiotics that you should prescribe for a patient with Sepsis?
	Communication/ Alerts	How is the communication with the nurse that will administer the antibiotics?
		How is the procedure for requesting and executing the Patient transfer to the ICU?
	System interactions	How do you register the data collected during medical evaluation (paper or system)?
		For a patient that was not identified with sepsis suspicion during triage, what actions should be performed?
Open Sepsis protocol	**Description**	When and how do you open the Sepsis protocol?
	Checklist for this activity	Where is the protocol placed after it is opened?
	Main outputs	Where is the protocol placed after the patient is transferred?
General questions	Do you need to report a Sepsis case to other departments in the hospital?	
	Which formularies do you need to fill for a patient with Sepsis suspicion or Sepsis?	
	When do you need to revaluate a patient with Sepsis suspicion or Sepsis?	
	What is done when a patient is already in septic shock when the symptoms are noticed?	
	How is the procedure of closing/excluding the protocol when, after medical evaluation, the doctor verifies that a patient that was with sepsis suspicion does not present Sepsis?	
	Do you wait for the lab exams results from the sepsis kit before prescribing antibiotics?	
	Who prescribe the kit sepsis exam collection?	
	How and when do you have access to the results of the lab exams?	

Table 8 – Questions to the Doctors. Source: Prepared by author.

General Questions	
Subject	**Questions**
Process Information	Sepsis detection points in the hospital
	Professionals involved and their responsibilities
	Activities description and sequencing, and process business rules
	Necessary equipment and resources in each activity
	Data generated and needed in each activity
	Staff interaction with paper formularies or system
	Systems integrations through the process
	How the communication works in each activity
	Process possible outcomes (patient death, discharge or transfer)
	Process critical resources
Data Mgt.	What are the formularies that need to be filled when there is a new sepsis case in the hospital?
	Which department in the hospital is responsible for managing the data collected for sepsis patients?
	Is there any obligation to report a sepsis case to a external institution or government?
	Is there any indicators for antibiotics administration time, volemic expansion and collecting blood exams? How are these indicator measured and managed?
	Is there any statistics for patients that leave the sepsis protocol?
	What is the protocol engagement rate? How is this indicator measured?
Sepsis treatment process	In which cases is not possible to follow the steps suggested in the Sepsis protocol (example: cardiac patients, kidney failure).
	How is the necessary equipment/resource to perform an activity requested in each step?
	Is there any documentation (such as patients authorization to perform a procedure) needed for any activity in the sepsis treatment process?

Table 9 –General Questions. Source: Prepared by author.

8.2.
Process Activities Description Report

This appendix presents the Sepsis Identification and Treatment Process Report for the selected guidelines:

The Irish National Clinical guideline: Sepsis Management - National Clinical Guideline (NCEC, 2014);

The German guideline: Prevention, Diagnosis, Therapy and Follow-up Care of Sepsis (Reinhart et al., 2010);

The Surviving Sepsis Campaign (SSC) guideline: international guidelines for management of severe sepsis and septic shock (Dellinger et al., 2013).

The Process Report describes in details the process elements represented in the Conceptual Process Model Presented in Figure 15.

1. Process Trigger

The process starts from the moment the hospital admits a patient.

The patient may be admitted in any department of the hospital, presenting or not the symptoms for Sepsis Suspicion. The patient may enter the hospital already in any of the Sepsis stages or he can be hospitalized for another reason and then develop Sepsis inside the hospital. For that, it is important that every medical staff be aware of the symptoms that raise the suspicion for Sepsis.

In 2004, an international survey found 86% of physicians agreed that patients need better monitoring to diagnose sepsis at the earliest possible stage and 84% agreed that patients are often treated too late to reverse the onset of sepsis (Poeze et al., 2004).

A survey taken by Assunção et al. (2010) among 917 Brazilian physicians, showed that the percentage of physicians correctly recognizing SIRS, infection, sepsis, severe sepsis, and septic shock was 78.2%, 92.6%, 27.3%, 56.7%, and 81.0%, respectively. The results demonstrated that physicians' knowledge of

sepsis and severe sepsis concepts is unsatisfactory, even among intensivists and those working in the ED, although the intensivist physicians presented a better performance as compared with non-intensivists.

2. Sub process: Sepsis suspicion screening

The screening for Sepsis suspicion can occur in any of the hospital's departments and mortality probability is associated with early detection of the condition.

The following diagnosis criteria are recommended by the guidelines for Sepsis Suspicion screening:

Guideline Recommendations	SSC	Irish	German
Fever (> 38.3°C)	x	x	
Hypothermia (core temperature < 36°C)	x	x	x
Heart rate > 90/min–1 or more than two sd above the normal value for age	x	x	x
Tachypnea	x	x	
Leukocytosis (WBC count > 12,000 µL–1)	x	x	x
Leukopenia (WBC count < 4000 µL–1)	x	x	x
Normal WBC count with greater than 10% immature forms	x	x	x
Arterial hypotension (SBP < 90mm Hg, MAP < 70mm Hg, or an SBP decrease > 40mm Hg in adults or less than two sd below normal for age)	x	x	
Fever (≥38°C) or hypothermia (≤36°C) confirmed by rectal, intravascular or intravesical measurement			x
Tachycardia: heart rate ≥90 bpm			x
Tachypnea (frequency ≥20/min) or hyperventilation (PCO2 ≤4.3 kPa/ ≤33 mmHg)			x
Leukocytosis (≥12000/mm3) or leukopenia (≤4000/mm3) or ≥10% immature neutrophils in differential blood count			x

Table 10 – Diagnosis Criteria for Sepsis Suspicion Screening. Source: Prepared by author.

It is important to notice that some of these criterions may not be available at this point if the process because they can only be measure via exam.

To generate the table above the user should use the following filters in the spreadsheet: [Sepsis Suspicion – Diagnosis Parameters = “x”].

2.1. Intermediate Event: “Is sepsis suspected?”

During the sepsis suspicion screening sub process, if there is a Sepsis suspicion, the flow will be affected. That means that the patient needs to be evaluated by a doctor to confirm or not that suspicion.

A business rule will guide the path of the flow. In the sepsis suspicion screening sub process the rule will activate an intermediate event that will change the process flow, leading to the start of the communication and referral sub process.

The studied guidelines recommend the following business rules for identifying Sepsis suspicion:

Guideline Recommendations	SSC	Irish	German
ED trigger			
Presenting complaint suggestive of infection or unwell and in at risk group for neutropenia + two SIRS criteria + Lactate > 2 mmol/L		x	
Adult in-patient trigger			
New NEWS score of 4 (5 if on O2) or higher = medical review		x	
Infection suspected as cause of physiological deterioration + two SIRS criteria = Sepsis		x	
II. Systemic inflammatory host response (SIRS) (at least 2 criteria)			x

Table 11 – Business rules for identifying Sepsis suspicion. Source: Prepared by author.

The table shows that the Irish guidelines specifies different triggers for each detection point in the process (Emergency Department or Wards).

To generate the table above the user should use the following filters in the spreadsheet: [Sepsis Suspicion – Business Rules for Diagnosis = “x”].

3. Sub process: Communication

As mentioned before, any professional can notice the criteria that raise the sepsis suspicion, so there is a need to have a communication sub process to referral the case to a doctor. The activities that will be part of this sub processes will depend on the specific hospital procedures and policies. For example, this sub process may include the following activities:

- Where the intern/external communication is made (Paper protocol or electronic protocol)
- Escalation to a doctor.
- Registering the suspicion in the Quality Department

The way that the communication happens also depends on the hospital. It can be done by system alerts (automatic or manual) or verbal communication, for example.

The Guidelines recommendations for this sub process are shown in Table 12:

Guideline Recommendations	SSC	Irish	German
Patients in whom severe sepsis or septic shock is suspected should be reviewed by a registrar, or more senior medical staff, immediately.		x	
Poor communication has been identified as a contributing factor to adverse incidents where clinical deterioration is not identified or properly managed. The recommended communication tool when communicating in relation to the deteriorating patient, is the ISBAR communication tool		x	
It is recommended that each clinical program/healthcare facility create or adopt treatment pathways for sepsis care that includes triggers for sepsis screening, facilitates the diagnosis of sepsis, severe sepsis/septic shock, and the treatment, resuscitation and appropriate referral to critical care.		x	

Table 12 – Guidelines Recommendations for Communication. Source: Prepared by author.

To generate the table above the user should use the following filters in the spreadsheet: [Communication = “x”].

4. Activity: Medical evaluation for sepsis

Once there is a Sepsis suspicion, the doctor must evaluate the patient to clinically confirm Sepsis (based on physical observation, patient complaints and historic).

During this activity, the doctor will perform all the tasks according to the hospital's procedure, like exam the patient, interview the patient's clinical and family historic and complaints, prescript medications and request exams. None of the guidelines studied define a standard procedure for this activity.

The guidelines suggest the parameter that should be evaluated for confirming Sepsis. Some criteria can be observed in a medical consult and other may require further exams.

The table below shows the guidelines recommendations for the Sepsis Diagnosis parameters that should be observed during the medical evaluation activity.

Guideline Recommendations	SSC	Irish	German
Confirmation of infection - Diagnosis of infection on the basis of microbiological evidence or clinical criteria			x

Table 13 – Sepsis Diagnosis Parameters. Source: Prepared by author.

It is important to notice that during medical evaluation the doctor also has to observe the diagnosis parameters for Severe Sepsis and for Septic Shock and define at witch stage the patient is.

To generate the table above the user should use the following filters in the spreadsheet: [Sepsis – Diagnosis parameters = "x"].

5. Gateway: "Is Sepsis clinically confirmed by doctor?"

During the medical evaluation activity, the doctor must determine if the patient will continue on the sepsis treatment. If the doctor clinically confirm Sepsis suspicion, even if there is a need for further exams to confirm the

diagnosis, the treatment shall begin. Research shows that there is a direct relation between the time the treatment begins and the survival probability. The chart below shows the probability of patient survival correlated with the early detection and administration of antimicrobial, which is the first intervention recommended by all the studied guidelines in the sepsis treatment sub process.

The x-axis represents time following first documentation of septic shock-associated hypotension. Black bars represent the fraction of patients surviving to hospital discharge for effective therapy initiated within the given time interval. The gray bars represent the cumulative fraction of patients having received effective antimicrobials at any given time point (Kumar et al., 2006).

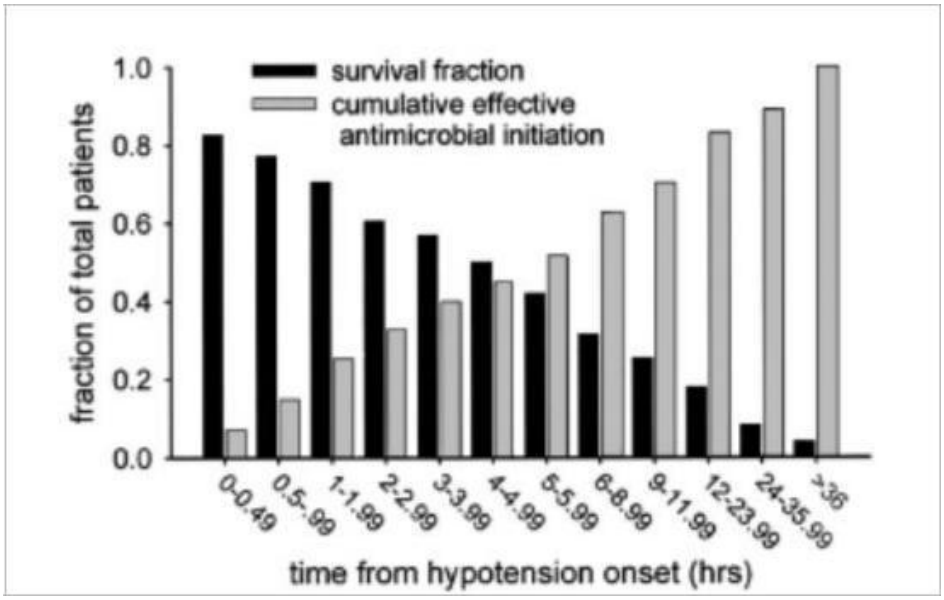

Figure 18 - Cumulative effective antimicrobial initiation following onset of septic shock-associated hypotension and associated survival. Source: Kumar et al., 2006.

The guidelines recommend the following business rules to be used in this decision point:

Guideline Recommendations	**SSC**	**Irish**	**German**
Infection suspected as cause of physiological deterioration + two SIRS criteria + organ dysfunction and/or shock = Severe sepsis/septic shock		x	
Sepsis: criteria I and II: I. Confirmation of infection - Diagnosis of an infection on the basis of microbiological evidence or clinical criteria II. Systemic inflammatory host response (SIRS) (at least 2 criteria)			x

Table 14 – Business Rules for Sepsis diagnosis. Source: Prepared by author.

To generate the table above the user should use the following filters in the spreadsheet: [Sepsis – Business rule for diagnosis = “x”].

6. Sub process: Initial Data Collection

Once the doctor clinically confirms Sepsis, the first activity to perform is the collection of patient’s blood sample. The doctor can prescribe other exams as well and they can be collected at this point, if there is no delay in the beginning of the treatment. If the doctor prescribes an exam that may take a long time to be collected (like imaging exams, for example) and that may delay the beginning of the treatment, it should be collect during the sub process “Sepsis Treatment”.

The recommendations on this topic provided by studied guidelines are listed in Appendix 8.3. To generate the table presented in this Appendix the user should use the following filters in the spreadsheet: [Initial data collection= “x”].

7. Parallel Gateway

This parallel gateway determines that both sub processes “8. Sepsis Treatment” and “9. Severe Sepsis Screening” can be executed at the same time.

The join parallel gateway determines that the process may continue only when both branches are terminated.

Figure 19 – Parallel Gateway. Source: Prepared by author.

8. Sub process: Sepsis Treatment

In the Treatment sub processes, the following classification fields were used to categorize the guidelines:

- Treatment Interventions;

- Treatment Parameters;
- Business Rules for Treatment;
- Treatment Recommendations.

The modelling of each sub process in detail will depend on specific characteristics of the hospital studied. However, this sub process will present the interventions necessary to perform the treatment, the parameters that should be monitored during the treatment, the business rules to decide to continue or not with the treatment and recommendations on how to execute the interventions and monitoring.

The recommendations for the Sepsis treatment are listed below:

Treatment Interventions: Recommendations that explicitly indicates an action of a nurse/doctor.

The studied Guidelines provide the following recommendations on treatments interventions for Sepsis:

Guideline Recommendations	SSC	Irish	German
It is recommended to institute antimicrobial therapy after obtaining blood cultures (see the Diagnosis of Infection section), but in any case as soon as possible (within 1 hour) after recognition of sepsis.			x

Table 15 – Sepsis Treatment Interventions. Source: Prepared by author.

To generate the table above the user should the following filters in the spreadsheet: [Sepsis - treatment interventions= “x”].

Treatment Parameters: Refers to variables that must be collected by exams or observed in a physical evaluation during treatment execution. These variables will be analyzed to monitor and guide the treatment.

For this sub process, there are no recommendations on *treatment parameters* in the guidelines studied.

Business Rules for Treatment: Rule to define the course of the treatment, usually based on a combination of observed/measured treatment parameters.

For this sub process, there are no recommendations on *Business Rules for Treatment* in the guidelines studied.

Treatment Recommendations: Recommendation related to a treatment procedure.

The recommendations on this topic provided by studied guidelines are listed in Appendix 8.4. To generate the table presented in this Appendix the user should use the following filters in the spreadsheet: [Sepsis - treatment recommendations= "x"].

9. Sub process: Severe Sepsis Screening

The sub process Severe Sepsis Screening initiates at the same time the sub process Sepsis Treatment initiates. It finishes either:

- When the doctor, during the activity "4. Medical Evaluation for Sepsis" have defined the stage the patient is in as Severe Sepsis or Septic Shock.
- When, during the sub process "8. Sepsis Treatment", the symptoms for Severe Sepsis are noticed and a doctor must evaluate the patient to confirm Severe Sepsis or;
- When the sub process Sepsis Treatment is terminated.

The symptoms of Severe Sepsis are the same as the Sepsis symptoms, plus at least one sign of organ dysfunction. If the patient is at this point in the process, it means either that:

- The doctor has already clinically confirmed the presence of Sepsis and during the sub process "8. Sepsis Treatment" the medical staff involved in the patient's treatment must observe the diagnosis parameters for Severe Sepsis.
- The doctor has already clinically confirmed Sepsis and defined the patient stage as Severe Sepsis or Septic Shock. In this case, the sub processes "13. Severe Sepsis Treatment" and "14. Septic Shock Screening" must start in parallel with the sub process "8. Sepsis Treatment".

The recommendations on this topic provided by studied guidelines are listed in Appendix 8.5. To generate the table presented in this Appendix the user should

use the following filters in the spreadsheet: [Severe Sepsis - diagnosis parameters= "x"].

10. Activity: Medical Evaluation for Severe Sepsis

In this activity, the doctor will evaluate the patient to confirm the diagnosis of Severe Sepsis and prescribe the treatment and request exams according to this diagnosis.

According to the studied guideline the following business rules defines the diagnosis for Severe Sepsis:

Guideline Recommendations	SSC	Irish	German
Severe sepsis definition = sepsis-induced tissue hypoperfusion or organ dysfunction (any of the following thought to be due to the infection)	x		
Severe Sepsis definition (any of the following thought to be due to infection): – Sepsis induced hypotension – Lactate above upper limits laboratory normal – Urine output < 0.5 mL/kg/hr for more than 2 hrs despite adequate fluid resuscitation – "Acute lung injury with PaO2 – /FIO2 < 250 in the absence of pneumonia as infection source" – Creatinine > 2.0 mg/dL (176.8 μmol/L) – Bilirubin > 2 mg/dL (34.2 μmol/L) – Platelet count < 100,000 μL – Coagulopathy (international normalized ratio > 1.5)		x	
Protocolized, quantitative resuscitation of patients with sepsis- induced tissue hypoperfusion (defined in this document as hypotension persisting after initial fluid challenge or blood lactate concentration ≥ 4 mmol/L). Goals during the first 6 hrs of resuscitation:	x		
Infection suspected as cause of physiological deterioration + two SIRS criteria + organ dysfunction and/or shock = Severe sepsis/septic shock		x	

Severe sepsis: criteria I, II and III: I. Confirmation of infection - Diagnosis of infection on the basis of microbiological evidence or clinical criteria. II. Systemic inflammatory host response (SIRS) (at least 2 criteria) III. Acute organ dysfunction (at least 1 criterion)			x

Table 16 – Severe Sepsis Business Rules for Diagnosis. Source: Prepared by author.

To generate the table above the user should use the following filters in the spreadsheet: [Severe Sepsis - business rule for diagnosis= "x"].

11. Gateway: "Is severe sepsis detected?"

If the doctor has confirm the patient's diagnosis as Severe Sepsis or Septic Shock during a Medical Evaluation activity, the patient must start immediately the sub processes "13. Severe Sepsis Treatment" and "14. Septic Shock Screening" in parallel with the sub process "8. Sepsis Treatment".

If the doctor does not confirm the patient's diagnosis as Severe Sepsis or Septic Shock, the flow returns to the sub process "9. Severe Sepsis Screening".

12. Parallel Gateway

This gateway indicates that both sub processes "13. Severe Sepsis Treatment" and "14. Septic Shock Screening" can be executed at the same time.

13. Sub process: Severe Sepsis Treatment

This sub process should occur in parallel with the sub processes "8. Sepsis Treatment" and "13. Septic Shock Screening".

The recommendations for the Sepsis Treatment are listed below:

Treatment Interventions: Recommendations that explicitly indicates an action of a nurse/doctor.

The studied Guidelines provide the following recommendations on treatments interventions for Severe Sepsis:

Guideline Recommendations	SSC	Irish	German
Protocolized, quantitative resuscitation of patients with sepsis- induced tissue hypoperfusion (defined in this document as hypotension persisting after initial fluid challenge or blood lactate concentration ≥ 4 mmol/L). Goals during the first 6 hrs of resuscitation:	x		
Administration of effective intravenous antimicrobials within the first hour of recognition of septic shock (grade 1B) and severe sepsis without septic shock (grade 1C) as the goal of therapy.	x		
Initial empiric anti-infective therapy of one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into tissues presumed to be the source of sepsis (grade 1B).	x		
Antiviral therapy initiated as early as possible in patients with severe sepsis or septic shock of viral origin (grade 2C).	x		
Administration of effective IV antimicrobials should occur within the first hour of recognition of severe sepsis or septic shock		x	
Antiviral therapy is suggested to be initiated as early as possible in patients with severe sepsis or septic shock of suspected viral origin.		x	
Administer broad spectrum antibiotics (to be completed in 3 hours)	x		
Administer 30 mL/kg crystalloid for hypotension or lactate 4mmol/L (to be completed in 3 hours)	x		
Complete Sepsis 6 within first hour. (3 Hour Bundle)		x	
Administer a minimum of 30 mL/kg isotonic crystalloid for hypotension or lactate >4mmol/L (3 Hour Bundle)		x	
Measures for initial hemodynamic stabilization			x
Volume replacement therapy is recommended as the initial hemodynamic stabilization measure			x

Table 17 – Severe Sepsis Treatment Interventions. Source: Prepared by author.

To generate the table above the user should use the following filters in the spreadsheet: [Severe Sepsis - treatment interventions = “x”].

Treatment Parameters: Refers to variables that must be collected by exams or observed in a physical evaluation during treatment execution. These variables will be analyzed to monitor and guide the treatment.

The studied guidelines provide the following recommendations on this topic:

Guideline Recommendations	SSC	Irish	German
URINE OUTPUT: Assess urine output and consider urinary catheterization for accurate measurement in patients with severe sepsis/septic shock.		x	
Central venous pressure 8–12mm Hg	x		
Mean arterial pressure (MAP) ≥ 65mm Hg	x		
Urine output ≥ 0.5 mL/kg/hr	x		
Central venous (superior vena cava) or mixed venous oxygen saturation 70% or 65%, respectively (grade 1C).	x		
In patients with elevated lactate levels targeting resuscitation to normalize lactate (grade 2C).	x		
Assess patient for response to resuscitation by monitoring clinical and haemo-dynamic response, measure hourly urinary output and repeat lactate measurement. (3 Hour Bundle)		x	
It is recommended that vasopressor therapy if required should initially target a mean arterial pressure (MAP) of 65mm Hg		x	
Patients with raised lactate levels on presentation should have repeat lactate levels performed within three hours.		x	
Measures for initial hemodynamic stabilization			x
The target parameter is central venous oxygen saturation (ScvO2) of > 70%. In order to attain a ScvO2 of > 70%, intravascular volume administration as well as the administration of dobutamine and packed red blood cells (when hematocrit is <30%) is recommended.			x
For the purpose of early hemodynamic stabilization, a set of the following hemodynamic target criteria is recommended: - CVP > 8 or > 12 mmHg in mechanical ventilation - MAP > 65 mmHg - Diuresis > 0.5 ml/kg/hr - Central venous oxygen saturation (ScvO2) > 70% [227] - Lactate < 1.5 mmol/l or a decrease in [blood] lactate levels			x

Table 18 – Severe Sepsis Treatment Parameters. Source: Prepared by author.

To generate the table above the user should use the following filters in the spreadsheet: [Severe Sepsis - treatment parameters= “x”].

Business Rules for Treatment: Rule to define the course of the treatment, usually based on a combination of observed/measured treatment parameters.

The studied guidelines provide the following recommendations on this topic:

Guideline Recommendations	SSC	Irish	German
Patients who develop fluid overload, (signs and symptoms include jugular venous distention, crepitations on chest auscultation, and decreased pulse oximetry readings), should have all IV fluids (boluses and background rate) discontinued until no longer deemed fluid overloaded.		x	
Patients who have persistent organ dysfunction and/or shock after 30mls/kg IV fluid has been administered should have a critical care consultation considered.		x	
Patients who present extremely unwell may require early critical care input to secure the airway and breathing as well as the circulation.		x	
Measures for initial hemodynamic stabilization			x
The target parameter is central venous oxygen saturation (ScvO2) of > 70%. In order to attain a ScvO2 of > 70%, intravascular volume administration as well as the administration of dobutamine and packed red blood cells (when hematocrit is <30%) is recommended.			x
For the purpose of early hemodynamic stabilization, a set of the following hemodynamic target criteriais recommended: - CVP > 8 or > 12 mmHg in mechanical ventilation - MAP > 65 mmHg - Diuresis > 0.5 ml/kg/hr - Central venous oxygen saturation (ScvO2) > 70% [227] - Lactate < 1.5 mmol/l or a decrease in [blood] lactate levels			x

Table 19 – Severe Sepsis Business Rules for Treatment. Source: Prepared by author.

To generate the table above the user should use the following filters in the spreadsheet: [Severe Sepsis - business rule for treatment= “x”].

Treatment Recommendations: Recommendation related to a treatment procedure.

The recommendations on this topic provided by studied guidelines are listed in Appendix 8.6. To generate the table presented in this Appendix the user should use the following filters in the spreadsheet: [Severe Sepsis - treatment recommendation= "x"].

14. Sub process: Septic Shock Screening

The sub process Septic Shock Screening initiates at the same time the sub process Severe Sepsis Treatment is initiated, and finishes either:

- When the doctor, during the activity "4. Medical Evaluation for Sepsis" have define the stage the patient is in as Septic Shock.
- When, during the sub process "13. Severe Sepsis Treatment", the symptoms for Septic Shock are noticed and a doctor must evaluate the patient to confirm Septic Shock or;
- When the sub process Severe Sepsis Treatment is terminated.

The symptoms of Septic Shock are the same as the Severe Sepsis symptoms, plus the development of fluid refractory cardiovascular dysfunction. If the patient is at this point in the Process, it means either that:

- The doctor has already clinically confirmed the presence of Severe Sepsis and during the sub process "13. Severe Sepsis Treatment" the medical staff involved in the patient's treatment must observe the diagnosis parameters for Severe Sepsis.
- The doctor has already clinically confirmed Severe Sepsis and defined the patient stage as Septic Shock. In this case, the sub process and "17. Septic Shock Treatment" must start in parallel with the sub processes "8. Sepsis Treatment" and "13. Severe Sepsis Treatment"

The guidelines recommended the following diagnosis parameters for Septic Shock:

Guideline Recommendations	SSC	Irish	German
Sepsis-induced tissue hypoperfusion is defined in this National Clinical Guideline as hypotension or blood lactate concentration ≥ 4 mmol/L persisting after initial isotonic crystalloid fluid challenge of 30mls/kg.		x	
Septic shock: criteria I and II, as well as a systolic arterial blood pressure of ≤90 mmHg for at least 1 hour, or mean arterial pressure of ≤65 mmHg, or the necessity of vasopressor administration to maintain a target systolic arterial pressure of ≥90 mmHg or mean arterial pressure of ≥65mmHg. Hypotension persists despite adequate volume resuscitation and cannot be explained by other causes.			x

Table 20 – Septic Shock Diagnosis Parameters. Source: Prepared by author.

To generate the table above the user should use the following filters in the spreadsheet: [Septic shock- diagnosis parameters= "x"].

15. Activity: Medical Evaluation for Septic Shock

In this activity, the doctor will evaluate the patient to confirm the diagnosis of Septic Shock and prescribe the treatment and request exams according to this diagnosis.

According to the studied guidelines the following business rules defines the diagnosis for Severe Sepsis:

Guideline Recommendations	SSC	Irish	German
Sepsis-induced tissue hypoperfusion is defined in this National Clinical Guideline as hypotension or blood lactate concentration ≥ 4 mmol/L persisting after initial isotonic crystalloid fluid challenge of 30mls/kg.		x	
Septic shock: criteria I and II, as well as a systolic arterial blood pressure of ≤90 mmHg for at least 1 hour, or mean arterial pressure of ≤65 mmHg, or the necessity of vasopressor administration to maintain a target systolic arterial pressure of ≥90 mmHg or mean arterial pressure of ≥65mmHg. Hypotension persists despite adequate volume resuscitation and cannot be explained by other causes.			x

Table 21 – Severe Sepsis Business Rules for Diagnosis. Source: Prepared by author.

To generate the table above the user should use the following filters in the spreadsheet: [Severe Sepsis- business rules for diagnosis= "x"].

16. Gateway: "Is septic shock detected?"

If the doctor has confirm the patient's diagnosis as Septic Shock during a Medical Evaluation activity, the patient must start immediately the sub processes and "17. Septic Shock Treatment" in parallel with the sub processes "8. Sepsis Treatment" and "13. Severe Sepsis Treatment".

If the doctor does not confirm the patient's diagnosis as Severe Sepsis or Septic Shock, the flow returns to the sub process "14. Septic Shock Screening".

17. Sub process: Septic Shock Treatment

The recommendations for the Septic Shock Treatment are listed below:

Treatment Interventions: Recommendations that explicitly indicates an action of a nurse/doctor.

The studied Guidelines provide the following recommendations on treatments interventions for Septic Shock:

Guideline Recommendations	SSC	Irish	German
ANTIMICROBIALS: Give IV antimicrobials according to local antimicrobial guidelines.		x	
5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg	x		
7) Remeasure lactate if initial lactate was elevated*	x		
TO BE COMPLETED WITHIN 6 HOURS OF DIAGNOSIS 1. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg. **A. Initial resuscitation** **Intravenous fluid resuscitation** Quantitative resuscitation of patients with sepsis-induced tissue hypoperfusion should be used (i.e. a fluid bolus given over a pre-determined time period and repeated as required).		x	

Therapy with inotropic agents and vasopressors If cardiac output remains decreased despite intravascular volume therapy, we recommend the use of dobutamine as the catecholamine of first choice [240]. If volume therapy fails to maintain the target mean arterial pressure (MAP) of >65 mmHg or adequate organ perfusion, it is recommended to use catecholamines with vasopressor effects.			**x**

Table 22 – Septic Shock Treatment Interventions. Source: Prepared by author.

To generate the table above the user should use the following filters in the spreadsheet: [Septic Shock - treatment interventions = "x"].

Treatment Parameters: Refers to variables that must be collected by exams or observed in a physical evaluation during treatment execution. These variables will be analyzed to monitor and guide the treatment. The studied Guidelines provide the following recommendations on this topic:

Guideline Recommendations	SSC	Irish	German
URINE OUTPUT: Assess urine output and consider urinary catheterisation for accurate measurement in patients with severe sepsis/septic shock.		x	
FLUIDS: Start IV fluid resuscitation if evidence of hypovolaemia and/or shock. 500ml–1000mls bolus of isotonic crystalloid over 15–30 minutes and give up to 30ml/kg, reassessing after each bolus for signs of hypovolaemia, euvolaemia, or fluid overload.		x	
Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg	x		
In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate 4 mmol/L (36 mg/dL): - Measure central venous pressure (CVP)* - Measure central venous oxygen saturation (ScvO2)*	x		
*Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, ScvO2 of 70%, and normalization of lactate.	x		

Goals during the first 6 hours of resuscitation include: SBP > 90mmHg or MAP > 65mmHg or within 10% of known baseline and not clinically deemed hypoperfused SBP > 90mmHg or MAP > 65mmHg, fluid replete/overloaded* and on vasopressors Central venous pressure 8–12 mm Hg Mean arterial pressure (MAP) ≥ 65 mm Hg Urine output ≥ 0.5 mL/kg/hr Central venous (superior vena cava) or mixed venous oxygen saturation 70% or 65%, respectively.		x	
H. Vasopressors: 1. Vasopressor therapy initially to target a mean arterial pressure (MAP) of 65mm Hg (grade 1C).	x		
Those with persistent shock should have invasive monitoring and ongoing fluid resuscitation guided by urinary output, repeat lactate and/or ScvO2 measurement and pressor administration, as required, to obtain a MAP > 65mmHg within 6 hours.		x	

Table 23 – Septic Shock Treatment Parameters. Source: Prepared by author.

To generate the table above the user should use the following filters in the spreadsheet: [Septic Shock - treatment parameters = "x"].

Business Rules for Treatment: Rule to define the course of the treatment, usually based on a combination of observed/measured treatment parameters.

The studied Guidelines provide the following recommendations on this topic:

Guideline Recommendations	**SSC**	**Irish**	**German**
FLUIDS: Start IV fluid resuscitation if evidence of hypovolaemia and/or shock. 500ml–1000mls bolus of isotonic crystalloid over 15–30 minutes and give up to 30ml/kg, reassessing after each bolus for signs of hypovolaemia, euvolaemia, or fluid overload.		x	
Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg	x		
Remeasure lactate if initial lactate was elevated*	x		

*Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, ScvO2 of 70%, and normalization of lactate.	x		
Re-measure lactate as indicated.		x	
Goals during the first 6 hours of resuscitation include: SBP > 90mmHg or MAP > 65mmHg or within 10% of known baseline and not clinically deemed hypoperfused SBP > 90mmHg or MAP > 65mmHg, fluid replete/overloaded* and on vasopressors Central venous pressure 8–12 mm Hg Mean arterial pressure (MAP) ≥ 65 mm Hg Urine output ≥ 0.5 mL/kg/hr Central venous (superior vena cava) or mixed venous oxygen saturation 70% or 65%, respectively.		x	
Those with persistent shock should have invasive monitoring and ongoing fluid resuscitation guided by urinary output, repeat lactate and/or ScvO2 measurement and pressor administration, as required, to obtain a MAP > 65mmHg within 6 hours.		x	

Table 24– Septic Shock Business Rules for Treatment. Source: Prepared by author.

To generate the table above the user should use the following filters in the spreadsheet: [Septic Shock – business rule for treatment = "x"].

Treatment Recommendations: Recommendation related to a treatment procedure.

The recommendations on this topic provided by studied guidelines are listed in Appendix 8.7. To generate the table presented in this Appendix the user should use the following filters in the spreadsheet: [Septic Shock - treatment recommendation = "x"].

18. Gateway: Is the Severe Sepsis Treatment sub process over?

This gateway guarantees the condition that the patient will be monitored for the progression of the syndrome to Septic Shock until the end of the Severe Sepsis treatment.

19. Gateway: Is the Sepsis Treatment sub process over?

This gateway guarantees the condition that the patient will be monitored for the progression of the syndrome to Severe Sepsis until the end of the Sepsis treatment.

Once the Sepsis treatment is over and the patient no longer presents signs of Sepsis, he may be discharged home or continue in the hospital to treat another condition. The patient then returns to the hospital care process and to the sub process “2. Sepsis Suspicion Screening” to monitor if the syndrome will develop again in this patient.

The process terminates when patient is discharged from the hospital.

8.3.
Recommendations for Initial Data Collection

Guideline Recommendations	SSC	Irish	German
CULTURES: Take blood cultures before giving antimicrobials (if no significant delay i.e. >45 minutes) and consider source control.		x	
BLOODS: Check lactate and full blood count.		x	
Cultures as clinically appropriate before antimicrobial therapy if no significant delay (> 45 mins) in the start of antimicrobial(s) (grade 1C).	x		
Imaging studies performed promptly to confirm a potential source of infection (UG).	x	x	
Appropriate cultures should be taken before antimicrobial therapy is started, as long as there is no significant delay (> 45 mins) in the start of antimicrobial(s)		x	
Measure lactate level (to be completed in 3 hours)	x		
Obtain blood cultures prior to administration ofantibiotics (to be completed in 3 hours)	x		
It is recommended to collect blood cultures when sepsis is clinically suspected or when one or more of the following criteria are met: fever, chills/shivering, hypothermia, leukocytosis, left shift in differential blood count, increase in procalcitonin or C-reactive protein (CRP) levels, and/or neutropenia [5, 8, 20].			x
It is recommended to collect blood cultures (2-3 sets) as soon as possible before instituting antimicrobial therapy [22, 23].			x
In patients on antimicrobial therapy, it is recommended to collect blood cultures immediately before administration of the next dose [24, 25].			x
Blood culture collection preferably prior to initiation of antimicrobial therapy, if applicable after therapy break or, in the case of therapy in progress, immediately prior to the administration of the next dose (low serum levels).			x

Guideline Recommendations	SSC	Irish	German
Aseptic technique used for blood culture collection: hand disinfection of the person drawing blood, disposable gloves, and skin disinfection at the site of puncture, disinfection of the rubber diaphragm of the culture bottle.			x
Blood volume of 20 ml per blood culture (i.e. 10 ml per culture bottle); in neonates and preterm babies as well as children with a body weight of under 44 lb (i.e. 20 kg) 1-5 ml depending on weight, using special blood culture bottles that are generally available.			x
Inoculation of two culture bottles: in adults and children with a body weight of over 44 lb (i.e. 20 kg), usually one aerobic and one anaerobic culture bottle			x
Collection of 2 to 4 sets of blood cultures from different puncture sites, occasionally necessitating a blood draw from an intravascular catheter			x
Label the culture bottles (name, date and time of blood collection); do not cover the bottle bottom and the bar code label			x
Laboratory requisition with patient's last name, first name, date of birth, sex; sender, ward, date of admission, date and time of blood culture collection, site of specimen collection, underlying illness, risk factors, working diagnosis, previous antimicrobial therapy			x
Transport: as soon as possible, but no later than 16 hours after blood culture collection. Temporary storage overnight only, at 36±1°C in a laboratory incubator or at room temperature, depending on manufacturer's instructions			x
When pneumonia is suspected, it is recommended to obtain secretions from deep airway segments before initiating antimicrobial therapy.			x

Table 25 – Recommendations for Initial Data Collection. Source: Prepared by author.

8.4.

Sepsis Treatment Recommendations

Guideline Recommendations	SSC	Irish	German
ANTIMICROBIALS: Give IV antimicrobials according to local antimicrobial guidelines.		x	
Initial empiric antimicrobial therapy of one or more antimicrobials that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into tissues presumed to be the source of sepsis is recommended.		x	
Local antimicrobial prescribing should be followed to guide best choice of empiric antimicrobial therapy. This is to ensure that the antimicrobial chosen is appropriate for the local epidemiology.		x	
The antimicrobial regimen should be reassessed daily for potential de-escalation.		x	
It is recommended to re-evaluate the selected antimicrobial regimen every 48-72 hours based on clinical and microbiological criteria in order to narrow the antimicrobial spectrum and thereby decrease the risk of resistance, toxicity and costs.			x
If an infection cannot be confirmed using clinical and/or microbiological criteria, it is recommended to stop antimicrobial therapy.			x
It is recommended to tailor the duration of antimicrobial therapy according to the clinical response; therapy continued for longer than 7-10 days is generally not required.			x
Depending on the local resistance patterns, it is recommended to use an antibiotic with Pseudomonas coverage (ureidopenicillin (piperacillin) or 3rd or 4th generation cephalosporins [ceftazidime or cefepime] or carbapenems (imipenem or meropenem))			x
In the presence of a high suspicion of a MRSA infection, it is recommended to initiate MRSA-effective therapy with linezolid or daptomycin (the latter in severe skin and soft tissue infections or in MRSA bacteremia of unknown origin)			x
In pulmonary MRSA infections, it is not recommended to employ monotherapy with glycopeptides because glycopeptides display limited tissue penetration due to their molecular size.			x

Guideline Recommendations	SSC	Irish	German
In confirmed cases of pulmonary MRSA infections as well as in skin and soft tissue infections, treatment with linezolid is recommended as it is superior to vancomycin monotherapy;			x
In sepsis secondary to community-acquired pneumonia, a combination therapy consisting of a beta-lactam antibiotic and a macrolide is recommended.			x
Antimycotic therapy is recommended in candidemia.			x
Calculated empiric therapy with antimycotic agents is not recommended for routine use in patients with severe sepsis and septic shock who are neither neutropenic nor immunosuppressed.			x

Table 26 – Sepsis Treatment Recommendations. Source: Prepared by author.

8.5.

Severe Sepsis Diagnosis Parameters

Guideline Recommendations	SSC	Irish	German
Altered mental status	x	x	
Arterial hypotension (SBP < 90mm Hg, MAP < 70mm Hg, or an SBP decrease > 40mm Hg in adults or less than two sd below normal for age)	x	x	
Organ dysfunction variables:			
Arterial hypoxemia (Pao2/Fio2 < 300)	x	x	
Acute oliguria (urine output < 0.5mL/kg/hr for at least 2 hrs despite adequate fluid resuscitation)	x	x	
Creatinine increase > 0.5mg/dL or 44.2 µmol/L	x	x	
Coagulation abnormalities (INR > 1.5 or aPTT > 60 s)	x	x	
Ileus (absent bowel sounds)	x	x	
Thrombocytopenia (platelet count < 100,000 µL–1)	x	x	
Hyperbilirubinemia (plasma total bilirubin > 4mg/dL or 70 µmol/L)	x	x	
Tissue perfusion variables:			
Hyperlactatemia (> 1 mmol/L)	x	x	
Decreased capillary refill or mottling	x	x	
Acute lung injury with PaO2 /FiO2 < 250 in the absence of pneumonia as infection source	x	x	
Acute lung injury with PaO2 /FiO2 < 300 in the presence of pneumonia as infection source		x	
Creatinine > 176.8 micromol/l	x	x	
Severe sepsis definition = sepsis-induced tissue hypoperfusion or organ dysfunction (any of the following thought to be due to the infection)	x		
Sepsis-induced hypotension	x	x	
Lactate above upper limits laboratory normal	x	x	
Urine output < 0.5mL/kg/hr for more than 2 hrs despite adequate fluid resuscitation	x	x	
Acute lung injury with Pao2/Fio2 < 200 in the presence of pneumonia as infection source	x	x	
Bilirubin > 2mg/dL (34.2 µmol/L)	x	x	
Platelet count < 100,000 µL	x	x	
Coagulopathy (international normalized ratio > 1.5)	x	x	

Guideline Recommendations	SSC	Irish	German
Sepsis induced hypotension		x	
Lactate above upper limits laboratory normal		x	
Urine output < 0.5 mL/kg/hr for more than 2 hrs despite adequate fluid resuscitation		x	
Acute lung injury with PaO2 /FIO2 < 250 in the absence of pneumonia as infection source		x	
Creatinine > 2.0 mg/dL (176.8 μmol/L)		x	
Bilirubin > 2 mg/dL (34.2 μmol/L)		x	
Platelet count < 100,000 μL		x	
Coagulopathy (international normalized ratio > 1.5)		x	
Systolic blood pressure < 90 mmHg or MAP < 65 mmHg		x	
Decrease in systolic blood pressure by 40mmHg from baseline and/or		x	
Lactate > 4 mmol/l. (18)		x	
Acute encephalopathy: reduced alertness, disorientation, agitation, delirium			x
Relative or absolute thrombocytopenia: decrease in platelet counts by more than 30% within 24 hours or a platelet count of less than 100.000/mm3.			x
Thrombocytopenia due to acute hemorrhage or immunological causes must be ruled out.			x
Arterial hypoxemia: PaO2 ≤10 kPa (≤75 mmHg) while breathing ambient air or a PaO2/FiO2 ratio of ≤33 kPa (≤250 mmHg) on oxygen administration.			x
A clinically manifest heart or lung disease must be ruled out as a cause of hypoxemia. *f*			x
Renal impairment: diuresis of ≤0.5 ml/kg/h for at least 2 hours despite adequate volume resuscitation and/or an increase in serum creatinine level to > twice the upper limit of normal (ULN). *f*			x
Metabolic acidosis: Base excess of ≤-5 mmol/L or lactate concentration of > 1.5× ULN.			x

Table 27 – Severe Sepsis Diagnosis Parameters. Source: Prepared by author.

8.6.

Severe Sepsis Treatment Recommendations

Guideline Recommendations	SSC	Irish	German
Antimicrobial regimen should be reassessed daily for potential deescalation (grade 1B).	x		
Use of low procalcitonin levels or similar biomarkers to assist the clinician in the discontinuation of empiric antibiotics in patients who initially appeared septic, but have no subsequent evidence of infection (grade 2C).	x		
Combination empirical therapy for neutropenic patients with severe sepsis (grade 2B) and for patients with difficult-to-treat, multidrugresistant bacterial pathogens such as Acinetobacter and Pseudomonas spp. (grade 2B). For patients with severe infections associated with respiratory failure and septic shock, combination therapy with an extended spectrum beta-lactam and either an aminoglycoside or a fluoroquinolone is for P. aeruginosa bacteremia (grade 2B). A combination of beta-lactam and macrolide for patients with septic shock from bacteremic Streptococcus pneumoniae infections (grade 2B).	x		
Empiric combination therapy should not be administered for more than 3–5 days. De-escalation to the most appropriate single therapy should be performed as soon as the susceptibility profile is known (grade 2B).	x		
Duration of therapy typically 7–10 days; longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with S. aureus; some fungal and viral infections or immunologic deficiencies, including neutropenia (grade 2C).	x		
Antimicrobial agents should not be used in patients with severe inflammatory states determined to be of noninfectious cause.	x		
Empiric antimicrobial prescribing: Antimicrobial prescribing should be based on locally approved guidelines, the patients' history of colonization/infection with antimicrobial resistant organisms and the site of infection as determined clinically		x	
Antimicrobial agents should NOT be used in patients with severe inflammatory states determined to be of non-infectious cause.		x	

Guideline Recommendations	SSC	Irish	German
Antimicrobials should be reviewed after 24-48 hours by a senior clinician and rationalized based on culture results and clinical response as outlined in the national antimicrobial prescribing care bundle.		x	
Combination Therapy: The Surviving Sepsis Guideline Development Group suggest combination empirical therapy for neutropenic patients with severe sepsis		x	
Combination Therapy: The Surviving Sepsis Guideline Development Group suggest combination empirical therapy for patients with difficult-to-treat, multi-drug resistant bacterial pathogens such as Acinetobacter and Pseudomonas spp.		x	
Duration of antimicrobial therapy: Empiric combination therapy should NOT be administered for more than 3–5 days. Deescalation to the most appropriate single therapy should be performed as soon as the antimicrobial susceptibility profile is known		x	
Duration of therapy of typically 7–10 days is suggested. This is dependent on the source of infection and the clinical response to therapy. Longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteraemia with S. aureus; some fungal and viral infections or immunologic deficiencies, including neutropenia.		x	
When source control in a severely septic patient is required, the effective intervention associated with the least physiologic insult should be used (eg, percutaneous rather than surgical drainage of an abscess) (UG).	x	x	
If intravascular access devices are a possible source of severe sepsis or septic shock, they should be removed promptly after other vascular access has been established (UG).	x	x	
Assess patient for response to resuscitation by monitoring clinical and haemo-dynamic response, measure hourly urinary output and repeat lactate measurement. (3 Hour Bundle)		x	

Guideline Recommendations	SSC	Irish	German
Measuring lactate and urinary output aids the identification of those with severe sepsis/septic shock and these patients should receive 30mls/kg IV isotonic crystalloid fluid guided by their clinical response to fluid resuscitation. Some patients will need more than this to be fluid replete i.e. warm, well perfused, normal mental status, with normal lactate and urinary output. =		x	
Patients who develop fluid overload, (signs and symptoms include jugular venous distention, crepitations on chest auscultation, and decreased pulse oximetry readings), should have all IV fluids (boluses and background rate) discontinued until no longer deemed fluid overloaded.		x	
Crystalloids as the initial fluid of choice in the resuscitation of severe sepsis and septic shock (grade 1B).	x		
Against the use of hydroxyethyl starches for fluid resuscitation of severe sepsis and septic shock (grade 1B).	x		
Albumin in the fluid resuscitation of severe sepsis and septic shock when patients require substantial amounts of crystalloids (grade 2C).	x		
Initial fluid challenge in patients with sepsis-induced tissue hypoperfusion with suspicion of hypovolemia to achieve a minimum of 30mL/kg of crystalloids (a portion of this may be albumin equivalent). More rapid administration and greater amounts of fluid may be needed in some patients (grade 1C).	x		
Fluid challenge technique be applied wherein fluid administration is continued as long as there is hemodynamic improvement either based on dynamic (eg, change in pulse pressure, stroke volume variation) or static (eg, arterial pressure, heart rate) variables (UG).	x		
It is recommended that isotonic crystalloids are used as the initial fluid of choice in the resuscitation of severe sepsis and septic shock.		x	
The Guideline Development Group recommends AGAINST the use of hydroxyethyl starches for fluid resuscitation of severe sepsis and septic shock		x	
Albumin in the fluid resuscitation of severe sepsis and septic shock is suggested when patients require substantial amounts of crystalloids and a colloid is being considered.		x	

Guideline Recommendations	SSC	Irish	German
A fluid challenge technique is recommended i.e. fluid administration is continued as long as there is hemodynamic improvement either based on dynamic (eg, change in pulse pressure, stroke volume variation) or static (eg, arterial pressure, heart rate) variables.		x	
It is recommended that vasopressor therapy if required should initially target a mean arterial pressure (MAP) of 65mm Hg		x	
Low-dose dopamine should NOT be used for renal protection.		x	
All patients requiring vasopressors should have an arterial catheter placed as soon as practical if resources are available.		x	
Noradrenaline is recommended as the first choice of vasopressor.		x	
Adrenaline (added to and potentially substituted for noradrenaline) may be used when an additional agent is needed to maintain adequate blood pressure.		x	
Vasopressin 0.03 units/minute can be added to noradrenaline with intent of either raising MAP or decreasing noradrenaline dosage.		x	
Low-dose vasopressin is not recommended as the single initial vasopressor for treatment of sepsis-induced hypotension and vasopressin doses higher than 0.03-0.04 units/minute should be reserved for salvage therapy (failure to achieve adequate MAP with other vasopressor agents).		x	
Dopamine as an alternative vasopressor agent to noradrenaline is only to be used in highly selective patients (e.g., patients with low risk of tachyarrhythmias and absolute or relative bradycardia).		x	
Phenylephrine is not recommended in the treatment of septic shock except in circumstances where (a) noradrenaline is associated with serious arrhythmias, (b) cardiac output is known to be high and blood pressure persistently low or (c) as salvage therapy when combined inotrope/vasopressor drugs and low dose vasopressin have failed to achieve MAP target.		x	
Corticosteroids not be administered for the treatment of sepsis in the absence of shock (grade 1D).	x	x	
Patients with raised lactate levels on presentation should have repeat lactate levels performed within three hours.		x	
According to current data, the administration of HAES solutions (200/0.5 and 200/0.62) in patients with severe sepsis or septic shock is not recommended.			x

Guideline Recommendations	SSC	Irish	German
According to current data, the use of low molecular weight HAES solutions and other artificial colloidal solutions in patients with severe sepsis and septic shock is not recommended.			x
In patients with severe sepsis or septic shock, the administration of human albumin may be considered.			x
For the purposes of hemodynamic stabilization we recommend volume restitution with the use of crystalloid solutions.			x
The use of dopexamine in the treatment of patients with severe sepsis or septic shock is not recommended [244-248].			x

Table 28 - Severe Sepsis Treatment Recommendations. Source: Prepared by author.

8.7.
Septic Shock Treatment Recommendations

Guideline Recommendations	SSC	Irish	German
FLUIDS: Start IV fluid resuscitation if evidence of hypovolaemia and/or shock. 500ml–1000mls bolus of isotonic crystalloid over 15–30 minutes and give up to 30ml/kg, reassessing after each bolus for signs of hypovolaemia, euvolaemia, or fluid overload.		x	
A sample fluid resuscitation algorithm is suggested as a guide to ongoing fluid resuscitation		x	
The elements of the 6-hour bundle may have to be initiated very early in patients presenting with profound hypotension. The 3 and 6-hour bundles do not have to be performed consecutively but rather according to patient need. However, the elements should be completed within their time frames i.e. Sepsis 6 within the first hour, and the bundles within 3 and 6 hours respectively.		x	
Norepinephrine as the first choice vasopressor (grade 1B).	x		
Epinephrine (added to and potentially substituted for norepinephrine) when an additional agent is needed to maintain adequate blood pressure (grade 2B).	x		
Vasopressin 0.03 units/minute can be added to norepinephrine (NE) with intent of either raising MAP or decreasing NE dosage (UG).	x		
Low dose vasopressin is not recommended as the single initial vasopressor for treatment of sepsis-induced hypotension and vasopressin doses higher than 0.03-0.04 units/minute should be reserved for salvage therapy (failure to achieve adequate MAP with other vasopressor agents) (UG).	x		
Dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients (eg, patients with low risk of tachyarrhythmias and absolute or relative bradycardia) (grade 2C).	x		
Phenylephrine is not recommended in the treatment of septic shock except in circumstances where (a) norepinephrine is associated with serious arrhythmias, (b) cardiac output is known to be high and blood pressure persistently low or (c) as salvage therapy when combined inotrope/vasopressor drugs and low dose vasopressin have failed to achieve MAP target (grade 1C).	x		
Low-dose dopamine should not be used for renal protection (grade 1A).	x		

Guideline Recommendations	SSC	Irish	German
All patients requiring vasopressors have an arterial catheter placed as soon as practical if resources are available (UG).	x		
Those with persistent shock should have invasive monitoring and ongoing fluid resuscitation guided by urinary output, repeat lactate and/or ScvO2 measurement and pressor administration, as required, to obtain a MAP > 65mmHg within 6 hours.		x	
Therapy with inotropic agents and vasopressors If cardiac output remains decreased despite intravascular volume therapy, we recommend the use of dobutamine as the catecholamine of first choice If left ventricular function remains impaired despite the administration of dobutamine, therapy with epinephrine, phosphodiesterase inhibitors or levosimendan may be considered. An increase in cardiac output to a predefined supranormal target value (the concept of "supramaximal oxygen supply“) is not recommended [241-243]. The use of dopexamine in the treatment of patients with severe sepsis or septic shock is not recommended [244-248]. If volume therapy fails to maintain the target mean arterial pressure (MAP) of >65 mmHg or adequate organ perfusion, it is recommended to use catecholamines with vasopressor effects. On the basis of currently available data, a clear-cut recommendation cannot be made for the use of a specific vasopressor agent [249]. We recommend administration of noradrenalin as the substance of first-choice [240, 250]. The routine use of vasopressin is not recommended. The use of low-dose dopamine (5 µg·kg-¹·min-¹) for renal protection is not recommended because neither any positive effects on kidney function nor a survival benefit could be established; moreover, dopamine displays adverse endocrinological and immunological side effects [259-264].			**x**

Table 29– Septic Shock Treatment Recommendations. Source: Prepared by author.