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Point of care methods to differentiate sepsis from similar groups of symptoms in the emergency department.

PhD thesis

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List of Abbreviations

ACTH – adrenocorticotropic hormone

AMS - altered mental state

ATP - adenosintriphosphat

aOR - adjusted odds ratio

CI - confidence intervals

CNS – central nervous system

CRH – corticotropin-releasing hormone

CT – computer tomography

DAMP - danger (or damage)-associated molecular pattern

DAP12 - DNAX-activating protein of **12** kDa

DBP - diastolic blood pressure

DNA - deoxyribonucleic acid

ER - emergency room

HMGB1 - high mobility group box-1 protein

HR - heart rate

ICAM-1 intercellular adhesion molecule-1

ICD - International Statistical Classification of Diseases and Related Health Problems

ICP – intracranial pressure

IDSA - Infectious Diseases Society of America

IL-1 – interleukin-1

IL-2 – interleukin-2

IL-6 – interleukin-6

IL-8 – interleukin-8

IL-10 – interleukin-10

IL-18 – interleukin-18

iNOS – inducible NO synthase

LPS - lipopolysaccharide

MAP - mean arterial pressure

MDL-1 - myeloid DAP12-associating lectin receptor

NET - neutrophil extracellular trap

NEWS - National Early Warning Score

NF- κB - nuclear factor κB

NLR - neutrophyl-limphocyte ratio

NO – nitric oxide

NOD - nucleotide-oligomerization domain

OR - odds ratio

PAI-1 – plasminogen activator inhibitor-1

PAMP - pathogen-associated molecular pattern

PIRO - predisposition, infection (present or suspected), response (immune system activation) and organ dysfunction

PMN - polymorphonuclear leukocytes

PoC - point of care

PRR - pattern recognition receptor

qSOFA - quick sequential organ failure assessment

RIG-I - retinoic-acid-inducible gene I

ROC - receiver operating characteristic

RR - respiratory rate

SBP - systolic blood pressure

SD - standard deviations

SIRS - systemic inflammatory response syndrome

SOFA – sequential/sepsis-related organ failure assessment

TF – tissue factor

TM - thrombomodulin

TLR – toll-like receptor

TNFα – tumor necrosis factor alpha

TREM-1 - triggering receptor expressed on myeloid cell

VCAM-1 - vascular cell adhesion molecule-1

1. Introduction

Sepsis presents a significant challenge for doctors and nurses alike, contributing to one in five global deaths (1). While improved recognition has led to an increase in identified sepsis cases, there remains a notable variation in mortality rates across regions, influenced by factors like GDP and overall population health. Early identification is crucial for effective treatment; however, the highly nonspecific symptoms associated with sepsis continue to pose challenges for timely management (2).

Normally, the immune system localizes and resolves infections. However, certain individual characteristics, including immune status and genetic variability, can lead to systemic inflammation triggered by infections. In the early 1990s, various inflammatory parameters like body temperature, respiratory rate (RR), heart rate (HR), leukocytosis, or leukopenia were used to diagnose sepsis (3,4). Although the widely accepted criteria known as systemic inflammatory response syndrome (SIRS) criteria have not been entirely replaced by the quick sequential organ failure assessment score (qSOFA), which is based on blood pressure, respiratory rate, and altered mental status (5), SIRS was excluded from the latest sepsis definition due to its limitations. Efforts to refine early recognition through different scoring systems have been considerable, but the complexity of the clinical picture and underlying pathophysiology remains a challenge in most cases (6).

The Sequential Organ Failure Assessment (SOFA) score has proven highly useful due to its focus on organ involvement, specifically evaluating the lungs, central nervous system, liver, kidneys, cardiovascular, and hemopoietic systems (7). Recent analysis by W. Zhang et al. (8) evaluated the predictive efficacy of SIRS and SOFA criteria for in-hospital death in sepsis. Their retrospective study revealed that the SOFA criteria were more robust in identifying sepsis compared to the SIRS criteria.

Criticism has been directed at the Sepsis-3 guidelines by Sartelli et al. for lacking prospective validation in a substantial patient cohort. Additionally, concerns have been raised regarding the predominantly U.S. and Germany-based data, casting doubt on the global applicability of these guidelines. The inclusion of organ dysfunction in the criteria has faced significant criticism as it is not among the initial detectable signs of sepsis.

Moreover, the calculation of the Sequential Organ Failure Assessment (SOFA) score at admission is impracticable due to the necessity for laboratory parameters (9).

Septic shock is defined when vasopressors are required to maintain a mean arterial pressure (MAP) above 65 mmHg, coupled with serum lactate levels exceeding 2 mM/l (7). While the ideal scenario advocates for the recognition and early stabilization of septic patients beginning in the emergency department, the vague presentation of sepsis often results in underdiagnosis or oversight in the early stages, leading to preventable sepsis-related deaths (10,11).

Basic parameters like body temperature fluctuations, heart rate variations, changes in blood pressure, and the assessment of acute phase proteins and biomarkers such as C-reactive protein (CRP), interleukin-6 (IL-6), procalcitonin, and lactate are considered unspecific predictors of sepsis (12).

Altered mental state (AMS) can indeed indicate sepsis, but it can also serve as a warning sign for various other conditions involving transient or permanent brain dysfunction resulting from toxins or blood flow disturbances (13). In settings such as the emergency department or prehospital environments, symptoms commonly associated with ischemic stroke, such as cognitive disorders or sensorimotor aphasia, can resemble AMS, creating similarities between stroke and sepsis presentations (13). Dehydration-induced symptoms like AMS can mimic the disorientation associated with sepsis, particularly among the elderly (13). Low blood pressure can further compromise blood supply to the brain, contributing to its dysfunction.

The PIRO (Predisposition, Infection, Response, Organ Dysfunction) concept views sepsis/septic shock as a complex and multidimensional process but does not yet fully approximate the diagnosis of sepsis when it is identified (14). The utilization of various sepsis scores, vital parameters, and laboratory results for sepsis diagnosis remains contentious (7,15). In the emergency department (15-18), where time constraints and lack of specific parameters limit the calculation of the SOFA score, there is a necessity for an improved diagnostic approach.

Most units in the emergency setting have access to a blood gas analyzer, which can provide crucial data on a patient within minutes. Lactate, easily measured in routine arterial or venous blood gas analysis, stands out as one of the most readily available parameters that can offer valuable diagnostic insights.

The median difference between arterial and venous lactate levels is indeed quite small, approximately 0.049 mM/l. The Sepsis Six approach, initially introduced in 2009 and still relevant in recent years (19,20), emphasizes the measurement of lactate levels. This approach involves a bundle of initial actions aimed at ensuring timely care for sepsis patients, including the prompt administration of crystalloids, oxygen, antibiotics within the first hour, along with microbiological sampling, assessment of urine output, and measurement of lactate levels. Although this approach has faced challenges, no alternative recommendations have been widely accepted or implemented as of yet (21).

At the triage level, it's important to identify and utilize parameters that can be rapidly and reliably measured, preferably with a turnaround time of less than 10 minutes. The National Early Warning Score (NEWS) is a commonly used tool to detect deterioration in a patient's condition over time. However, it might not always be feasible to apply this score at the triage level due to time constraints. Nonetheless, during the observation and monitoring of patients, NEWS remains a valuable approach for assessing and responding to clinical deterioration.

Developing a new set of parameters that are easy to use and provide rapid results at the triage level for the diagnosis of sepsis is indeed a significant goal. However, incorporating the neutrophil-lymphocyte ratio (NLR) into a newly designed scoring system might be a potential focus for future investigations. Nevertheless, utilizing NLR for triage purposes might not be feasible due to its relatively time-consuming nature.

The creation of more personalized scoring systems, especially for conditions requiring tailored management such as elevated intracranial pressure (ICP) or other diseases necessitating specific MAP targets, could be a possibility for exploration in later stages of research.

While there might not be extensive literature directly comparing sepsis, stroke, and dehydration, these pathologies are among the most common reasons for emergency room (ER) admissions. Arbitrarily selecting these syndromes for comparison could be a starting point to identify similarities, differences, and potential diagnostic parameters that might aid in distinguishing between them in the future. However, comprehensive research and comparative studies would be essential to validate any proposed parameters or scoring systems for their effectiveness in differentiation and early diagnosis at the triage level.

1.1. Pathophysiology of sepsis

The body's response to a microbial invasion is a complex and orchestrated process. When tissues are injured due to an infection, the normal host response to this invasion involves several key steps:

1. **Repair Mechanisms:** The body initiates mechanisms to repair the damaged tissue as part of the immune response to infection.
2. **Activation of Phagocytic Cells:** Immune cells, particularly phagocytes like neutrophils and macrophages, are activated. These cells are responsible for engulfing and destroying pathogens to prevent the spread of infection.
3. **Inflammatory Response:** In response to the infection, both proinflammatory and anti-inflammatory mediators are produced. This balance of mediators is critical in modulating the immune response and maintaining tissue homeostasis. The proinflammatory mediators help in eliminating the invading pathogens, while the anti-inflammatory mediators work to regulate and control the inflammatory process, preventing excessive tissue damage.

However, if the response to the infection becomes widespread and involves tissues beyond the initial site of invasion, the process can escalate, resulting in sepsis. In sepsis, the body's response to the infection becomes dysregulated, leading to a systemic and uncontrolled inflammatory state. This dysregulated response can cause damage to multiple organs and systems in the body, leading to multi-organ dysfunction syndrome (MODS).

The pathophysiology of sepsis involves a cascade of events triggered by the body's response to the infection, resulting in an overwhelming inflammatory response, vascular changes, impaired coagulation, and cellular dysfunction. Understanding these mechanisms is crucial in developing strategies for the early recognition and management of sepsis to prevent its progression to severe stages and organ dysfunction (22).

1.2. Normal response to infection

The immune response to infection involves an intricate interplay between the host's recognition of pathogens and the body's reaction to these foreign invaders. This

recognition primarily occurs through pattern recognition receptors (PRRs) present on immune cells. These receptors are crucial for detecting pathogen-associated molecular patterns (PAMPs) associated with various microbes (23).

PRRs are categorized into several families, including:

1. **Toll-like receptors (TLRs):** These receptors are located on the surface of immune cells and can identify specific molecular patterns associated with pathogens. Different TLRs recognize distinct PAMPs, such as bacterial cell wall components, viral nucleic acids, and fungal cell wall constituents.
2. **Nucleotide-oligomerization domain (NOD)-like receptors:** These receptors are located intracellularly within the cytosol and can detect bacterial components.
3. **Retinoic-acid-inducible gene I (RIG-I)-like helicases:** These receptors are involved in recognizing viral ribonucleic acid (RNA) and triggering the immune response against viruses.

Apart from PAMPs, the immune system also responds to endogenous danger signals or damage-associated molecular patterns (DAMPs). DAMPs are molecules released from damaged or stressed cells during inflammation. These molecules, which include various cellular components like heat shock proteins, adenosine-triphosphate (ATP), high mobility group box-1 protein (HMGB1), mitochondrial DNA, and S100 proteins, signal the presence of cellular damage or stress (24). DAMPs are recognized by PRRs and contribute to the immune response by amplifying inflammation and activating immune cells.

Moreover, other receptors, such as triggering receptor expressed on myeloid cells-1 (TREM-1) and myeloid DAP12-associating lectin-1 (MDL-1), are also involved in recognizing microbial components and modulating the host immune response (25).

The recognition and response mechanisms mediated by PRRs and the sensing of DAMPs and other microbial components play crucial roles in initiating and modulating the immune response during infection, influencing the body's ability to combat pathogens and regulate inflammation.

Neutrophil extracellular traps (NETs) are structures composed of DNA, histones, and antimicrobial proteins released by neutrophils to trap and kill pathogens. These NETs play a crucial role in the immune system's defense against invading microorganisms (26).

However, excessive or dysregulated NET formation can also contribute to tissue damage and inflammation (27).

In conditions like sepsis, vascular diseases, chronic lung disease, and glomerulonephritis, NETs have been implicated in contributing to tissue damage and exacerbating the inflammatory response. They can lead to endothelial damage, contribute to inflammatory responses, and promote thrombosis due to the release of bactericidal proteins, DNA, and histones.

Upon binding of microbial components to immune cell surface receptors like TLRs, it triggers signaling cascades that lead to the activation of cytosolic nuclear factor κB (NF-κB). NF-κB translocates from the cytoplasm to the nucleus and binds to specific DNA sequences, thereby activating a wide array of genes involved in the inflammatory response.

These activated genes include various mediators such as:

1. **Chemokines:** These signaling molecules attract immune cells to the site of infection or inflammation. Examples include interleukin-8 (IL-8) and others that facilitate the recruitment of immune cells.
2. **Cell adhesion molecules:** Proteins like intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) help in the adhesion of immune cells to the endothelium and promote their migration to inflamed tissues.
3. **Nitric oxide (NO):** This molecule has various roles in inflammation including regulating blood vessel dilation, neurotransmission and the immune response.
4. **Proinflammatory cytokines:** Tumor necrosis factor-alpha (TNFα) and interleukin-1 (IL-1) are potent cytokines that can trigger inflammation, promote immune cell activation, and induce fever, among other effects.

The activation of these genes and subsequent production of inflammatory mediators form a complex network that regulates the immune response during infection. However, when dysregulated, this process can contribute to tissue damage and exacerbate inflammatory conditions.

When the body activates polymorphonuclear leukocytes (PMNs) in response to an infection or injury, adhesion molecules are expressed on their surface. This leads to the aggregation and margination of PMNs along the endothelial lining of blood vessels.

Simultaneously, the endothelium responds by expressing adhesion molecules to further stimulate and attract these leukocytes.

The migration of PMNs from the blood vessels to the site of injury or infection occurs in a series of steps:

1. **Rolling:** PMNs initially attach and roll along the vessel walls, facilitated by weak interactions between selectins on endothelial cells and their ligands on leukocytes.
2. **Adhesion:** Following rolling, leukocytes firmly adhere to the endothelium via interactions between integrins on leukocytes and endothelial cell adhesion molecules, like ICAM-1 and VCAM-1.
3. **Diapedesis:** Leukocytes undergo diapedesis or transmigration, moving through the endothelial cells' intercellular junctions and migrating towards the site of tissue injury or infection.
4. **Chemotaxis:** PMNs navigate through the tissues following chemical gradients, a process known as chemotaxis, guided by chemical signals or chemokines released at the site of inflammation (28).

Local inflammation manifests as visible signs such as erythema (redness) and warmth due to increased blood flow (hyperemia) and vasodilation in the affected area. Additionally, there is protein-rich edema caused by increased microvascular permeability, leading to fluid leakage from blood vessels into the surrounding tissue.

At the site of infection or injury, PMNs release mediators that can be either proinflammatory or anti-inflammatory in nature. These mediators include various cytokines, chemokines, and other signaling molecules that regulate the local immune response. The purpose of this response is to eliminate invading microorganisms and facilitate tissue repair (29-31).

There is an intricate balance between proinflammatory and anti-inflammatory mediators, pivotal in the regulation of the body's immune response:

1. **Proinflammatory Cytokines:** TNFα and IL-1 are prominent proinflammatory cytokines. TNFα is released through autocrine secretion, affecting the same cells producing it. Other cytokines and mediators like eicosanoids, interferon, IL-1, interleukin-2 (IL-2), IL-6, IL-8, interleukin-10 (IL-10), and platelet-activating factor are released through paracrine secretion, influencing nearby cells. These

cytokines and mediators recruit more PMNs and macrophages, amplifying the proinflammatory response.

2. **Anti-inflammatory Mediators:** These mediators serve to counterbalance the proinflammatory response by inhibiting the production of TNFα and IL-1. They suppress the immune system by reducing cytokine production in mononuclear cells and T helper cells dependent on monocytes. However, some anti-inflammatory mediators, such as IL-10 and IL-6, have effects that are not entirely anti-inflammatory. They can enhance B cell function, stimulating proliferation and immunoglobulin secretion, and promote the development of cytotoxic T cells (32).

The regulation of the inflammatory process involves a delicate equilibrium between proinflammatory and anti-inflammatory mediators. This balance orchestrates critical immune functions like cellular adherence, chemotaxis, phagocytosis of invading microorganisms, bacterial killing, and clearance of debris from injured tissue. Successful resolution of the insult leads to the restoration of homeostasis, where the immune system returns to a balanced state (33).

1.3 Transition to sepsis

Description of the progression from a localized infection to the systemic reaction of sepsis:

1. **Sepsis as a widespread reaction:** When the inflammatory mediators extend beyond the boundaries of the infected tissue due to an infection, it leads to sepsis, characterized as a widespread reaction. This response is uncontrolled, self-sustaining, and disseminated via the bloodstream.
2. **Characteristics of sepsis:** Sepsis can be termed "malignant" because it lacks regulation, perpetuates itself, and becomes widespread. It is "intravascular" as the inflammatory mediators travel through the blood and it is fundamentally an amplified version of the normal inflammatory response (34).
3. **Factors leading to sepsis:** The reasons why localized immune responses occasionally progress to sepsis are not fully understood. This progression could be due to direct effects of invading microorganisms or their toxic products, a

massive release of proinflammatory mediators, and the activation of the complement system. Individual genetic susceptibility and immune status also likely contribute as risk factors.

4. **Microorganisms and sepsis progression:** Microorganisms and their byproducts, like endotoxins, play a role in advancing a local infection to the systemic syndrome of sepsis. Notably, the serum of septic patients often contains endotoxin, highlighting its potential involvement in the sepsis cascade (35).

   Viral infections in human cells often result in cellular degeneration and necrosis, eliciting both local and systemic inflammatory responses. These infections trigger humoral and cell-mediated reactions, along with phagocytosis and apoptosis (36). Viral infections' pathophysiology often involves the degeneration and necrosis of infected cells, causing localized and systemic inflammatory responses. The body's defense mechanisms encompass phagocytosis, humoral and cell-mediated responses, as well as the generation of interferons that facilitate apoptosis (36).

   Elevated levels of endotoxins in the bloodstream are observed in established shock conditions.

Introducing endotoxins into humans can replicate several characteristics of sepsis, including the activation of complement, coagulation, and fibrinolytic systems (37,38). These effects may lead to microvascular thrombosis and the liberation of vasoactive compounds such as bradykinin.

Initially, during sepsis, serum levels of TNFα and IL-1 are notably high, but become immeasurable as the condition progresses. These cytokines are capable of instigating symptoms like elevated body temperature, decreased blood pressure, and leukocytosis. Additionally, they activate proinflammatory cytokines and influence coagulation and fibrinolysis processes.

TNFα holds significance in sepsis based on research findings. In septic patients, TNFα levels are elevated, distinguishing them from other types of shock (39). Injecting TNFα into rats induces symptoms typical of septic shock (40). However, these results have not been fully replicated in humans (41), although the clinical presentation remains strikingly similar.

Endotoxin binds to lipopolysaccharide (LPS)-binding proteins, forming complexes that bind to macrophage CD14 receptors. This interaction prompts heightened TNFα production, contributing to increased TNFα levels in sepsis (42).
The complement system, a protein cascade, serves a crucial role in eliminating pathogens from the body (43,44).

1.4. Systemic effects of sepsis

When the immune response extends beyond the initial site of infection, cells in distant locations may suffer injury. The progression towards organ dysfunction often begins with cellular damage, though the precise mechanisms are still under investigation. This type of injury is commonly observed in both the endothelium and the parenchyma. Tissue ischemia, cellular injury, and changes in apoptosis rates are considered potential underlying mechanisms.
Sepsis frequently involves tissue ischemia, a condition arising from alterations in metabolic autoregulation. This regulatory process typically balances the tissue's oxygen requirements with its oxygen availability. In some cases, damage to the microcirculation and endothelium can reduce the available area for tissue oxygen exchange.
Disturbances in the coagulation and fibrinolysis processes may also contribute to abnormalities in the microcirculation.
Endothelial lesions may develop as a result of interactions between endothelial cells and activated PMNs. This interaction induces the secretion of reactive oxygen species, lytic enzymes, and vasoactive substances into the extracellular space, potentially injuring endothelial cells (45). Moreover, the inability of activated PMNs to deform within the systemic microcirculation can lead to significant disparities in microcirculatory blood flow (46-48).
Tissue ischemia in sepsis is further exacerbated by mitochondrial dysfunction, such as impaired mitochondrial electron transport. This dysfunction can result from proinflammatory mediators and other inflammation-related products, impacting mitochondrial electron transport complexes, causing oxidative stress damage, and leading to mitochondrial DNA breakdown (49).

Studies have indicated that molecules like endotoxin, TNFα, and NO have the capacity to damage mitochondrial inner membrane and matrix proteins, thereby deteriorating mitochondrial ultrastructure. Subsequent alterations in other cell organelles occur later in this process. Consequently, abnormal electron transport in mitochondria, dysfunctional energy metabolism, and cytotoxicity may result (50).

Studies have indicated that septic animals exhibit adequate or even elevated oxygen levels in their organs, suggesting impaired mitochondrial oxygen consumption. Increased oxygen levels were observed in the ileomucosa and bladder epithelium of endotoxemic pigs and rats, according to research (51,52).

Mitochondrial repair or regeneration, known as biogenesis, might represent a potential target for future therapies aimed at hastening organ dysfunction recovery and sepsis cure.

Various cell death pathways can be activated during sepsis including necrosis, apoptosis, necroptosis, pyroptosis and autophagy-induced cell death.

Apoptosis, often termed programmed cell death, involves a sequence of physiological and morphological changes within the cell leading to its decay. Proinflammatory cytokines slowing down apoptosis in activated macrophages and neutrophils can prolong or intensify the inflammatory response, contributing to the development of multiple organ failure. In sepsis, there is substantial lymphocyte and dendritic cell apoptosis, reducing the rate at which invading microorganisms are eliminated. Animal studies have demonstrated that inhibiting apoptosis can protect organs from dysfunction and prevent mortality (53,54).

1.5. Organ specific effects of sepsis

The circulatory, respiratory, hepatic, renal, and nervous systems are commonly affected in sepsis, with multiple organs often being involved simultaneously. The severity of the condition is typically correlated with the number of affected organ systems, directly influencing the overall outcome.

1.5.1. Cardiovascular system

A prominent indication of sepsis manifests as decreased blood pressure, attributed to vasoactive molecules like prostacyclin and NO released from endothelial cells, which prompt vasodilation.

NO plays a crucial role in dilating blood vessels across various circulatory levels by suppressing metabolic autoregulation. Endotoxin interaction with vascular endothelium can stimulate the production of NO through smooth muscle inducible NO synthase (iNOS) (55,56). Additionally, NO has been associated with central nervous system injury in areas governing autonomic control (57).

In managing septic patients, guidelines recommend increasing systemic and microcirculatory flow, aiming for a targeted MAP of at least 65 mmHg. Notably, individuals with septic shock display decreased serum levels of the antidiuretic hormone vasopressin compared to those with cardiogenic shock, despite having comparable blood pressure values (3.1 versus 22.7 pg/ml) (58). Conversely, several studies have indicated the beneficial effects of vasopressin in enhancing blood pressure values (59-62).

The use of norepinephrine as a primary treatment is clear, but there remains a debate regarding the adjunctive use of vasopressin or other vasopressors alongside norepinephrine (63).

In sepsis, changes in endothelial permeability and arterial vascular tone lead to increased capillary pressure, facilitating the redistribution of intravascular fluid. Beyond these broad effects on circulation, localized impacts are observed:

- Early hypotension arises due to compromised systolic and diastolic ventricular function.
- Microcirculation assumes an increasingly significant role in sepsis. Decreased functional capillaries result in incomplete oxygen extraction (64,65). This reduction may stem from tissue edema compression, endothelial swelling, and occlusion of capillaries by white blood cells or red blood cells.
- Endothelial dysfunction contributes to abnormal coagulation, stiffening of red blood cell membranes, platelet and leukocyte adhesion, and alterations in the glycocalyx (66). These effects may lead to generalized tissue edema.

- The myocardial depressant factor holds substantial importance in shock pathophysiology. It is a small circulating peptide found in all mammals and is produced by proteolytic enzymes from the ischemic pancreas. This factor diminishes myocardial contractility, constricts splanchnic arteries, and impairs the reticuloendothelial system's phagocytic function (67).

1.5.2. Respiratory system

Endothelial injury (68,69) leads to interstitial and alveolar pulmonary edema. Neutrophil leukocytes within lung capillaries exacerbate damage to the alveolocapillary membrane, furthering pulmonary edema. The mismatch between ventilation and perfusion causes hypoxemia, frequently observed in septic patients and resulting in acute respiratory distress syndrome (ARDS), a common condition in intensive care units. The systemic impact of sepsis on myocardial function could also contribute to respiratory insufficiency.

1.5.3. Gastrointestinal tract

The aforementioned significant vascular alterations contribute to compromised gut barrier function, facilitating the entry of microorganisms into the circulation (68-71). Animal studies corroborate this phenomenon (72).

The intestinal microbiome plays a crucial role in sepsis development. Patients with sepsis experience increased morbidity and mortality when alterations occur in the intestinal microbiome (73), primarily due to circulatory factors or extensive antibiotic usage.

The gut's microbial environment is established in early childhood and remains relatively stable in adulthood, unless disrupted by antibiotic therapy. This disruption may compromise the body's ability to resist colonization by exogenous organisms, known as colonization resistance. Antibiotic treatment can adversely affect this balance, potentially leading to infections caused by enteric pathogens and resistant bacteria, including resistant gram-negative bacilli and vancomycin-resistant enterococci (74).

1.5.4. Liver

In a normally functioning state, the reticuloendothelial system of the liver effectively eliminates microorganisms and their byproducts that might exit the gut and enter the portal system. However, if the liver's preventive function is compromised, primarily due to tissue hypoperfusion, these various products can bypass this barrier and enter the bloodstream.

1.5.5. Renal system

Certainly, acute renal failure is a common occurrence in septic patients, but its precise etiology remains incompletely understood. A prevalent theory suggests that acute tubular necrosis, a condition where renal tubules suffer damage, might occur due to decreased blood pressure and/or reduced oxygen levels (68,69). However, in addition to these factors, several other contributors likely play a role in renal dysfunction during sepsis. These include reduced blood pressure, constriction of renal blood vessels, the impact of cytokines such as TNFα, and the activation of neutrophils.

1.5.6. Central and peripheral nervous system

Altered mental status presents challenges in differential diagnosis. Changes in the central nervous system among septic patients are not uncommon and often precede the dysfunction of other organs. Although the precise mechanism remains unclear, inflammatory mediators are suspected culprits, potentially influencing metabolic processes and cellular signaling. The blood-brain barrier may also contribute, potentially impeding leukocyte infiltration, rendering the brain susceptible to harmful mediators, and facilitating the transport of cytokines across the barrier (75). Disruptions in both mitochondria and the microvasculature are implicated in central nervous system (CNS) alterations (76).

Emerging evidence suggests the involvement of the parasympathetic nervous system in the systemic inflammation associated with sepsis. Various animal studies support this notion. Stimulation of the afferent vagus nerve leads to increased secretion of

corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol during sepsis (75,77). Experimental vagotomy has shown reduced hyperthermia in response to IL-1 (77,78). Additionally, the anti-inflammatory impact of efferent parasympathetic activity affects cytokine profiles, diminishing the expression of proinflammatory cytokines such as TNF, IL-1, IL-6, and IL-18 in vitro (79). Studies involving vagotomized animals suggest delayed onset of shock, while external vagus nerve stimulation lessens the response to sepsis (79), and an acetylcholine receptor agonist reduces its severity (80).

1.5.7. Haematopoesis

Hematopoietic abnormalities significantly impact the functionality of both white blood cells and red blood cells. Neutropenia, primarily arising from bone marrow depletion, is attributed partly to apoptosis and sustained by a halt in the differentiation of hematopoietic stem cells. In terms of red blood cells, escalated erythropoiesis can be a natural reaction to acute inflammation. However, certain infections may deplete erythroid precursors, consequently leading to anemia (81,82).

1.5.8. Glycocalyx

Sepsis has an early impact on the endothelial glycocalyx, which comprises cell-bound proteoglycans, glycosaminoglycan side chains, and sialoproteins covering the luminal side of endothelial cells, typically measuring 1 to 3 micrometers in thickness. Sepsis-induced changes in endothelial permeability contribute to the generation of endogenous DAMPs. These molecules play a pivotal role in initiating severe consequences within the cardiovascular system through proinflammatory cascades seen in septic shock. Specific clinical manifestations of sepsis, such as acute kidney injury, respiratory failure, and septic cardiomyopathy, can be attributed to these processes. Additionally, the extent of glycocalyx degradation serves as an indicator of both endothelial dysfunction and the severity of sepsis (83).

1.5.9. Coagulation

The interplay between inflammatory mediators and endothelial cells can disrupt the usual thromboresistant characteristics (84). In vitro experiments using endothelial cells exposed to bacterial lipopolysaccharide and/or cytokines illustrate procoagulant responses (66,85). These reactions include reduced synthesis of thrombomodulin (TM), tissue-type plasminogen activator, and heparin sulfat, as well as heightened expression of tissue factor (TF) and plasminogen activator inhibitor-1 (PAI-1). Additionally, the production of procoagulant microparticles is observed (86).

In patients with severe sepsis, the coagulation cascade is typically activated. The presence of tissue factor on activated monocytes and macrophages triggers clotting, leading to heightened thrombin generation and fibrin formation. This process can result in severe consequences, including depletion of coagulation factors, disseminated intravascular coagulation, and damage to vital organs (84).

Over 20 randomized sepsis trials involving more than 10,000 patients have explored various therapies for severe sepsis, such as anti-endotoxin, anti-cytokine, anti-prostaglandin, anti-bradykinin, anti-platelet activating factor strategies, antithrombin, activated protein C, and tissue factor pathway inhibitor. Unfortunately, none of these treatments have succeeded in reducing mortality, and thus, specific treatments targeting sepsis are not currently available (87).

2. Objectives

Recently there has been some dispute about the usefulness of the otherwise generally recommended classic parameters and approach endorsed by the Surviving Sepsis Guidelines. The reason for this dispute is the controversies regarding, for example, the time to initiation of empiric antibiotic therapy, distinguishing sepsis from noninfectious syndromes, as issued by the Infectious Diseases Society of America (IDSA) (88), along with administration of 30 ml/kg crystalloids within a short time frame irregardless of the patient's fluid status. This and other uprising issues in the early recognition of sepsis focusing on previously unmeasured cofounders (89) make the situation more complicated despite the fact that simple and straight guidelines would be desirable to be able to initiate timely sepsis management.

Little is known about whether basic physiologic and metabolic parameters in addition to those that form part of prior sepsis diagnostic criteria could be used to differentiate between sepsis and other conditions with similar initial presentations, such as dehydration and stroke. Therefore, the aim of our research was to assess the relationship profile of basic physiologic and metabolic parameters to sepsis risk, and to simulate clinical decision-making by comparing a data-driven model to a model that is built based on currently existing sepsis guidelines understanding that no classical approach apart from a blend of recommendations and scores are available in the emergency department triage, unlike in an intensive care unit, where laboratory results, invasive monitoring and clinical experience assist in sepsis care.

3. Results

3.1. Sample description

Charts of 228 sepsis patients, 274 dehydration patients, and 228 stroke patients were extracted. Altogether 40 observations were deleted because they were repeat visits, and altogether 26 observations (13 patients) were removed from the data because those patients had presented with more than one of the three diagnoses of interest. No influential outliers were identified. Therefore, the final analysis data set included a total of 664 patients with one observation each: 205 (30.9%) were septic, 244 (36.7%) were dehydrated, and 215 (32.4%) were stroke patients; about half (54.1%) were female and the mean age was 70.2 years (SD=15.7). Table 1 shows the mean (SD) values and the ranges for the vital parameters and the PoC results.

Table 1 Description of sample characteristics		
Characteristic	***N* (%) or mean (SD)**	**Range**
Demographic characteristics		
Gender		
Female	359 (54.1)	N/A
Male	305 (45.9)	N/A
Age–years	70.2 (15.7)	19–99
Vital parameters		
Body temperature – °C	36.9 (0.9)	32.3–40.2
Respiratory rate – per minute	18.7 (6.1)	10–50
Heart rate – per minute	91.0 (23.2)	23–194
Systolic blood pressure – mmHg	135.3 (36.2)	40–250
Diastolic blood pressure – mmHg	75.7 (19.9)	14–142
Mean arterial pressure – mmHg	95.6 (23.8)	26.3–176.7
Point of care test results		
Lactate level – mM/L	2.6 (2.2)	0.1–19.3
pH	7.40 (0.09)	6.82–7.66
Bicarbonate level – mM/L	22.9 (5.3)	3.7–59.6
Diagnosis		
Sepsis	205 (30.9)	N/A

Table 1 Description of sample characteristics		
Characteristic	***N* (%) or mean (SD)**	**Range**
Stroke	215 (32.4)	N/A
Dehydration	244 (36.7)	N/A

Note: N/A – not applicable.

3.2. Inflexion points

No inflexion points were observed for SBP, DBP, MAP, and RR, so these variables were kept as continuous (Fig. 1a-1j).

Age showed a reverse U-shaped curve: higher-risk cutoffs were identified for age between 56 years and 83 years.

Body temperature showed a W-shaped curve: higher-risk cutoffs were identified for temperatures under 35.6°C and above 37.3°C.

Bicarbonate and HR showed U-shaped curves: higher-risk cutoffs were identified at under 22.3 mM/L for bicarbonate, and under 53 bpm and above 91 bpm for HR.

Lactate and pH showed V-shaped curves: higher-risk cutoffs were identified at 1 mM/L or under and above 2.5 mM/L for lactate, and under 7.34 and above 7.45 for pH.

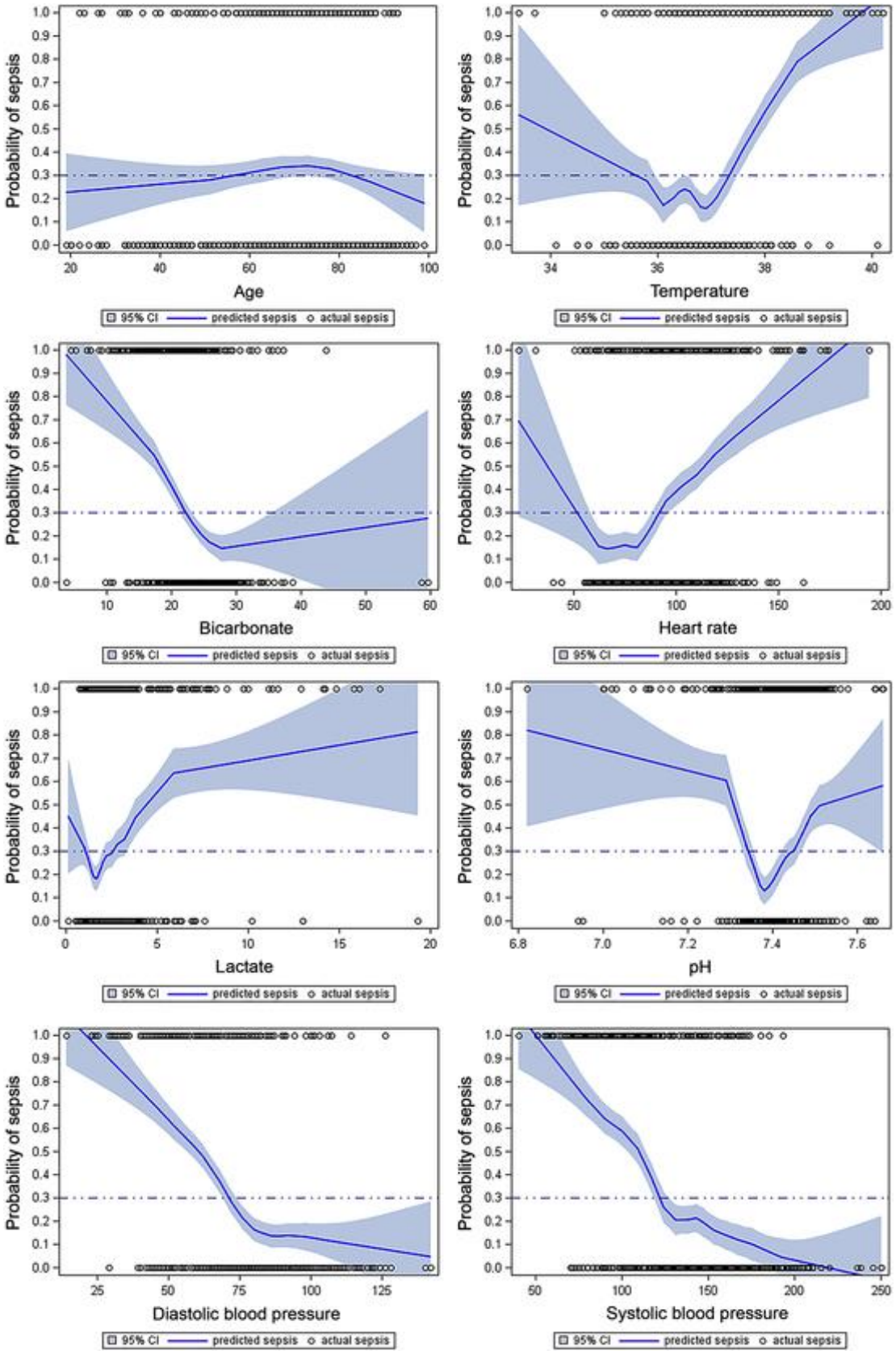

Figure. 1 Loess regression plots depicting the relationship between the predicted probability of sepsis and a. age, b. body temperature, c. bicarbonate level, d. heart rate, e.

lactate, f. pH, g. diastolic blood pressure, h. systolic blood pressure, i. mean arterial pressure, and j. respiratory rate. *Note:* The high-risk vs. low-risk cutoff level based on actual population prevalence is marked with a dotted line at $P = 0.3$

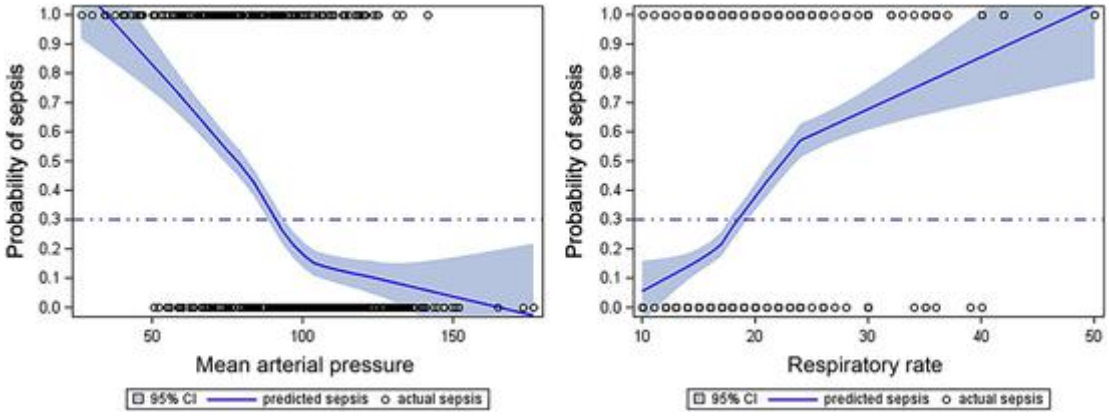

Figure. 1 Continued

3.3. Univariate and multivariable analyses

In the univariate analysis of the data-driven model, RR and old age, bicarbonate, HR, lactate, pH, and temperature were positively associated; and MAP was inversely associated with sepsis risk (Table 2).

Table 2. Univariate and multivariable associations with sepsis – data-driven model

Characteristic	**Sepsis**		**Univariate**	**Preliminary multivariable**	**Final multivariable**
	No	**Yes**			
	***N* (%) or mean (SD)**	***N* (%) or mean (SD)**	**OR (95%CI)**	**aOR (95%CI)**	**aOR (95%CI)**
Total	459 (100%)	205 (100%)	–	–	–
Demographic characteristics					
Gender					
Female	260 (72.4)	99 (27.6)	ref	ref	
Male	199 (65.2)	106 (34.8)	**0.7 [0.5-1.0]**	0.8 [0.5–1.2]	–
Age					
Under 56 or above 83 years	182 (74.3)	63 (25.7)	ref	ref	ref
Between 56 and 83 years	277 (66.1)	142 (33.9)	**1.5 [1.1-2.1]**	**1.7 [1.04-2.7]**	**1.7 [1.1-2.8]**
Vital parameters					

Table 2. Univariate and multivariable associations with sepsis – data-driven model

Characteristic	Sepsis		Univariate	Preliminary multivariable	Final multivariable
	No	**Yes**			
	***N* (%) or mean (SD)**	***N* (%) or mean (SD)**	**OR (95%CI)**	**aOR (95%CI)**	**aOR (95%CI)**
Body temperature					
Between 35.6 °C and 37.3 °C	380 (79.7)	97 (20.3)	ref	ref	ref
Under 35.6 °C or above 37.3 °C	79 (42.2)	108 (57.8)	**5.4 [3.7-7.7]**	**3.3 [2.0-5.3]**	**3.4 [2.1-5.4]**
Respiratory rate, per minute	16.9 (4.3)	22.8 (7.5)	**1.2 [1.2-1.3]**	**1.1 [1.1-1.2]**	**1.1 [1.1-1.2]**
Heart rate					
Between 53 and 91 per minute	324 (82.4)	69 (17.6)	ref	ref	ref
Under 53 or above 91 per minute	135 (49.8)	136 (50.2)	**4.7 [3.3-6.7]**	**2.6 [1.6-4.2]**	**2.7 [1.7-4.3]**
Mean arterial pressure, mmHg	103.2 (20.4)	78.4 (21.8)	**0.95 [0.94-0.95]**	**0.95 [0.94-0.96]**	**0.95 [0.94-0.96]**
Point of care test results					

Table 2. Univariate and multivariable associations with sepsis – data-driven model

Characteristic	Sepsis		Univariate	Preliminary multivariable	Final multivariable
	No	Yes			
	N (%) or mean (SD)	*N* (%) or mean (SD)	OR (95%CI)	aOR (95%CI)	aOR (95%CI)
Lactate level					
Between 1.0 and 2.5 mM/L	329 (76.5)	101 (23.5)	ref	ref	ref
Under 1.0 or above 2.5 mM/L	130 (55.6)	104 (44.4)	**2.6 [1.8-3.6]**	1.5 [0.9–2.4]	–
pH					
Between 7.34 and 7.45	335 (78.8)	90 (21.2)	ref	ref	ref
Under 7.34 or above 7.45	124 (51.9)	115 (48.1)	**3.1 [2.2-4.4]**	**1.7 [1.1-2.7]**	**1.6 [1.04-2.6]**
Bicarbonate level					
22.3 mM/L and above	315 (80.2)	78 (19.8)	ref	ref	ref
Under 22.3 mM/L	144 (53.1)	127 (46.9)	**3.6 [2.5-5.0]**	**2.0 [1.3-3.2]**	**2.1 [1.3-3.3]**

Note: **Statistically significant values are bolded**.

In the final multivariable analysis, RR and higher-risk age, bicarbonate, HR, pH, and temperature were positively associated; and MAP was inversely associated with sepsis risk – gender and lactate did not stay in the final model as significant correlates. Table 3 shows the results of the guidelines-based model.

Table 3 Multivariable associations with sepsis – guidelines-based model

Characteristics	**Sepsis**		**Multivariable analysis**
	No	**Yes**	**aOR (95%CI)**
	***N* (%)**	***N* (%)**	
Body temperature			
Between 36 °C and 38 °C	410 (76.2)	128 (23.8)	ref
Under 36 °C or above 38 °C	49 (38.9)	77 (61.1)	**3.5 [2.2–5.7]**
Heart rate			
90 per minute or under	318 (82.2)	69 (17.8)	ref
Above 90 per minute	141 (50.9)	136 (49.1)	**3.2 [2.1–4.9]**
Respiratory rate			
22 per minute or under	414 (78.3)	115 (21.7)	ref
Above 22 per minute	45 (33.3)	90 (66.7)	**3.8 [2.3–6.1]**

Table 3 Multivariable associations with sepsis – guidelines-based model			
Characteristics	**Sepsis**		**Multivariable analysis**
	No	**Yes**	**aOR (95%CI)**
	***N* (%)**	***N* (%)**	
Lactate level			
2 mM/L or under	293 (77.9)	83 (22.1)	ref
Above 2 mM/L	166 (57.6)	122 (42.4)	**1.7 [1.1–2.5]**
Blood pressure measures			
SBP 100 mmHg or above and MAP 70 mmHg or above	430 (76.1)	135 (23.9)	ref
SPB under 100 mmHg or MAP under 70 mmHg	29 (29.3)	70 (70.7)	**6.1 [3.8–9.7]**

Note: **Statistically significant values are bolded**.

In summary, compared to the guidelines-based model, the data-driven final model contained additional variables (age, pH, bicarbonate) and did not include lactate. The area under the ROC curve was 0.9021 for the data-driven model, and 0.8536 for the guidelines-based model (Fig. 2).

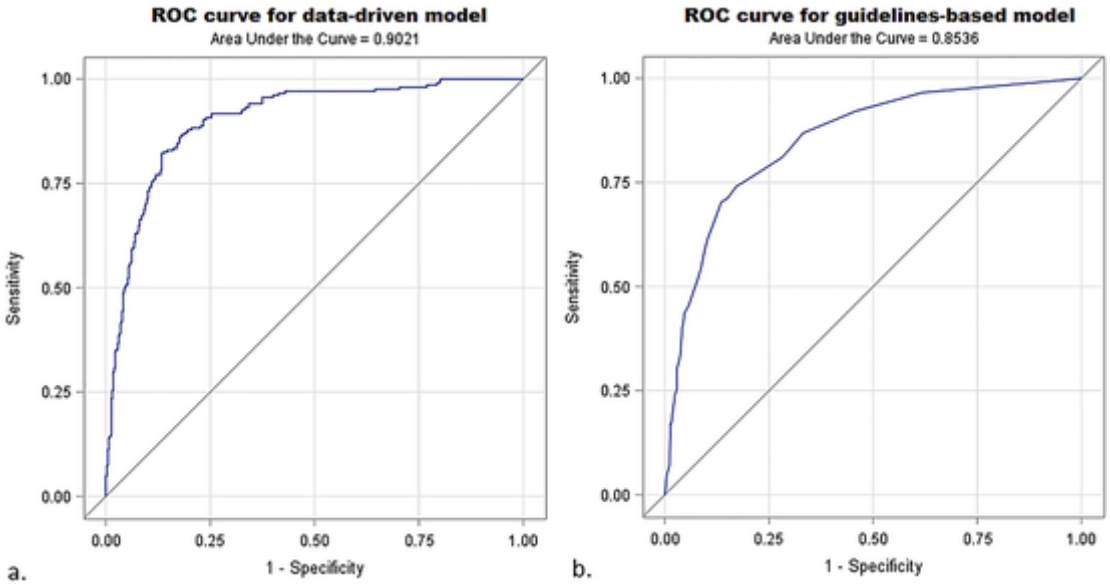

Figure. 2 A Receiver Operating Characteristics (ROCs) curve showing the true positive rate against the false positive rate for the different possible cutoff points of a. the data-driven final multivariable regression model (Area Under the Curve = 0.9021) and b. the guidelines-based multivariable model (Area Under the Curve = 0.8536)

Fig. 3 shows the relationship between predicted probability and cumulative actual probability for both models. As seen in the section of the curves above the reference line at y=30, when a cut-off for the predicted probability is set at the actual probability (30% - which is the reference line at y=30), then the data-driven model correctly identifies about 85% of the cases (true positives: the blue curve above the dotted line) and incorrectly identifies 15% of non-cases (false positives: the red curve above the dotted line). In contrast, the guidelines-based model had a true positive rate of about 70% and a false positive rate of about 15%.

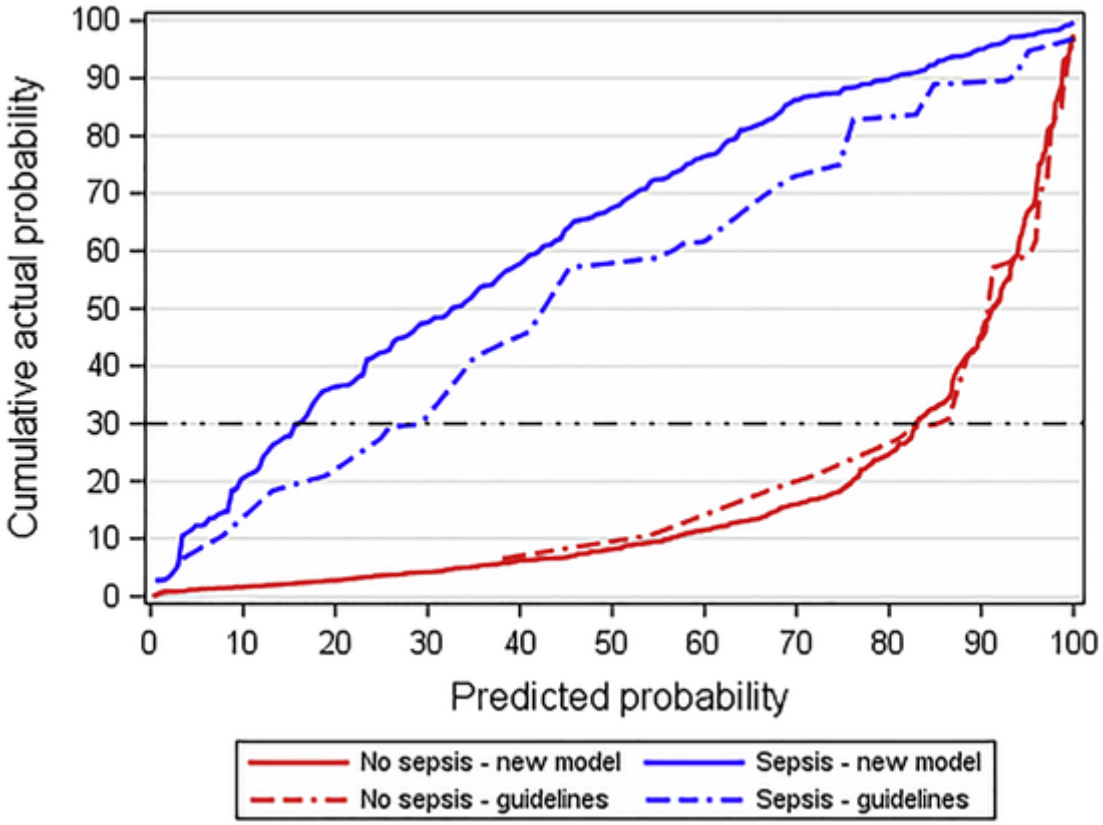

Figure. 3 A curve showing the cumulative predicted probability against the predicted probability for both the data-driven model and the guidelines-based model. *Note:* The dotted black line shows the actual probability of $P = 0.3$. The solid blue and red lines depict the data-driven new model, and the dotted blue and red lines depict the guidelines-based model, showing about 85% true positives for the data-driven model and about 70% true positives for the guidelines-based model, and showing about the same true negatives for both.

4. Discussion

Our research provides further evidence that improved tools to identify sepsis at early time points, such as in the emergency room are much needed. We found that while some variables have non-linear associations with sepsis risk and therefore require binarization, the binary cut-off values are slightly different from the cutoff values that are used in current sepsis guidelines. Additionally, while guidelines have set cut-of-shaped values for other variables, we found sepsis risk for those variables linear and therefore binarization inappropriate. Moreover, in contrast to the guidelines-based model, the data-driven final model contained additional variables such as age, pH and bicarbonate (that are – to our knowledge – not in any of the guidelines for sepsis diagnosis), and did not include lactate (an important predictor in current guidelines). Ultimately, the data-driven model proved to be superior to the guidelines-based model in identifying sepsis cases.

SIRS postulates sepsis risk under 36°C or above 38°C *body temperature* (3,4). While we found a W-shaped curve that indicates both lower and higher body temperatures (under 35.6°C and above 37.3°C) as risk factors for sepsis, our findings indicate that the risk limits of infection induced temperature change might be shifted towards higher temperatures. As such, we found that between 35.6°C and 36°C the risk is the same as between 36°C and 37.3°C, and therefore SIRS might over-diagnose the risk of sepsis at lower temperatures (between 35.6°C and 36°C) and under-diagnose at higher temperatures (between 37.3°C and 38°C). This might suggest that while accurate measurements of body temperature will play an important role in the diagnosis of sepsis, hypothermia and normal body temperature range still remain to be defined more clearly (90,91). Our results also indicate that no fever is needed to have elevated sepsis risk, but a febrile condition might already be a risk indication.

SIRS also predicates sepsis risk at a *heart rate* above 90 bpm (3,4). While our results support this as an upper value, we also identified a lower limit (a HR under 53 bpm) under which there was increased sepsis risk. Currently, a lower HR value is not in any sepsis guideline recommendation, although it is understood that bradycardia in sepsis might be associated with sepsis induced myocardial dysfunction that might impair survival (92). We would therefore recommend taking into consideration HR values below about 50 bpm

as higher-risk – in addition to the currently used value of above 90 bpm – when considering the diagnosis of sepsis.

Respiratory rate above 22 breaths per minute is another sepsis risk criterion (3,4). Given that we found no inflexion point for this variable, risk related to RR appears to be a sliding scale as opposed to a real cutoff: the higher the RR the higher the risk of patients having sepsis.

One of the criteria of severe sepsis is a serum *lactate level* above 2 mM/L (7). While our results suggest that a 2 mM/L cutoff point might be somewhat low (compared to our cutoff point of 2.5 mM/L), we also identified a cutoff of 1 mM/L or under. Interestingly enough though, lactate did not stay in the multivariable model as a correlate. There has been an ongoing debate on alternative signs or predictors such as the use of lactate as an accurate biomarker of septic shock. Garcia-Alvarez et al dispute that lactate is a precedent of sepsis and propose that it is a result of it (93), and Marik argues that lactate is not an accurate indicator of tissue hypoxia, because experimental models have failed to demonstrate cellular hypoxia in sepsis (94). Our finding that in an ER setting sepsis was not associated with lactate levels but with pH instead, appears to confirm this proposition. Indeed, other researchers failed to demonstrate direct connections among oxygen carrying capacity, mixed venous oxygen saturation and levels of lactate, along with lacking evidence of direct tissue hypoxia in sepsis. It is therefore not surprising that we did not find lactate levels to be associated with sepsis. Therefore, we provide further evidence that net lactate levels might be interpreted cautiously in septic patients, or that at least lactate *per se* may not be a pure indicator of severity of circulatory derangement (95). Considering that we found two cutoff points of lactate risk, further clarification is needed how lactate levels lower than 1 mM/l (or even lactate in general) are associated with sepsis.

With regard to *blood pressure*, the defined cut off values used by qSOFA for SBP ≤100 mmHg and by SOFA for MAP <70 mmHg might be easy and user-friendly values (7,96). We, however, found no inflexion point but rather a sliding scale. In addition, our findings suggest that the previously defined MAP of 65 mmHg might be too permissive in terms of perfusion pressure (97). We understand that no direct correlation can be established between MAP/SBP and tissue perfusion (97), however, our results suggest that higher target pressures might be set in terms of fluid and vasoactive therapy.

Normal *pH values* are described as those between 7.35-7.45, and indeed we found a sepsis risk outside this exact interval. Although pH is an easily measurable parameter that has not been explicitly pinpointed yet as a factor in diagnosing sepsis, it seems that our findings might give basis to pH measurement along with or instead of other metabolic parameters, such as lactate. Even though the extent of pH change is influenced by a variety of parameters, lactate per se is not likely to affect pH unless clear lactate acidosis is diagnosed (98). This, however, is not a characteristic pathophysiological pathway in sepsis (99).

To our knowledge, *bicarbonate* has not been used in the diagnosis of sepsis. The normal levels for serum bicarbonate are postulated to be between 22 and 29 mM/L (100), and we indeed found an increased sepsis risk under 22.3 mM/L. We found no indication for an upper risk cutoff value.

A defined risk cutoff level for bicarbonate might help to differentiate sepsis from other disease states that mimic it, such as dehydration and stroke. Caution should be exercised though when using bicarbonate as a definitive parameter because of the commonly ill-defined origin of acidosis.

Additionally, *age* has not been identified as a sepsis risk in any scoring system. In their study of 47,475 patients, Inada-Kim et al. found a gradual increase in the number of admissions with increasing age until age 85, when the number of admissions started to decline (16). Our findings that the risk of sepsis was highest between the ages of 56 years and 83 years correspond with the results of the above study, suggesting this age range as a probability variable in assessing the risk of sepsis.

Some limitations of this study are noteworthy. First, this analysis is based on a retrospective chart review of mostly elderly adult patients, so therefore our results might not be directly applicable to other age groups. However, most septic patients are elderly, and since age - albeit as a binary variable - was included in the final multivariable model, this might somewhat control for this limitation. Moreover, not all patients admitted to the emergency room (ER) were assessed for the parameters examined in this study, but only those where the physician in charge considered such evaluation necessary. Our goal was not to assess sepsis risk among all ER admissions, but to differentiate the diagnosis among those patients that present with conditions that mimic sepsis, such as stroke and dehydration. Additionally, the study is based on a single center retrospective dataset, and

therefore our findings might not be representative of all patient populations, either in Hungary or in other countries. This study focused only on early recognition and not on survival, and therefore survival data are unavailable.

5. Conclusions

We can conclude that in addition to some SIRS and qSOFA parameters that are easy to measure at triage level, other readily measurable variables, such as pH, bicarbonate levels and age might be useful in the diagnosis of sepsis in the ER and have a higher accuracy and better differentiating power than the tools provided by current sepsis guidelines. Since the currently used sepsis criteria are rather unspecific, our results suggest that the model and its variables that we constructed in this analysis and that proved to have excellent predictability might be such a tool that would aid in a more specific identification of sepsis in the first line of care. Therefore, future studies should duplicate our analysis with these variables in order to confirm our findings. Ideally, a new tool might be developed that would help rapid and early identification of sepsis on a triage level, enabling the physician to perform the necessary actions that target lower mortality. Our findings contribute to the growing body of evidence in the quest of finding improved tools to identify sepsis at early time points, such as in the emergency room (15-18).

6. Summary

Summary in English

Introduction: Conditions that have similar initial presentations as sepsis may make early recognition of sepsis in an emergency room (ER) difficult.

Objectives: We investigated whether selected physiologic and metabolic parameters can be reliably used in the emergency department to differentiate sepsis from other disease states that mimic it, such as dehydration and stroke.

Results: Age, bicarbonate, HR, lactate, pH, and body temperature had U, V, W or reverse U-shaped associations with identifiable inflexion points, but the cutoff values we identified were slightly different from guideline cutoff values. In contrast to the guidelines, no inflexion points could be observed for the association of sepsis with SBP, DPB, MAP, and RR and therefore were treated as continuous variables. Compared to the guidelines-based model, the triage data-driven final model contained additional variables (age, pH, bicarbonate) and did not include lactate. The data-driven model identified about 85% of sepsis cases correctly, while the guidelines-based model identified only about 70% of sepsis cases correctly.

Conclusion: Our findings contribute to the growing body of evidence to find improved tools to identify sepsis at early time points, such as in the ER.

Summary in Hungarian

Bevezetés: A szepszis kezdeti tüneteihez hasonló megjelenéssel bíró kórképek a szepszis korai felismerését megnehezítik a sürgősségi betegellátó osztályon.

Cél: Kiválasztott fiziológiai és metabolikus paramétereket vizsgáltunk, hogy azok megbízhatóan használhatóak-e a sürgősségi betegellátó osztályon a szepszis differenciáldiagnosztikájában az ahhoz hasonló kórállapotoktól való elkülönítésben, mint a kiszáradás és a sztroke.

Eredmények: Az életkor, a bikarbonát, a szívfrekvencia, a laktát, a pH és a testhőmérséklet U, V, W vagy fordított U alakú görbéket adtak beazonosítható inflexiós pontokkal, de az általunk meghatározott értékek kis mértékben különbözőek voltak az iránymutatásokban használt értékektől. Az iránymutatásokkal ellentétben nem volt inflexiós pont megfigyelhető a szepszissel összefüggésben a szisztolés vérnyomás, a diasztolés vérnyomás, az artériás középnyomás és a légzésszám esetén ezért ezeket folyamatos változókként kezeltük.

Az iránymutatásokon alapuló modellel összehasonlítva az adatainkon alapuló modell magában foglalt még változókat (életkor, pH, bikarbonát) és nem tartalmazta a laktátot. Az adatainkon alapuló model 85%-ban pontosan határozta meg a szepszises eseteket, míg az iránymutatásokon alapuló model 70%-ban határozta meg korrektül a szepszises eseteket.

Következtetések: Eredményeink hozzájárulnak - az egyre növekvő bizonyítékok halmazához - a még jobb eszközök megtalálásához a szepszis diagnózisának minél korábbi felállításában, mint például a sürgősségi betegellátó osztályon.

7. References

1. University of Minnesota, Center for Infectious Disease Research and Policy. 2020 [accessed June 04, 2021]. Available from: https://www.cidrap.umn.edu/news-perspective/2020/09/who-says-sepsis-causes-20-global-deaths.

2. Kanizsai P, Molnár Gy, Sztudva R, Berényi T, Hornyák I. (2018) Does level of training predetermine the success rate of prehospital sepsis assessment? A prospective survey on early recognition. Developments in Health Sciences, 1, 2: 33-38.

3. Balk RA. (2014) Systemic inflammatory response syndrome (SIRS): where did it come from and is it still relevant today? Virulence 5, 1: 20-6.

4. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM,Sibbald WJ. (1992) 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. 101, 6: 1644-55.

5. Quinten VM, van Meurs M, Wolffensperger AE, Ter Maaten JC, Ligtenberg JJM. (2018) Sepsis patients in the emergency department: stratification using the Clinical Impression Score, Predisposition, Infection, Response and Organ dysfunction score or quick Sequential Organ Failure Assessment score? Eur J Emerg Med, 25, 5: 328-334.

6. Molnár G, Gyarmathy VA, Takács J, Sándor S, Kiss B, Fazakas J, Kanizsai PL. (2021) Differentiating sepsis from similar groups of sysmptoms at triage level in emergency care Physiol Int, 108, 1: 106-120.

7. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC. (2016) The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA, 315, 8: 801-10.

8. Zhang W, Zheng Y, Feng X, Chen M, Kang Y. (2019) Systemic inflammatory response syndrome in Sepsis-3: a retrospective study. BMC Infect Dis, 19, 1: 139.

9. Sartelli M, Kluger Y, Ansaloni L, Hardcastle TC, Rello J, Watkins RR, Bassetti M, Giamarellou E, Coccolini F, Abu-Zidan FM, Adesunkanmi AK, Augustin G, Baiocchi GL, Bala M, Baraket O, Beltran MA, Jusoh AC, Demetrashvili Z, De Simone B, de Souza

HP, Cui Y, Davies RJ, Dhingra S, Diaz JJ, Di Saverio S, Dogjani A, Elmangory MM, Enani MA, Ferrada P, Fraga GP, Frattima S, Ghnnam W, Gomes CA, Kanj SS, Karamarkovic A, Kenig J, Khamis F, Khokha V, Koike K, Kok KYY, Isik A, Labricciosa FM, Latifi R, Lee JG, Litvin A, Machain GM, Manzano-Nunez R, Major P, Marwah S, McFarlane M, Memish ZA , Mesina C, Moore EE, Moore FA, Naidoo N, Negoi I, Ofori-Asenso R, Olaoye I, Ordoñez CA , Ouadii M, Paolillo C, Picetti E, Pintar T, Ponce-de-Leon A, Pupelis G, Reis T, Sakakushev B, Kafil HS, Sato N, Shah JN, Siribumrungwong B, Talving P, Tranà C, Ulrych J, Yuan KC, Catena F. (2018) Raising concerns about the Sepsis-3 definitions. World J Emerg Surg, 13, 6.

10. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE,Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb S, Beale RJ, Vincent JL, Moreno R. (2013) Surviving Sepsis Campaign Guidelines Committee including The Pediatric Subgroup. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock. Intensive Care Med, 39, 2: 165-228.

11. Molnár G, Gyarmathy VA, Zádori N, Hegyi P, Kanizsai P. (2021) Severe Hypertriglyceridemia-Induced Acute Pancreatitis. Case Rep Gastroenterol, 15, 1: 218-224.

12. Saeed K, González Del Castillo J, Backous C, Drevet S, Ferrer R, Gavazzi G, Gluck E, Jensen JU, Kanizsai P, Ruiz-Rodríguez JC, Molnar G, Fazakas J, Umpleby H, Townsend J, Schuetz P. (2019) Hot topics on procalcitonin use in clinical practice, can it help antibiotic stewardship? Int J Antimicrob Agents, 54, 6: 686-696.

13. Golzari SE, Mahmoodpoor A. (2014) Sepsis-associated encephalopathy versus sepsis-induced encephalopathy. Lancet Neurol, 13, 10: 967-8.

14. Rathour S, Kumar S, Hadda V, Bhalla A, Sharma N, Varma S. (2015) PIRO concept: staging of sepsis. J Postgrad Med, 61, 4: 235-42.

15. Yealy DM, Huang DT, Delaney A, Knight M, Randolph AG, Daniels R, Nutbeam T. (2015) Recognizing and managing sepsis: what needs to be done? BMC Med, 13, 98.

16. Inada-Kim M, Page B, Maqsood I, Vincent C. (2017) Defining and measuring suspicion of sepsis: an analysis of routine data. BMJ Open. 7, 6:e014885.

17. Alsolamy S, Al Salamah M, Al Thagafi M, Al-Dorzi HM, Marini AM, Aljerian N, Al-Enezi F, Al-Hunaidi F, Mahmoud AM, Alamry A, Arabi YM. (2014) Diagnostic accuracy of a screening electronic alert tool for severe sepsis and septic shock in the emergency department. BMC Med Inform Decis Mak 14, 105.

18. Guerra WF, Mayfield TR, Meyers MS, Clouatre AE, Riccio JC. (2013) Early detection and treatment of patients with severe sepsis by prehospital personnel. J Emerg Med, 44, 6: 1116-25.

19. Daniels R, Nutbeam T, McNamara G, Galvin C. (2011) The sepsis six and the severe sepsis resuscitation bundle: a prospective observational cohort study. Emerg Med J, 28, 6: 507-12.

20. Frankling C, Patel J, Sharif B, Melody T, Yeung J, Gao F, Szakmany T. (2019) A Snapshot of Compliance with the Sepsis Six Care Bundle in Two Acute Hospitals in the West Midlands, UK. Indian J Crit Care Med, 23, 7: 310–315.

21. Xantus G, Kiss B, Molnar G, Matheson C, Gyarmathy VA, Kanizsai PL. (2021) Lactate reloaded–reevaluation of the importance of lactate monitoring in the management of adult sepsis in the emergency department. BIOCELL, 45, 3: 445–449.

22. Neviere R, (2021) Pathophysiology of sepsis. [accessed June 05, 2021] Available from:https://www.uptodate.com/contents/pathophysiology-of-sepsis?_ escaped_fragment_=

23. Cinel I, Dellinger RP. (2007) Advances in pathogenesis and management of sepsis. Curr Opin Infect Dis, 20, 4: 345-52.

24. Chen GY, Nuñez G. (2010) Sterile inflammation: sensing and reacting to damage. Nat Rev Immunol, 10, 12: 826-37.

25. Bouchon A, Facchetti F, Weigand MA, Colonna M. (2001) TREM-1 amplifies inflammation and is a crucial mediator of septic shock. Nature, 410, 6832: 1103-7.

26. O'Brien XM, Biron BM, Reichner JS. (2017) Consequences of extracellular trap formation in sepsis. Curr Opin Hematol, 24, 1: 66-71.

27. Kaplan MJ, Radic M. (2012) Neutrophil extracellular traps: double-edged swords of innate immunity. J Immunol, 189, 6: 2689-95.

28. Movat HZ, Cybulsky MI, Colditz IG, Chan MK, Dinarello CA. (1987) Acute inflammation in gram-negative infection: endotoxin, interleukin 1, tumor necrosis factor, and neutrophils. Fed Proc, 46, 1: 97-104.

29. van der Poll T, Lowry SF. (1995) Tumor necrosis factor in sepsis: mediator of multiple organ failure or essential part of host defense? Shock, 3, 1: 1-12.
30. Pruitt JH, Copeland EM 3rd, Moldawer LL. (1995) Interleukin-1 and interleukin-1 antagonism in sepsis, systemic inflammatory response syndrome, and septic shock. Shock, 3, 4: 235-51.
31. Barriere SL, Lowry SF. (1995) An overview of mortality risk prediction in sepsis. Crit Care Med, 23, 2: 376-93.
32. Szabo G, Kodys K, Miller-Graziano CL. (1991) Elevated monocyte interleukin-6 (IL-6) production in immunosuppressed trauma patients. I. Role of Fc gamma RI cross-linking stimulation. J Clin Immunol, 11, 6: 326-35.
33. Bone RC. (1996) Immunologic dissonance: a continuing evolution in our understanding of the systemic inflammatory response syndrome (SIRS) and the multiple organ dysfunction syndrome (MODS). Ann Intern Med, 125, 8: 680-7.
34. Pinsky MR, Matuschak GM. (1989) Multiple systems organ failure: failure of host defense homeostasis. Crit Care Clin, 5, 2: 199-220.
35. Pugin J. Recognition of bacteria and bacterial products by host immune cells in sepsis. In: Yearbook of Intensive Care and Emergency Medicine, Vincent JL (Ed), Springer-Verlag, Berlin 1996: 11-23.
36. Amin P., Amin V. Viral Sepsis. In: Vincent JL. (eds) Annual Update in Intensive Care and Emergency Medicine 2015. Annual Update in Intensive Care and Emergency Medicine 2015, vol 2015. Springer, Cham.2015: 37-59.
37. Suffredini AF, Fromm RE, Parker MM, Brenner M, Kovacs JA, Wesley RA, Parrillo JE. (1989) The cardiovascular response of normal humans to the administration of endotoxin. N Engl J Med, 321, 5: 280-7.
38. Tapper H, Herwald H. (2000) Modulation of hemostatic mechanisms in bacterial infectious diseases. Blood, 96, 7: 2329-37.
39. Pinsky MR, Vincent JL, Deviere J, Alegre M, Kahn RJ, Dupont E. (1993) Serum cytokine levels in human septic shock. Relation to multiple-system organ failure and mortality. Chest, 103, 2: 565-75.
40. Tracey KJ, Beutler B, Lowry SF, Merryweather J, Wolpe S, Milsark IW, Hariri RJ, Fahey TJ 3rd, Zentella A, Albert JD. (1986) Shock and tissue injury induced by recombinant human cachectin. Science, 234, 4775: 470-4.

41. Abraham E, Anzueto A, Gutierrez G, Tessler S, San Pedro G, Wunderink R, Dal Nogare A, Nasraway S, Berman S, Cooney R, Levy H, Baughman R, Rumbak M, Light RB, Poole L, Allred R, Constant J, Pennington J, Porter S. (1998) Double-blind randomised controlled trial of monoclonal antibody to human tumour necrosis factor in treatment of septic shock. NORASEPT II Study Group. Lancet, 351, 9107: 929-33.

42. Lamping N, Dettmer R, Schröder NW, Pfeil D, Hallatschek W, Burger R, Schumann RR. (1998) LPS-binding protein protects mice from septic shock caused by LPS or gram-negative bacteria. J Clin Invest, 101, 10: 2065-71.

43. Walport MJ. (2001) Complement. First of two parts. N Engl J Med, 344, 14: 1058-66.

44. Walport MJ. (2001) Complement. Second of two parts. N Engl J Med, 344, 15: 1140-4.

45. McGown CC, Brown NJ, Hellewell PG, Brookes ZL. (2011) ROCK induced inflammation of the microcirculation during endotoxemia mediated by nitric oxide synthase. Microvasc Res, 81, 3: 281-8.

46. Piagnerelli M, Boudjeltia KZ, Vanhaeverbeek M, Vincent JL. (2003) Red blood cell rheology in sepsis. Intensive Care Med, 29, 7: 1052-61.

47. Piagnerelli M, Boudjeltia KZ, Brohee D, Vincent JL, Vanhaeverbeek M. (2003) Modifications of red blood cell shape and glycoproteins membrane content in septic patients. Adv Exp Med Biol, 510: 109-14.

48. Kirschenbaum LA, Aziz M, Astiz ME Saha DC, Rackow EC. (2000) Influence of rheologic changes and platelet-neutrophil interactions on cell filtration in sepsis. Am J Respir Crit Care Med, 2000; 161, 5: 1602-7.

49. Harrois A, Huet O, Duranteau J. (2009) Alterations of mitochondrial function in sepsis and critical illness. Curr Opin Anaesthesiol, 22, 2: 143-9.

50. Crouser ED, Julian MW, Blaho DV, Pfeiffer DR. (2002) Endotoxin-induced mitochondrial damage correlates with impaired respiratory activity. Crit Care Med, 30, 2: 276-84.

51. VanderMeer TJ, Wang H, Fink MP. (1995) Endotoxemia causes ileal mucosal acidosis in the absence of mucosal hypoxia in a normodynamic porcine model of septic shock. Crit Care Med, 23, 7: 1217-26.

52. Rosser DM, Stidwill RP, Jacobson D, Singer M. (1996) Cardiorespiratory and tissue oxygen dose response to rat endotoxemia. Am J Physiol, 271(3 Pt 2): H891-5.
53. Marshall JC, Watson RW. Apoptosis in the resolution of systemic inflammation. In: Yearbook of Intensive Care and Emergency Medicine, Vincent JL (Ed), Springer-Verlag, Berlin, 1997: 100.
54. Coopersmith CM, Stromberg PE, Dunne WM, Davis CG, Amiot DM 2nd, Buchman TG, Karl IE, Hotchkiss RS. (2002) Inhibition of intestinal epithelial apoptosis and survival in a murine model of pneumonia-induced sepsis. JAMA, 287, 13: 1716-21.
55. Parrat JR, Stoclet JC. Vascular smooth muscle function under conditions of sepsis and ARDS. In: Role of Nitric Oxide in Sepsis and ARDS, Fink MP, Payen D (Eds), Springer-Verlag, Berlin, 1995: 44.
56. Vincent JL, Zhang H, Szabo C, Preiser JC. (2000) Effects of nitric oxide in septic shock. Am J Respir Crit Care Med, 161, 6: 1781-5.
57. Sharshar T, Gray F, Lorin de la Grandmaison G, Hopkinson NS, Ross E, Dorandeu A, Orlikowski D, Raphael JC, Gajdos P, Annane D. (2003) Apoptosis of neurons in cardiovascular autonomic centres triggered by inducible nitric oxide synthase after death from septic shock. Lancet, 362, 9398: 1799-805.
58. Landry DW, Levin HR, Gallant EM, Ashton RC Jr, Seo S, D'Alessandro D, Oz MC, Oliver JA. (1997) Vasopressin deficiency contributes to the vasodilation of septic shock. Circulation, 95, 5: 1122-5.
59. Landry DW, Levin HR, Gallant EM, Seo S, D'Alessandro D, Oz MC, Oliver JA. (1997) Vasopressin pressor hypersensitivity in vasodilatory septic shock. Crit Care Med, 25, 8: 1279-82.
60. Tsuneyoshi I, Yamada H, Kakihana Y, Nakamura M, Nakano Y, Boyle WA 3rd. (2001) Hemodynamic and metabolic effects of low-dose vasopressin infusions in vasodilatory septic shock. Crit Care Med, 29, 3: 487-93.
61. Malay MB, Ashton RC Jr, Landry DW, Townsend RN. (1999) Low-dose vasopressin in the treatment of vasodilatory septic shock. J Trauma, 47, 4: 699-703; discussion 703-5.
62. Patel BM, Chittock DR, Russell JA, Walley KR. (2002) Beneficial effects of short-term vasopressin infusion during severe septic shock. Anesthesiology, 96, 3: 576-82.

63. Scheeren TWL, Bakker J, De Backer D, Annane D, Asfar P, Boerma EC, Cecconi M, Dubin A, Dünser MW, Duranteau J, Gordon AC, Hamzaoui O, Hernández G, Leone M, Levy B, Martin C, Mebazaa A, Monnet X, Morelli A, Payen D, Pearse R, Pinsky MR, Radermacher P, Reuter D, Saugel B, Sakr Y, Singer M, Squara P, Vieillard-Baron A, Vignon P, Vistisen ST, van der Horst ICC, Vincent JL, Teboul JL. (2019) Current use of vasopressors in septic shock. Ann Intensive Care, 9, 1: 20.

64. Astiz ME, DeGent GE, Lin RY, Rackow EC. (1995) Microvascular function and rheologic changes in hyperdynamic sepsis. Crit Care Med, 23, 2: 265-71.

65. Neviere R, Mathieu D, Chagnon JL, Lebleu N, Millien JP, Wattel F. (1996) Skeletal muscle microvascular blood flow and oxygen transport in patients with severe sepsis. Am J Respir Crit Care Med, 153, 1:191-5.

66. Aird WC. (2003) The role of the endothelium in severe sepsis and multiple organ dysfunction syndrome. Blood, 101: 3765.

67. Lefer, A.M. (1982) The pathophysiologic role of myocardial depressant factor as a mediator of circulatory shock. Klin Wochenschr, 60: 713–716.

68. Luce JM. (1987) Pathogenesis and management of septic shock. Chest, 91, 6: 883-8.

69. Ghosh S, Latimer RD, Gray BM, Harwood RJ, Oduro A. (1993). Endotoxin-induced organ injury. Crit Care Med, 21, 2 Suppl: 19-24.

70. Hassoun HT, Kone BC, Mercer DW, Moody FG, Weisbrodt NW, Moore FA. (2001) Post-injury multiple organ failure: the role of the gut. Shock, 15, 1: 1-10.

71. Upperman JS, Deitch EA, Guo W, Lu Q, Xu D. (1998) Post-hemorrhagic shock mesenteric lymph is cytotoxic to endothelial cells and activates neutrophils. Shock, 10, 6: 407-14.

72. Doig CJ, Sutherland LR, Sandham JD, Fick GH, Verhoef M, Meddings JB. (1998) Increased intestinal permeability is associated with the development of multiple organ dysfunction syndrome in critically ill ICU patients. Am J Respir Crit Care Med, 158, 2: 444-51.

73. Haak BW, Wiersinga WJ. (2017) The role of the gut microbiota in sepsis. Lancet Gastroenterol Hepatol, 2, 2: 135-143.

74. Sears CL, Garrett WS. (2014) Microbes, microbiota, and colon cancer. Cell Host Microbe, 15, 3:317-328.

75. Gaykema RP, Dijkstra I, Tilders FJ. (1995) Subdiaphragmatic vagotomy suppresses endotoxin-induced activation of hypothalamic corticotropin-releasing hormone neurons and ACTH secretion. Endocrinology, 136, 10: 4717-20.
76. Rosengarten B, Hecht M, Auch D, Ghofrani HA, Schermuly RT, Grimminger F, Kaps M. (2007) Microcirculatory dysfunction in the brain precedes changes in evoked potentials in endotoxin-induced sepsis syndrome in rats. Cerebrovasc Dis, 23, 2-3:140-7.
77. Fleshner M, Goehler LE, Schwartz BA, McGorry M, Martin D, Maier SF, Watkins LR. (1998) Thermogenic and corticosterone responses to intravenous cytokines (IL-1beta and TNF-alpha) are attenuated by subdiaphragmatic vagotomy. J Neuroimmunol, 86, 2: 134-41.
78. Romanovsky AA, Simons CT, Székely M, Kulchitsky VA. (1997) The vagus nerve in the thermoregulatory response to systemic inflammation. Am J Physiol, 273, 1 Pt 2: R407-13.
79. Borovikova LV, Ivanova S, Zhang M, Yang H, Botchkina GI, Watkins LR, Wang H, Abumrad N, Eaton JW, Tracey KJ. (2000) Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. Nature, 405, 6785: 458-62.
80. Wang H, Liao H, Ochani M, Justiniani M, Lin X, Yang L, Al-Abed Y, Wang H, Metz C, Miller EJ, Tracey KJ, Ulloa L.(2004) Cholinergic agonists inhibit HMGB1 release and improve survival in experimental sepsis. Nat Med, 10, 11: 1216-21.
81. Rodriguez S, Chora A, Goumnerov B, Mumaw C, Goebel WS, Fernandez L, Baydoun H, HogenEsch H, Dombkowski DM, Karlewicz CA, Rice S, Rahme LG, Carlesso N. (2009) Dysfunctional expansion of hematopoietic stem cells and block of myeloid differentiation in lethal sepsis. Blood, 114, 19: 4064-76.
82. Glatman Zaretsky A, Engiles JB, Hunter CA. (2014) Infection-induced changes in hematopoiesis. J Immunol, 192, 1: 27-33.
83. Martin L, Koczera P, Zechendorf E, Schuerholz T. (2016) The Endothelial Glycocalyx: New Diagnostic and Therapeutic Approaches in Sepsis. Biomed Res Int, 2016: 3758278.
84. Katherine A Hajjar, MDWilliam C Aird, MD. (2021) The endothelium: A primer [accessed June 07, 2021]. Available from: https://www.uptodate.com/contents/the-endothelium-a-

primer?search=The%20endothelium:%20A%20primer%20&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H1854645.
85. Lemichez E, Lecuit M, Nassif X, Bourdoulous S. (2010) Breaking the wall: targeting of the endothelium by pathogenic bacteria. Nat Rev Microbiol, 8, 2: 93-104.
86. Lacroix R, Sabatier F, Mialhe A, Basire A, Pannell R, Borghi H, Robert S, Lamy E, Plawinski L, Camoin-Jau L, Gurewich V, Angles-Cano E, Dignat-George F.(2007) Activation of plasminogen into plasmin at the surface of endothelial microparticles: a mechanism that modulates angiogenic properties of endothelial progenitor cells in vitro. Blood, 110, 7: 2432-9.
87. Cohen J, Vincent JL, Adhikari NK, Machado FR, Angus DC, Calandra T, Jaton K, Giulieri S, Delaloye J, Opal S, Tracey K, van der Poll T, Pelfrene E. (2015) Sepsis: a roadmap for future research. Lancet Infect Dis, 15, 5:581-614.
88. IDSA Sepsis Task Force, Infectious Diseases Society of America (IDSA) POSITION STATEMENT (2018) Why IDSA Did Not Endorse the Surviving Sepsis Campaign Guidelines, Clinical Infectious Diseases, 66, 10: 1631–1635.
89. Filbin MR, Lynch J, Gillingham TD, Thorsen JE, Pasakarnis CL, Nepal S, Matsushima M, Rhee C, Heldt T, Reisner AT. (2018) Presenting Symptoms Independently Predict Mortality in Septic Shock: Importance of a Previously Unmeasured Confounder. Crit Care Med, 46, 10: 1592-1599.
90. Bakker J. (2015) Lost in translation: on lactate, hypotension, sepsis-induced tissue hypoperfusion, quantitative resuscitation and Surviving Sepsis Campaign bundles. Crit Care Med, 43, 3:705-6.
91. Sessler DI. (1997) Mild perioperative hypothermia. N Engl J Med., 336, 24:1730-7.
92. Lv X, Wang H. (2016) Pathophysiology of sepsis-induced myocardial dysfunction. Mil Med Res, 3: 30.
93. Garcia-Alvarez, M., Marik, P. & Bellomo, R. (2014) Sepsis-associated hyperlactatemia. Crit Care, 18, 503.
94. Marik PE. SEP-1. (2018) The Lactate Myth and Other Fairytales. Crit Care Med, 46, 10: 1689-1690.
95. Cecconi M, De Backer D, Antonelli M, Beale R, Bakker J, Hofer C, Jaeschke R, Mebazaa A, Pinsky MR, Teboul JL, Vincent JL, Rhodes A. (2014) Consensus on

circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. Intensive Care Med, 40, 12: 1795-815.
96. Vincent JL, Martin GS, Levy MM. (2016) qSOFA does not replace SIRS in the definition of sepsis. Crit Care, 20, 1, 210.
97. Hasanin A, Mukhtar A, Nassar H. (2017) Perfusion indices revisited. J Intensive Care, 5, 24.
98. Foucher CD, Tubben RE (2018): Lactic Acidosis. StatPearls Publishing. [accessed April 08, 2019]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470202/.
99. Suetrong B, Walley KR.(2016) Lactic Acidosis in Sepsis: It's Not All Anaerobic: Implications for Diagnosis and Management. Chest, 149, 1: 252-61.
100. Bronfenbrener R: Acid-Base Interpretation [accessed April 08, 2019]. Available from: https://emedicine.medscape.com/article/2058760-overview.

8. Bibliography of the candidate's publications

Related to the thesis

1. Fekete J, Kanizsai P, Pótó Zs, **Molnár Gy**, Xantus G, Eklics K (2023) The potential role of improvisational training to optimize communication in emergency care Orv Hetil 164, 19: 739-746. **IF: 0,707***

*Expected value

2. **Molnár G**, Gyarmathy VA, Takács J, Sándor S, Kiss B, Fazakas J, Kanizsai PL. (2021) Differentiating sepsis from similar groups of sysmptoms at triage level in emergency care Physiol Int, 108, 1: 106-120. **IF: 1,697**

3. **Molnár G**, Gyarmathy VA, Zádori N, Hegyi P, Kanizsai P. (2021) Severe Hypertriglyceridemia-Induced Acute Pancreatitis. Case Rep Gastroenterol, 15, 1: 218-224.

4. Xantus G, Kiss B, **Molnar G**, Matheson C, Gyarmathy VA, Kanizsai PL. (2021) Lactate reloaded–reevaluation of the importance of lactate monitoring in the management of adult sepsis in the emergency department. BIOCELL, 45, 3: 445–449. **IF: 1,110**

5. Saeed K, González Del Castillo J, Backous C, Drevet S, Ferrer R, Gavazzi G, Gluck E, Jensen JU, Kanizsai P, Ruiz-Rodríguez JC, **Molnar G**, Fazakas J, Umpleby H, Townsend J, Schuetz P. (2019) Hot topics on procalcitonin use in clinical practice, can it help antibiotic stewardship? Int J Antimicrob Agents, 54, 6: 686-696. **IF: 4,621**

6. Kanizsai P, **Molnár Gy**, Sztudva R, Berényi T, Hornyák I. (2018) Does level of training predetermine the success rate of prehospital sepsis assessment? A prospective survey on early recognition. Developments in Health Sciences, 1, 2: 33-38.

Not related to the thesis

1. **Molnar Gy**, Roberts G, Thorpe C. (2013): Improving data capture on obstetric anaesthesia procedures and complications – role of coding International Journal of Obstetric Anaesthesia, 22: 34.

Cumulative impact factor of the candidate's publications: **8,135*** *Expected value

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