Diplomarbeit

Improvement of septic shock management in children in the last 20 years

A retrospective study

eingereicht von

Benedikt Küllinger

zur Erlangung des akademischen Grades

Doktor der gesamten Heilkunde

(Dr.med.univ.)

an der

Medizinischen Universität Graz

ausgeführt an der

Universitätsklinik für Kinder- und Jugendheilkunde

Gemeinsame Einrichtung Pädiatrische Intensivstation

unter der Anleitung von

Ao.Univ.-Prof. Dr. Siegfried Rödl

Dr.in med.univ. Ingrid Christine Marschitz

Graz, 29.04.2021

EIDESSTATTLICHE ERKLÄRUNG

Ich erkläre ehrenwörtlich, dass ich die vorliegende Arbeit selbstständig und ohne fremde Hilfe verfasst habe, andere als die angegebenen Quellen nicht verwendet habe und die den benutzten Quellen wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht habe.

Graz, am 29.04.2021

_____

Benedikt Küllinger eh

ACKNOWLEDGEMENT

First of all, I would like to seize this opportunity to thank the people who supported me during the years of my medical studies, especially when I was writing this diploma thesis.

I would like to express my special thanks to my mentor Ao.Univ.-Prof. Dr.med.univ. Siegfried Rödl for his guidance and explanations. His knowledge on intensive care medicine and pediatric specifities was of great benefit for my understanding of this disease and its management. I also want to thank him for his instructions on data collection and statistical analysis.

Since medical studies can be demanding sometimes, I want to thank my flatmates Paul, Simon and Benjamin for their support and distraction in stressful times during my studies. I will miss our amusing chats and the good times we had. I will always keep this time in happy memories.

Last but not least I want to thank my parents Leonhard and Lucia for their personal and financial support. They have enabled me to follow my dream and study medicine. Without them, I would not have been able to accomplish this.

Thank you!

Content

Abbreviations

ACCM	American College of Critical Care Medicine
ALT	alanine transaminase
APC	activated protein C
APSC	Acute Physiologic Score for Children
ARDS	acute respiratory distress syndrome
AT III	antithrombin
ATP	adenosine triphosphate
BP	blood pressure
CaO_2	arterial oxygen content
CO	cardiac output
CO_2	carbon dioxide
CRP	C-reactive protein
CVP	central venous pressure
DAMP	damage-associated molecular pattern
DIC	disseminated intravascular coagulation
DO_2	oxygen delivery
DP	diastolic blood pressure
FiO_2	fraction of inspired oxygen
GCS	Glasgow Coma Scale
Hb	hemoglobin
HR	heart rate
ICU	intensive care unit
IL-1β	interleukin 1β

IL-6	interleukin 6
INR	international normalized ratio
IQR	interquartile range
MAP	mean arterial pressure
NA	not applicable
NO	nitrogen monoxide
$PaCO_2$	arterial partial pressure of carbon dioxide
PAF	platelet activating factor
PAI-1	plasminogen activator inhibitor-1
PAMP	pathogen-associated molecular pattern
PaO_2	arterial partial pressure of oxygen
PICU	pediatric intensive care unit
PRR	pattern recognition receptor
$PvaCO_2$	carbon dioxide gap
$PvCO_2$	venous partial pressure of carbon dioxide
PvO_2	venous partial pressure of oxygen
PWP	pulmonary wedge pressure
qSOFA	quick sequential organ failure assessment
SaO_2	arterial oxygen saturation
$ScvO_2$	central venous oxygen saturation
SD	standard deviation
SIRS	systemic inflammatory response syndrome
SOFA	sequential organ failure assessment
SP	systolic blood pressure

SSC	Surviving Sepsis Campaign
SV	stroke volume
SvO_2	venous oxygen saturation
SVR	systemic vascular resistance
TAFI	thrombin-activatable fibrinolysis inhibitor
TF	tissue factor
TM	thrombomodulin
TNF-α	tumor necrosis factor α
t-PA	tissue-type plasminogen activator
US	United States
VIS	Vasoactive-Inotropic Score
VO_2	oxygen consumption

Tables and figures

Zusammenfassung

Hintergrund: Septischer Schock ist nach wie vor eine häufige Todesursache auf pädiatrischen Intensivstationen. Die Forschung auf diesem Gebiet erfolgt jedoch in erster Linie an Erwachsenen, deren Mortalität und Morbidität sich in den letzten Jahren verbesserte. Aufgrund diverser physiologischer Unterschiede können Leitlinien für Erwachsene jedoch nicht ohne weiteres bei Kindern angewendet werden. Diese Studie soll einen Überblick über Veränderungen hinsichtlich Behandlung und Therapieerfolg des kindlichen septischen Schocks in den letzten 20 Jahre bieten sowie Ansätze für zukünftige Verbesserungen aufzeigen.

Methoden: In dieser retrospektiven explorativen Studie wurden 22 Patienten und Patientinnen inkludiert, welche zwischen 2000 und 2019 aufgenommen wurden und zur besseren Vergleichbarkeit in zwei Gruppen, abhängig vom Aufnahmedatum, aufgeteilt. Mortalität und Aufenthaltsdauer auf der Intensivstation waren die primären Endpunkte der Studie. Zudem wurden einige sekundäre Endpunkte untersucht, unter anderem welche Medikamente verabreicht wurden. Zusätzlich zu den Unterschieden in Behandlung und Therapieergebnis wurden auch Korrelationen zwischen der Verabreichung einiger Medikamente und dem Therapieergebnis untersucht.

Ergebnisse: Während die erste Gruppe eine Mortlität von 58,3% aufwies, betrug diese lediglich 20% in der späteren Gruppe. Hinsichtlich Mortalität und Aufenthaltsdauer auf der Intensivstation konnte jedoch kein signifikanter Unterschied gezeigt werden. Die angewandte Therapie zeigte kaum Unterschiede, die größten Änderungen konnten im Hinblick auf verwendete Katecholamine sowie Anzahl und Art der Antibiotika festgestellt werden. Zudem konnte eine starke Assoziation von Noradrenalin mit besserem Therapieergebnis gefunden werden.

Schlussfolgerung: Die beobachteten Änderungen der Therapie des septischen Schocks haben zu einer Verbesserung des Therapieerfolgs geführt, auch wenn diese nicht sicher bewiesen werden konnte. Die Hauptgründe für diese Entwicklung waren einerseits eine Umstellung der Kreislaufunterstützung mittels unselektiven Katecholaminen (Dopamin, Adrenalin) zu selektiverer und physiologischerer Unterstützung mit Noradrenalin und andererseits Kombination verschiedener Antibiotika sowie eine vermehrte Adaptierung der antibiotischen Behandlung.

Abstract

Background: Septic shock is still a common cause of death in pediatric intensive care units (PICUs). However, most research is conducted among adult patients and therefore, mortality and morbidity among them have decreased over the last years. Since there are some major differences to children, guidelines provided for management of septic shock in adults only have limited applicability in children. The aim of this study is to provide an overview on how treatment of septic shock in children has changed over the last 20 years and to point out potential future improvements.

Methods: In this retrospective, explorative study, 22 patients with septic shock administered to PICU between 2000 and 2019 were included. In order to compare them, they were split into two groups, depending on their date of admission. Primary outcomes investigated were hospital mortality and PICU length of stay. Various secondary outcomes were evaluated as well, including the medication these patients received. Differences in treatment and outcome between both groups were explored as well as correlation of administration of certain drugs and outcome.

Results: Whilst mortality rate was 58,3% in the first group, it accounted for 20% in the second group. Neither did they differ significantly in regard of mortality rate nor PICU length of stay. Most therapy administered did not show alterations between the two groups. Management mainly varied in type of catecholamine used for circulatory support as well as number and types of antibiotics given. Administration of norepinephrine also was strongly associated with survival and longer PICU length of stay.

Conclusion: Observed changes in septic shock management showed some improvement of outcome, even though it could not be proven. The observed main reasons for this development were a switch from nonselective catecholamines with potential adverse effects (dopamine, epinephrine) towards a more selective and physiological cardiovascular support with norepinephrine on the one hand and antibiotic combination treatment and more frequent adjustment of the antibiotic therapy on the other hand.

1 Introduction

1.1 Definition

The first definition of Sepsis was estabilshed in 1992 by the American College of Chest Physicians and the Society of Critical Care Medicine at a consensus conference. This conference stated that sepsis is a systemic inflammatory response syndrome (SIRS) caused by infection. Bone et al. defined infection as microbial phenomenon accompanied by an inflammatory response to microorganisms or the invasion of otherwise sterile host tissue by those organisms. SIRS can be caused by multiple triggers besides infection and is defined as syndrome showing two or more of the following acute clinical findings in absence of other known causes (e.g. Chemotherapy). (1)

1. Temperature >38°C or <36°C
2. Heart rate (HR) >90 beats per minute
3. Respiratory rate (RR) >20 or Hyperventilation with PaO_2 <32mmHg
4. White blood cell count >12.000/mm³ or <4.000/mm³ or >10% immature neutrophils

According to this first definition, sepsis is a clinical picture proceeding in continuous phases through severe sepsis to septic shock. Severe sepsis was defined as sepsis accompanied by organ dysfunction, hypotension or hypoperfusion, which may present in lactic acidosis, oliguria or acute mental alteration. Septic shock was considered a subgroup of severe sepsis and was specified as sepsis-induced hypotension, meaning systolic blood pressure (SP) of less than 90mmHg or reduction of SP by more than 40mmHg from baseline, persisting despite appropriate fluid resuscitation, occuring with either hypoperfusion or organ dysfunction. (1)

In 2016, the third international consensus definitions for sepsis and septic shock (Sepsis-3) were presented by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine. This task force stated, that the prior model of sepsis following a continuum through severe sepsis to septic shock was outdated and recommended to dismiss the term severe sepsis and to cut down the various definitions to two: sepsis and septic shock. (2)

The Sepsis-3 conference also determined that the SIRS criteria were obsolete and revised the original definitions from 1992. The Sepsis-3 definitions are currently considered the latest for sepsis and septic shock. Sepsis is now defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection and the SIRS score was replaced by the sequential organ failure assessment (SOFA) score (Table 1) due to its higher predictive validity for hospital mortality. Organ dysfunction can be assumed with a change in SOFA score of 2 points or more from baseline in patients with infection and is associated with an increase in mortality of approximately 10%. In patients without any known organ dysfunction, the baseline SOFA score should be assumed to be 0. (2–4)

Table 1: Sequential Organ Failure Assessment (SOFA) Score (2)

	Score				
System	**0**	**1**	**2**	**3**	**4**
Respiration PaO_2/FiO_2, mmHg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation Platelets, x10³/µL	≥150	<150	<100	<50	<20
Liver Bilirubin, mg/dL	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-104)	>12.0 (204)
Cardiovascular[a]	MAP ≥70 mmHg	MAP <70 mmHg	Dopamine <5 OR dobutamine (any dose)	Dopamine 5.1-15 OR epinephrine ≤0.1 OR norepinephrine ≤0.1	Dopamine >15 or epinephrine >0.1 OR norepinephrine >0.1
Central nervous system Glasgow Coma Scale score[b]	15	13-14	10-12	6-9	<6
Renal Creatinine, mg/dL, (µmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Abbreviations: PaO_2: arterial partial pressure of oxygen; FiO_2: fraction of inspired oxygen; MAP: mean arterial pressure.

[a] Catecholamine doses are given as µg/kg/min for at least 1 hour.

[b] Glasgow Coma Scale (GCS) score ranges from 3-15; higher score indicates better neurological function.

Since the SOFA score requires laboratory testing and may be influenced by external factors such as iatrogenic interventions, its implementation is only recommended in intensive care unit (ICU) settings. For immediate bedside identification of patients with infection and increased risk of poor outcome outside the ICU, another score has been implemented, called quick SOFA (qSOFA). Since the assessment of this

score can be accomplished simply and quickly, it can be applied to quickly evaluate organ dysfunction, indication for initiation or escalation of therapy and transfer to ICU. The qSOFA is considered positive, if 2 of the following 3 clinical aspects can be found in a patient with suspected infection. (2, 3)

1. Altered mental status – Glasgow Coma Scale (GCS) <15
2. Respiratory rate ≥22/min
3. Systolic blood pressure ≤100mmHg

The Sepsis-3 task force also revised the definition of septic shock which is now defined as subset of sepsis with circulatory and cellular or metabolic abnormities, profound enough to substantially increase mortality. They provided following clinical criteria to identify septic shock. (2)

1. Sepsis
2. Persisting Hypotension requiring vasopressors to maintain mean arterial pressure (MAP) ≥65mmHg
3. Hyperlactatemia with serum lactate >2mmol/L (18mg/dL) despite adequate fluid resuscitation

Albeit understanding of sepsis and septic shock has improved and the approach to this clinical picture has changed in adults, the latest definition of sepsis and septic shock in children were published in 2005. The Sepsis-3 definitions are not applicable in children, not only because of significant differences in pathophysiology, clinical presentation and therapeutic approach to adults, but also because of missing evaluation. (5–7)

In consequence to these differences, the definitions of SIRS, severe sepsis and septic shock were revised for children. SIRS in children is defined as two or more of the following findings, with one of them being abnormal temperature or leukocyte count. Since tachycardia and tachypnea are frequent findings in pediatric diseases SIRS should not be diagnosed solely on the basis of elevated HR and RR. (5)

1. Core temperature >38.5°C or <36°C
2. Tachycardia (mean HR >2 SD above age specific norm or otherwise unexplained persistent elevation over 0.5-4 hours)

OR for Children <1 year: Bradycardia (mean HR <10th percentile for age or otherwise unexplained persistent depression over 0.5 hours)

3. Tachypnea (mean RR >2 SD above age specific norm or mechanical ventilation without underlying neuromuscular disease or receipt of general anesthesia)
4. Leukocyte count elevated or depressed OR >10% immature neutrophils

Disparity between adults and children in terms of physiology as well as variability between child age groups have a great influence on the clinical factors used for SIRS classification. Therefore, the pediatric consensus conference appointed 6 age groups among children, which show differing norms in vital signs and laboratory findings, to make the SIRS score applicable in pediatrics. These age-specific norms for SIRS evaluation can be found in Table 2. (5)

Table 2: Age groups and their age-specific vital signs and laboratory findings (5)

Age group	Heart Rate, Beats/min		Respiratory Rate, Breaths/min	Leukocyte Count, Leukocytes x $10^3/mm^3$	Systolic Blood Pressure, mmHg
	Tachycardia	Bradycardia			
Newborn *(0 days - 1 wk)*	>180	<100	>50	>34	<65
Neonate *(1 wk - 1 mo)*	>180	<100	>40	>19.5 or <5	<75
Infant *(1 mo - 1 yr)*	>180	<90	>34	>17.5 or <5	<100
Toddler and preschool *(2-5 yrs)*	>140	NA	>22	>15.5 or <6	<94
School age child *(6-12 yrs)*	>130	NA	>18	>13.5 or <4.5	<105
Adolescent and young adult *(13 - 18 yrs)*	>110	NA	>14	>11 or <4.5	<117

NA: not applicable.
Lower values for heart rate, leukocyte count and systolic blood pressure are for the 5th percentile.
Upper values for heart rate, respiration rate and leukocyte are for the 95th percentile.

Whilst the definitions for infection and sepsis remain unchanged from those released for adults in 1992 by Bone et al., the definitions for severe sepsis and septic shock were amended for use in pediatrics. In contrast to adults, the term severe sepsis is still in use for children and is now defined as sepsis with either cardiovascular organ dysfunction, acute respiratory distress syndrome (ARDS) or at least two other organ dysfunctions. (5)

Cardiovascular dysfunction in children can be diagnosed if the following findings occur despite adequate fluid resuscitation with isotonic boluses of at least 40 mL/kg in 1 hour. (5)

- Hypotension (decrease in BP <5th percentile or <2 SD below normal for age)
  OR
- Need for vasopressors to maintain BP in normal range (dopamine >5µg/kg/min or dobutamine, epinephrine, or norepinephrine at any dose)
  OR
- Two of the following:
    a. Unexplained metabolic acidosis (base deficit >5.0mEq/L)
    b. Increased arterial lactate (>2 times upper limit of normal)
    c. Oliguria (urine output <0.5mL/kg/h)
    d. Prolonged capillary refill (>5 secs)
    e. Difference of core to peripheral temperature (>3°C)

For the diagnosis of ARDS a PaO_2/FiO_2 ratio ≤200mmHg, bilateral pulmonary infiltrates, acute onset and no evidence of left heart failure must be present. The criteria for respiratory organ dysfunction in general are as following. (5)

1. PaO_2/FiO_2 <300 in absence of cyanotic heart disease or preexisting lung disease
   OR
2. $PaCO_2$ >20mmHg over baseline
   OR
3. Proven need of >50% FiO_2 to maintain saturation ≥92%
   OR
4. Need for nonelective invasive or noninvasive mechanical ventilation

Patients presenting with a maximum GCS of 11 or acute mental alteration with a decrease of at least 3 points in GCS from baseline should be diagnosed with neurologic organ dysfunction. (5)

Findings of a platelet count under 80.000/mm³, platelet reduction of 50% in 3 days or an international normalized ratio (INR) higher than 2 indicate dysfunction of the hematologic system. (5)

Renal organ dysfunction is defined as serum creatinine rise to values of at least 2 times the upper limit of normal for age or to 2 times the baseline value. (5)

Criteria for hepatic organ dysfunction are either a total bilirubin of at least 4 mg/dL or an alanine transaminase (ALT) value of 2 times the upper limit of normal for age. Since total bilirubin may be increased in newborns, this parameter is not applicable in this group. (5, 8)

Finding a definition for pediatric septic shock remained challenging since children may maintain blood pressure (BP) during initial phases of septic shock. For this reason, pediatric septic shock is defined as sepsis with cardiovascular organ dysfunction. In children, tachycardia with signs of decreased perfusion may occur before hypotension and hence should be considered a sign of shock. (5, 9)

1.2 Epidemiology

Severe sepsis, including septic shock, is a life-threatening syndrome frequently occurring in children which is associated with high mortality and morbidity. Although recent research improved our understanding of severe sepsis, it remains a highly prevalent cause of death in patients assigned to pediatric intensive care units (PICUs). As the definitions of sepsis, severe sepsis and septic shock have changed several times since the first consensus conference in 1991, epidemiologic data for severe sepsis and septic shock among children is widely varying.

Nevertheless, one large study (SPROUT) investigated the global numbers of prevalence and mortality of severe sepsis and septic shock. This study showed that this disease is prevalent in 8,2% of PICU patients and is accountable for more than 8% of all critically ill children. Overall hospital mortality rates of pediatric severe sepsis found by the SPROUT study accounted for 25%. (1, 2, 10)

Due to recent advances in research and establishment of sepsis bundles, mortality of severe sepsis and septic shock has improved over the last years. Prevalence of severe sepsis in United States (US) PICUs however, increased from 6,2% in 2004 to 7,7% in 2012. Septic shock prevalence showed an increase of 2,6% per year. During this period, mortality of severe sepsis in these US PICUs could be reduced from 18,9% to 12,0%. According to the SPROUT study, there are no significant differences in terms of prevalence in PICU and hospital mortality between Europe and North America. (10–13)

A large prospective multicenter study conducted in PICUs of 7 European countries between 2012 and 2016 found that 59% of all patients admitted to these PICUs with community-acquired sepsis presented with septic shock. Mortality increased from 6% in patients with sepsis to 10% among those with septic shock. Survivors of community-acquired sepsis showed a disability rate of 31%, including those who had underlying conditions. 24% of primary healthy patients showed some disability at discharge, among septic shock survivors this rate accounted for 35%. (14)

1.3 Pathophysiology

1.3.1 Types of shock

In general, shock describes the condition of acute generalized circulatory insufficiency, a discrepancy of cardiac output (CO) and required oxygen supply. This state of potential tissue hypoxia, ischemia, metabolic acidosis, impaired metabolism or even cell death is a potential trigger of organ dysfunction and organ failure. (15)

There are different types of shock, which are hypovolemic, cardiogenic and distributive shock. They are differentiated according to their pathophysiological cause. Regardless of the subtype, an alteration of at least one out of three parameters must occur in order to develop shock. These parameters are circulating blood volume, cardiac output and vascular tone. (15)

Hypovolemic shock is characterized by lack of intravascular volume, typically caused by bleeding, volume shift into the interstitium, gastrointestinal loss of fluids, extensive wounds or renal dysfunction. (15)

Cardiogenic shock can be found in patients with acute heart failure, myocardial infarction, cardiomyopathy, negative inotropic medication (e.g. betablockers) or arrythmias. This type of shock is characterized by reduced cardiac output. Obstruction of the right ventricular outflow tract potentially caused by pulmonary embolism, aortic stenosis, pericardial tamponade or tension pneumothorax can affect the left ventricular filling and results in decreased cardiac output as well. For this reason, cardiogenic shock is called obstructive shock. (15)

The last subtype is distributive shock, caused by reduced vascular tone. There are four different vasoactive substances potentially triggering vasodilation due to their effects on microcirculation. According to these triggering factors, there are four subclasses of distributive shock. Whereas the development of septic shock is typically triggered by toxins, anaphylactic shock is caused by histamine released during an allergic reaction. Then again, neurogenic shock can be the result of trauma, spinal shock or heat stroke. The last subclass of distributive shock is endocrine shock which can be triggered by hormonal imbalance. (15)

All forms of prolonged shock develop severe microcirculatory alterations with endogenous mediator release, followed by irreversible loss of vascular tone and

result in circulatory failure. This stage is referred to as refractory shock if it remains uncontrollable despite application of all available treatment. (15)

A characteristic finding in shock is centralization of circulation, a mechanism of the body to ensure perfusion of vital organs (i.e. brain and heart) by maintaining arterial BP. Since MAP is defined as CO multiplied by systemic vascular resistance (SVR) and CO is defined as stroke volume times HR, the body can raise MAP with the following mechanisms. (15)

1. The central nervous sympathetic adrenergic system raises CO by increasing HR and myocardial contractility. In addition, it causes vasoconstriction of arterioles, resulting in elevated SVR and altered blood flow to brain and heart at the expense of other, less vital organs.
2. Adrenaline, liberated from the adrenal cortex, enhances the effect of the sympathetic adrenergic system.
3. As consequence of renal BP drop, the renin-angiotensin-aldosterone system is activated. Release of angiotensin II and aldosterone lead to increased SVR by vasoconstriction and an increase of CO by renal volume retention.
4. Atrial receptors recognize intravascular hypovolemia and may trigger a release of antidiuretic hormone from the hypophysis, resulting in vasoconstriction and water retention and therefore also increases SVR and CO.

In distributive shock, a distinction between hyper- and hypodynamic circulatory failure needs to be made. Hyperdynamic shock describes a phase, in which the body tries to compensate shock with increased cardiac output. Typical concomitant findings are hypotension, low SVR, low central venous pressure (CVP), tachycardia, low pulmonary wedge pressure (PWP) and elevated oxygen concentrations in pulmonary-artery blood. Persisting microcirculatory disorder leads to aggravation of shock and hypodynamic circulatory failure. This condition is characterized by low CO, high SVR, hypotension, tachycardia, increased PWP and CVP. (15, 16)

1.3.2 Septic shock

Septic shock is triggered by toxins which can be produced by bacterica, viruses or fungi. Bacterial toxins however remain the main cause for this pathology, hence we will focus on this pathophysiological pathway. (10, 17–22)

Cells of the innate immune system possess pattern recognition receptors (PRR), enabling them to detect pathogen-associated molecular pattern (PAMPs) which derive from microorganisms. Among others, endotoxins, exotoxins and superantigens are attributable to these PAMPs and are responsible for the development of septic shock. An example for endotoxins are lipopolysaccharides that can be found in cell walls of gram-negative bacteria. Exotoxins are excretions of certain bacteria and superantigens are products of gram-positive bacteria. (15, 21, 23–25)

Macrophages, neutrophils and dendritic cells, as part of the innate immune system, carry PRRs (e.g. toll-like receptors) and therefore, are capable of recognizing microorganisms and initiate the immune response by releasing cytokines. The most crucial of these proinflammatory cytokines for the development of septic shock are tumor necrosis factor alpha (TNF-α), Interleukin 1β (IL-1β) and Interleukin 6 (IL-6). IL-1β and IL-6 are responsible for activation of endothelial cells, stimulation of T- and B-lymphocytes of the adaptive immune system, development of fever and stimulation of the acute-phase-protein (e.g. c-reactive protein (CRP)) production in the liver. TNF-α is an important factor to contain a local infection. This containment is achieved by 1) increasing vascular permeability to enhance transfer of plasma proteins into the interstitium, 2) stimulating the expression of adhesion molecules (i.e. selectins and integrins) to increase extravasation of leukocytes and 3) triggering of blood clotting in small vessels to prevent spreading of the microorganisms. This agent also stimulates the production of acute-phase-proteins, attracts dendritic cells to the site of infection and leads to a release of neutrophils from the bone marrow. In the event of an infection spreading to the bloodstream, TNF-α is released by macrophages located in liver, spleen and other sites in the body. If released systemically, the impact of TNF-α is more severe than in local infections since it causes vasodilation and increased vascular permeability of small vessels, known as capillary leakage, which leads to loss of BP and plasma volume and subsequently results in shock. Furthermore, TNF-α contributes to disseminated intravascular coagulation (DIC). This complication of septic shock is characterized by blood clotting in small vessels throughout the body with consumption of clotting factors, leading to impaired coagulation. (15, 20, 21, 23, 26, 27)

Septic shock is a process taking place in the terminal vessels (i.e. arterioles, venules and capillaries). As the body tries to take countermeasures against loss of BP, the sympathetic adrenergic system triggers vasoconstriction of pre- and postcapillary sphincters, resulting in decelerated capillary blood flow. This supports leakage of fluids into the interstitium, causing increased blood viscosity and aggregation of blood cells. If the resulting stasis of blood interacts with simultaneously occurring activation of the coagulation system, then irreversible capillary occlusions may develop. (15)

PRR carrying cells of the innate immune system not only are able to detect PAMPs but also damage-associated molecular pattern (DAMP), which derive from autologous cells and are liberated in case of trauma, ischemia or other occurrence of tissue damage. Hence, damaged cells can also trigger a response of the immune system in absence of microbial invasion. (21, 25)

There are some endogenous agents that play essential roles in the development of septic shock. For this reason, they are described briefly in the following, including their part in pathophysiology of septic shock.

Damaged endothelial cells cause a local release of chemotactic ligands and proinflammatory cytokines which increase adhesion and migration of neutrophils into subendothelial tissue. There, they release oxygen radicals and other agents, causing addiational harm on endothelial cells. Whereas endothelial cells are able to release nitrogen monoxide (NO), a potent vasodilating agent, damaged endothelial cells are unable to release sufficient amounts of NO, which results in vasospasm and aggravation of hypoxia. At the same time, vital endothelial cells are stimulated by proinflammatory cytokines and platelet-activating factor (PAF) and release exuberant amounts of NO, causing potentially monocytes, granulocytes, lymphocytes, thrombocytes and endothelial cells, which has stimulating effects on chemotaxis, adhesion and transmigration of granulocytes and monocytes. Furthermore, it leads to activation and aggregation of thrombocytes and to capillary leakage. (15, 23)

Tissue factor (TF), a cell-membrane bound protein, can be found at locations like vascular adventitia, organ capsules and mucosa without direct contact to the blood stream. Due to raised levels of proinflammatory mediators, the production of TF is

increased in sepsis. Disruption of the endothelial layer allows interaction of TF with factor VIIa, a component of the coagulation system located in the blood stream. This results in activation of coagulation, cleavage of prothrombin to thrombin and consequently fibrin formation. (15, 23, 28)

Thrombomodulin (TM), a membrane protein located on endothelial cells, binds free thrombin and thus reduces the amount of circulating thrombin. Proinflammatory cytokines in septic shock lead to decreased synthesis of TM and therefore to higher levels of thrombin, favoring the formation of clots. Furthermore, interaction of TM with thrombin triggers activation of protein C to activated protein C (APC), which therefore shows decreased levels in septic shock. APC has anticoagulant and profibrinolytic functions, as it not only inhibits factors Va and VIIIa, and thus disturbs the coagulation cascade, but also blocks plasminogen activator inhibitor-1 (PAI-1) and thrombin-activatable fibrinolysis inhibitor (TAFI). The TM-thrombin complex triggers activation of TAFI which prevents plasminogen and tissue-type plasminogen activator (t-PA) from resolving formed clots and therefore inhibits fibrinolysis. (15, 23, 29–31)

Plasminogen is a plasma zymogen of plasmin, which plays an essential role in fibrinolysis by degrading fibrin. The conversion of plasminogen is conducted by physiological activators, such as t-PA. Synthesis of t-PA is stimulated by fibrin generation, whereas PAI-1 effectively inactiveates it. Since synthesis of t-PA is reduced and synthesis of PAI-1 is increased in septic shock, less plasminogen is converted into plasmin, which leads to impaired fibrinolysis. (15, 32, 33)

Antithrombin (AT III) is a potent endogenous anticoagulant and serves as main inhibitor of thrombin and factor Xa. Septic patients show decreased levels of AT III due to decreased hepatic synthesis and increased consumption by formation of antithrombin-thrombin complexes. Additionally, activated neutrophils release an elastase that degrades AT III. These processes lead to decreased levels of AT III in septic shock and amplification of the prothrombotic state. (15, 23, 34)

Despite activation of fibrinolytic systems by proinflammatory cytokines and endotoxins in early stages of septic shock, prothrombotic factors are predominant in proceeded stages. This occurs due to the interaction of the described factors. Consumption and insufficient activation of anticoagulant factors on the one hand

and increased thrombogenicity on the other hand lead to insufficient fibrinolysis and result in an exuberant coagulopathy with generalized microthrombosis, known as DIC. Since overall fibrinolysis is also increased, products of fibrinogen cleavage are apparent as D-dimer in laboratory analyses. (15, 23, 35)

Sympathetic adrenergic stimulation, as countermeasure to shock, induces glycogenolysis, lipolysis and proteolysis to provide quickly metabolizable substrate in the form of glucose and free fatty acids. However, high levels of catecholamines also lead to resistance of peripheral cells to insulin, resulting in an accumulation of free fatty acids and amino acids. At the same time, reduced supply of oxygen as occuring in septic shock, leads to lower utilization of free fatty acids and amino acids by the citric acid cycle which are consequently degraded to ketones and keto acids. The reduced supply of oxygen also triggers the activation of anaerobic glycolysis. Products of this metabolic pathway are adenosine triphosphate (ATP) and lactate. The accumulation of lactate, ketones and keto acids may cause severe metabolic acidosis, leading to aggravation of the microvascular disorder. Lactate levels can be quantified in laboratory analysis. In accordance to the lactate rise in anaerobic glycolysis, this parameter indicates tissue hypoxia in septic shock. (15)

Microvascular alterations, caused by the previously stated mechanisms, lead to decreased capillary density and consequently to heterogenicity of perfusion, which results in an increased diffusion distance for oxygen in tissue. Even though total blood flow in the organs is maintained, heterogenous blood flow may cause hypoxic areas due to alterations in oxygen extraction. Since heterogenous perfusion leads to poorer oxygenation and oxygen extraction than homogenously decreased perfusion, this seems to be a crucial aspect in the development of organ dysfunction. Compared to normal conditions, heterogeneity of microvascular perfusion is additionally increased in presence of hypoperfusion. Since an improvement of the microcirculation leads to a proportional decrease of the lactate level, this indicates that these microvascular alterations lead to cellular damage by affecting tissue oxygenation. (36–40, 40–43)

Capillary leakage in septic shock causes a loss of plasma into the tissue, leading to edema and consequently to impairment of oxygen and metabolite diffusion. Hence, edema contributes to progression of organ dysfunction. When occurring in the lungs,

pulmonary edema results in impeded oxygenation and increased work of breathing. Septic patients are at risk to develop a vicious cycle, since increased severity of sepsis leads to increased endothelial permeability, causing greater fluid losses and therefore increasing the amount of needed fluid input. Fluid input then again increases the transmural hydrostatic pressure. According to the Frank-Starling principle, increased capillary transmural hydrostatic pressure results in increased fluid leak into the tissue interstitium. This leads to enhanced organ edema, organ dysfunction and increasing mortality. (27, 44)

Organ dysfunction is a secondary condition in septic shock caused by insufficient organ perfusion, insufficient oxygen supply and systemically induced inflammation. Since all of these alterations occur systemically, dysfunction of almost all organ systems is possible. Cardiac dysfunction needs to be mentioned particularly in this context, since the heart may develop a sepsis-induced cardiomyopathy. Albeit an early, hyperdynamic stage may occur in septic shock, multiple factors (e.g. metabolic acidosis, endotoxins, TNF-α and IL-1β) have a negative effect on inotropy, resulting in reduced contractility of cardiomyocytes and consequently in hypodynamic septic shock. This condition usually resolves within 7-10 days in surviving patients. (15, 27, 45)

1.3.3 Differences in children

There are two major differences in pathophysiology of septic shock between children and adults. Whilst adults present with hyperdynamic shock (low SVR, hypotension, normal or increased CO), also called warm shock, almost 90%, children show signs of hypodynamic shock (increased SVR, no hypotension, low CO) , also called cold shock, in 50% at presentation. Maintenance of cardiac output can be achieved by two factors, which are increase of HR and decrease of SVR. Since young children have a higher resting HR, cardiac reserve in case of decreased stroke volume is limited. Therefore, the main response to decreasing cardiac output is vasoconstriction, leading to further impaired cardiac output, cardiac failure and ultimately death. Although hypovolemia is a frequently occuring issue in pediatric septic shock, hypotension may be a late sign in children due to this mechanism. (7)

The second discrepancy may occur in neonates. Fetal circulation is characterized by a circulation bypassing the lungs through the patent ductus arteriosus and the foramen ovale. These structures usually close at birth due to lower pulmonary artery pressure. However, acidosis and hypoxia in septic shock cause increased pulmonary vascular resistance and consequently increased pulmonary artery pressure, resulting in a patent ductus arteriosus, persistent pulmonary hypertension and subsequently persistent fetal circulation. Other cardiovascular impairments may derive from pulmonary hypertension, such as increased right ventricle afterload, cardiac failure, tricuspid regurgitation or hepatomegaly. In contrast to adult septic shock, where septic shock is associated with increased release of NO and subsequent hypotension, these patients may profit from inhaled NO. (7)

1.4 Hemodynamic monitoring and parameters

The previously described changes of the cardiocirculatory system affect hemodynamics of patients with septic shock. For recognition and treatment, these changes somehow need to be monitored. There are some parameters to assess the patient's current condition. None of the following parameters provides reliable information on its own and therefore, they should be interpreted collectively. (46)

To understand the interplay of the different hemodynamic parameters, there are some equations showing how these values are influenced.

$$\mathbf{CO = SV \times HR}$$

Cardiac Output is defined as product of stroke volume (SV) and heart rate. Therefore, CO can be raised by increasing either SV or HR. SV can be affected by preload, afterload and contractility. Simply put, preload can be seen as the left ventricular end-diastolic volume. According to the Frank Starling mechanism, improving preload has a strong positive impact on CO until the curve flattens and fluid overload leads to ventricular dilatation and decreased ejection fraction. (7, 15, 46, 47)

$$\mathbf{BP = CO \times SVR}$$

Blood pressure can be calculated by cardiac output multiplied with systemic vascular resistance. BP is a crucial factor for afterload, which is the pressure that must be generated by the ventricle to eject blood during the systole, hence must exceed the BP that is present in the aorta. For this reason, CO not only has an impact on BP, but BP also affects CO. (15, 47)

$$\mathbf{CaO_2 = Hb \times SaO_2 \times 1{,}34 + PaO_2 \times 0{,}0031}$$

This formula describes the arterial oxygen content (CaO_2), which is the amount of oxygen transported by 1 dL of blood. Since oxygen is not only carried bound to hemoglobin (Hb), but also dissolved in blood, both of them need to be considered in this equation, even though the impact of dissolved oxygen is negligible under normal circumstances. To calculate the venous oxygen content (CvO_2), the values for SaO_2 and PaO_2 need to be replaced with SvO_2 and PvO_2. (47, 48)

$$DO_2 = CO \times CaO_2$$

Oxygen delivery (DO_2) represents the amount of oxygen that is available to the body in one minute and is defined as product of cardiac output and arterial oxygen content. For this reason, the available amount of oxygen can be increased either by greater CO or an increase in CaO_2, which is obtainable by improving SaO_2 or raising Hb levels. (47)

$$VO_2 = CO \times (CaO_2 - CvO_2)$$

To calculate the consumption of oxygen (VO_2), the difference between arterial and venous oxygen content needs to be multiplied with CO. This value is the amount of oxygen the body extracts from the blood in one minute. Consumption of oxygen remains constant for some time during episodes of decreased DO_2. As the extracted fraction of available oxygen increases until a critical threshold is reached, lower SvO_2 levels are measurable. (47, 48)

1.4.1 Arterial blood pressure and mean arterial pressure

Decreased BP and MAP is a common finding in septic shock. In children however, they may be maintained during the early phase. BP can be measured either noninvasively or invasively. (7)

MAP is the average pressure in the arterial system during one cardiac cycle. Its importance to assess the cardiovascular function and to target an adequate therapy will be explained later. MAP either can be measured directly, most commonly with oscillometry or invasively with arterial catheterization, or it can also be calculated approximately with the following formula. (49, 50)

$$MAP = DP + 0{,}412 \times (SP - DP)$$

In this formula DP stands for diastolic blood pressure and SP for systolic blood pressure. It does not provide exact values, yet allows a rough estimation of the MAP when using sphygmomanometry. (49)

There are different methods to measure BP noninvasively. The most common techniques are sphygmomanometry and oscillometry. Sphygmomanonetry, better known as auscultatory method, requires a blood pressure cuff (sphygmomanometer) and a stethoscope and needs to be done manually. First the cuff needs to be inflated with pressure exceeding the SP, stopping the blood flow.

When blood flow restarts during deflation, turbulances are generated, the so-called Koratkov sounds, which can be heard with a stethoscope. While the manometer's pressure at this point represents the systolic value, DP is reached when no further Koratkov sounds can be heard. At this point, the cuff's pressure falls below DP and no further turbulences occur. (50)

However, since the auscultatory method can not be done automatically, the one of choice in monitorised patients is the oscillometric method. This technique recognizes changes in the cuff's pressure during deflation, which occurs when blood flow returns. The detected changes are highest with a pressure close to MAP. For this reason, MAP is more accurate in Oscillometry than the systolic and diastolic value. As mentioned before, this method is usually performed automatically and therefore, is well applicable for semicontinuous monitoring. (50)

Invasive BP measurement is usually applied in critically ill patients, including septic shock. This method requires a catheter to be placed in an artery. The most common location for its insertion is the radial artery, though brachial or femoral artery are also possible sites for an arterial catheter. After insertion, a fluid filled system is attachet to connect the catheter with a transducer. This fluid column is in hydrostatic continuity with the arterial blood stream and transmits the pulse pressure to the transducer which converts this physical impulse into an electrical signal. To obtain a correct value, it is crucial to place the transducer at the right level, which is usually the one of the right atrium. (50, 51)

Invasive BP monitoring allows a continuous, real-time measurement of DP, SP and MAP. Furthermore, it also provides a pulse curve, allowing the physician to interpret the waveform and collect further information on the patient's current cardiovascular condition. (50, 51)

1.4.2 Central venous pressure

To survey the CVP, a central venous catheter is required, also connected to a transducer. This method is an equivalent to the invasive arterial BP measurement, just located in another part of the vascular system, the superior vena cava. Since the placement of the catheter is just before the right atrium, the CVP may be considered as right atrial pressure and, with limitations, as enddiastolic right ventricular pressure. The CVP depends on multiple factors, such as intravasal

volume, vascular resistance, cardiac output, body position, breathing and mechanical ventilation. For this reason, CVP is no longer considered a reliable parameter to evaluate right venricular function or the filling condition of the venous system. It is however, when measured repetitively, useful for interpretation of the patient's temporal progress and for evaluation of the effects of executed treatments. It is also involved when it comes to the calculation of perfusion pressure. (46, 51)

1.4.3 Perfusion pressure

Following physical rules, blood flows along the gradient from the high pressure system to the low pressure system. In organs, the difference of BP entering the organ (quantified as MAP) and BP remaining after the organ (quantified as CVP) is called perfusion pressure. Although this parameter provides a rough impression on organ perfusion, other parameters need to be considered as well to evaluate the actual organ perfusion. This is because BP is dependent on CO as well as on SVR, enabling MAP and CVP to remain in a physiological range while CO is reduced. For example in case of hypovolemia, the compensating mechanism of vascular constriction would maintain a normal MAP for some time, giving the wrong impression of normal organ perfusion. This can be illustrated by the following equation. (46, 51, 52)

Perfusion pressure = MAP – CVP = CO x SVR

However, since perfusion pressure is essential for tissue and organ perfusion, MAP should be maintained over a minimal threshold. The Surviving Sepsis Campaign recommends to target a value over 65 mmHg to ensure organ perfusion. High CVP can diminish perfusion pressure, hence it should not be neglected, particularly in ventilated patient's and those with low MAP. However, for simplicity MAP usually is assumed to be an approximate perfusion pressure in clinical settings. (4, 46, 51)

1.4.4 Capillary refill and core-peripheral temperature gradient

Both capillary refill and core to peripheral temperature gradient are quickly obtainable and safe parameters. Prolonged capillary refill and increased gradient of temperature are signs of centralization as blood flow is decreased in peripheral tissue and circulation focuses on vital organs. Studies investigating the association between these parameters and hemodynamic variables found that capillary refill time has a stronger correlation to them than the core-peripheral temperature

gradient. However, both parameters show limitations and should be interpreted with caution. For this reason, they may be helpful to get a rough impression on the circulatory situation in early phases of treatment, in advanced stages of intensive care other parameters should be favored to evaluate the circulatory situation. (53)

1.4.5 Central venous oxygen saturation

According to previous explanations, central venous oxygen saturation ($ScvO_2$) is directly dependant from VO_2. Low CO is correlated with decreased levels of $ScvO_2$, making this value a direct indicator for sufficient CO. Under physiological circumstances, an appropriate CO and a normal SaO_2 of 100% result in a $ScvO_2$ greater than 70%. Following current guidelines for septic shock, this parameter can be used to target therapy, in which case a value of more than 70% $ScvO_2$ should be aimed for. (46)

1.4.6 Carbon dioxide gap

In metabolic processes, carbon dioxide (CO_2) is one of the main products. From the site of production, it needs to be transferred to the lung for elimination. Since the blood stream is responsible for transport, CO_2 values are higher in the venous system directly before elimination than in the arterial system. This difference between $PvCO_2$ and $PaCO_2$ is called carbon dioxide gap ($PvaCO_2$) and is below 6mmHg under normal conditions. (54, 55)

In critically ill patients, some factors are able to influence this gap. CO is one parameter that affects the amount of CO_2 that can be eliminated in a certain time. Whilst a decrese of CO results in a higher $PvaCO_2$, increased CO can reduce this gap, it is therefore inversely related. Another possible reason for an increased $PvaCO_2$ is increased production of CO_2, which could be caused by microcirculatory dysfunction. To distinguish the cause for elevated $PvaCO_2$ levels, it is necessary to include $ScvO_2$ into consideration. Raised $PvaCO_2$ levels coming along with $ScvO_2$ values below 70% would indicate a decrease in CO. On the other hand, increased $PvaCO_2$ combined with a normal $ScvO_2$ would reflect microcirculatory dysfunction. (54, 55)

1.4.7 Lactate

During the process of glycolysis, oxygen is required for aerobic degradation of pyruvate to ATP, water (H_2O) and CO_2. In absence of oxygen, pyruvate will not enter the Krebs cycle and is anaerobically transformed into lactate. Therefore, this parameter can be used to detect tissue hypoxia and to monitor effectiveness of treatment. Although hyperlactatemia in critically ill patients is associated with hypoxia, mild hyperlactatemia in septic patients without cardiovascular failure needs to be interpreted with caution. The inflammatory mediators that are present in sepsis may lead to accelerated aerobic glycolysis with an overshoot of pyruvate and increased production of lactate despite adequate levels of oxygen. Increased levels of lactate can also be a result of impaired lactate clearence. In early phases of shock, hyperlactatemia is associated with hypoxia, while persisting hyperlactatemia is more often of nonhypoxic origin. (54, 56)

1.4.8 Pulmonary artery catheter

To obtain exact and reliable values of CO and various intravascular pressures, a pulmonary artery catheter with transpulmonal thermodilution can be set in place. This method is one of the most invasive monitoring techniques and, due to possible complications, should be reserved to those patients not responding to initial treatment. Since the pulmonary artery catheter was not put to use in any of our patients, this method will not be described in detail, yet should be mentioned here. (51, 54)

1.5 Objectives

Prevalence of septic shock in PICU has risen throughout the last years and despite new scientific findings mortality and morbidity in children with septic shock are still high. This is because research in septic shock is focused on adults and most current guidelines provide guidance for these patients only. Since there are major differences between adults and children in terms of pathophysiology and clinical presentation, guidelines for management of septic shock need to be developed for children specifically. For adult patients, new definitions of septic shock have been designed which include the SOFA score, whereas those for children still build upon the first definition of sepsis, using SIRS criteria for diagnosis.

Among adults, scientific findings allowed the development of new therapeutic approaches and in consequence survival rates improved. However, within the last few years research of pediatric septic shock started to increase. The aim of this study is to explore what changes in management of septic shock were made over the last 20 years and to evaluate their potential impact on the patient's outcome. Since septic shock is a highly complex disease with potential involvement of all organ systems, evaluation of all treatment would be too extensive for this study. For this reason, this work mainly focuses on support of the cardiovascular system and the immune system.

This study does not intend to provide updated guidelines for septic shock managenent in children, but to give an overview of recent changes in therapy and their possible effects on outcome. Furthermore, findings of this exploration may also reveal new scientific approaches for future research.

2 Materials and Methods

This retrospective study was designed as a monocentric, explorative data analysis, conducted at the PICU of the University Hospital of Graz and received approval of the ethics committee of the Medical University of Graz (ethics committee approval number 32-058 ex 19/20).

We screened all admissions to the PICU between January 1st, 2000 and September 30th, 2019 manually for the diagnoses of sepsis, septic shock, toxic shock syndrome, purpura fulminans and severe infection to find potential patients. Since we wanted to focus on those patients in serious condition, they had to meet the following inclusion criteria:

- Meet the criteria of pediatric septic shock
- Bacterial cause of sepsis
- Age between 0 and 19 years
- Catecholamine-dependent shock
- Mechanical ventilation
- Initial Acute Physiologic Score for Children (APSC) of 20 points or higher (57)

The APSC was designed to provide information on severity of illness and prognosis of critically ill patients. This score takes the following parameters into account: temperature, HR, BP, RR, need for ventilation, PaO_2/FiO_2, urine output, serum creatinine, bilirubin, serum-Na^+, Serum-K^+, blood glucose level, arterial pH, hematocrit, leukocyte count, thrombocyte count, GCS, severe chronic illness and prior surgery. (57)

Exclusion criterion was preexisting severe illness that could affect the patient's outcome in septic shock (e.g. leukemia, congenital heart disease) and hence falsify the findings of this study.

We identified 22 patients who met our criteria and split them into two groups for comparison. The first group included 12 patients, admitted between January 1st, 2000 and December 31st, 2009 (group 2000). The second group (group 2010) included 10 patients, admitted between January 1st, 2010 and September 30th, 2019. Of those patients, we collected data about various vital parameters, laboratory results and therapies they received in the first 7 days after admission (Table 3). We

used “Medocs”, the hospital’s electronic information system and the patient’s medical chart for data acquisition. Each patient received an ID and all data obtained was stored pseudonymously in a Microsoft Excel sheet.

Table 3: Collected parameters of included patients

Vital parameters	Heart rate [x/min] Blood pressure [mmHg] MAP [mmHg] Respiratory rate [x/min] Temperature (core and peripheral) [°C] Capillary refill time [s] SvO_2 [%] $PvaCO_2$ [mmHg] Initial GCS
Laboratory results	pH Lactate [mmol/l] CRP [mg/l] White blood cell count [G/l] Platelet count [G/l] Hemoglobin [g/dl] Activated partial thromboplastin time (aPTT) [s] Quick’s value [%] D-dimer [mg/l] Creatinine [mg/dl] Aspartate transaminase (AST) [U/l] Alanine transaminase (ALT) [U/l] Lactate dehydrogenase (LDH) [U/l] Bilirubin [mg/dl] NT-ProBNP [pg/ml] Troponin T [pg/ml]
Therapy	Duration of ventilation Fluids Packed red blood cells Platelet concentrate Buffer solution Catecholamines Hydrocortisone Diuretics Anticoagulants Thrombolysis Antithrombin Antibiotics

Both study populations were surveyed for structural equality and similarity of the initial cardiovascular situation to evaluate whether initial differences between the groups had a probable impact on the outcome or not. For initial evaluation of the state of the cardiovascular system, we investigated following initial parameters: APSC, HR, RR, BP, MAP, CVP, perfusion pressure, capillary refill time,

temperature, core-peripheral temperature gradient, SvO_2, $PvaCO_2$, lactate, CRP, leukocyte count.

Primary outcomes investigated in this study were hospital mortality as well as PICU length of stay. Both of them were considered separately as well as jointly since a high rate of hospital mortality might influence PICU length of stay. Furthermore, we defined following secondary outcomes:

- Length of intubation
- Length of catecholamine use
- Dosage of catecholamines
- Time to administration of fluids and antibiotics
- Fluids given within the initial 3 hours
- Administered drugs

Secondary outcomes did not only undergo comparative analysis between both groups, but were also screened for correlation to hospital mortality and PICU length of stay. However, length of intubation and length of catecholamine use were not included in this analysis because of questionable meaningfulness. Amongst administered drugs, we only included those substances into correlation analysis which showed statistical significance in comparison of our groups. The purpose of this analysis was to explore potential association between administered treatment and outcome.

Collecting data on therapy, we only considered the first 7 days after admission since latest research and guidelines have a strong focus on initial treatment. Furthermore, we considered this period as adequate for evaluation of treatment alterations that could effectively influence the patient's outcome. (4, 58)

Since various catecholamines and inotropic drugs with unequal potency were given, the vasoactive-inotropic score (VIS) was calculated for reliable comparison of catecholamine dosages. This score includes dopamine, dobutamine, epinephrine, norepinephrine, milrinone and vasopressin and weights them differently, depending on the agent's potency. Different substances of corticosteroids were in use as well and for this reason, we calculated the hydrocortisone equivalent dose to facilitate comparability of doses given. (59, 60)

The statistical analysis was performed using IBM SPSS Statistics 26. For presentation of our continuously measured data, we chose either mean and standard deviation (SD) or median and interquartile range (IQR), depending on whether or not the values of the parameter in question were normally distributed. Normal distribution of continuously measured parameters was examined with the Kolmogorov-Smirnov test and for comparison between the two groups we used either independent t-test or Mann-Whitney U test. Categorical data are presented as frequencies and percentages. This analysis was conducted with chi-squared test and Fisher's exact test. The p-value threshold for statiscial significance was set to $p<0,05$. For correlation analysis, we calculated the Phi coefficient for dichotomous data, the Eta coefficient for combinations of categorical and continuous data and the Spearman-Rho correlation coefficient for continous data.

3 Results

3.1 Study population

This study included 22 patients admitted to PICU throughout the period from 01/01/2000 to 09/30/2019. Of those patients, 8 were male (36,4%) and 14 were female (63,6%). Group 2000 included 3 male (25%) and 9 female (75%) patients, while group 2010 included 5 male (50%) and 5 female (50%) patients (p=0,378; Figure 1).

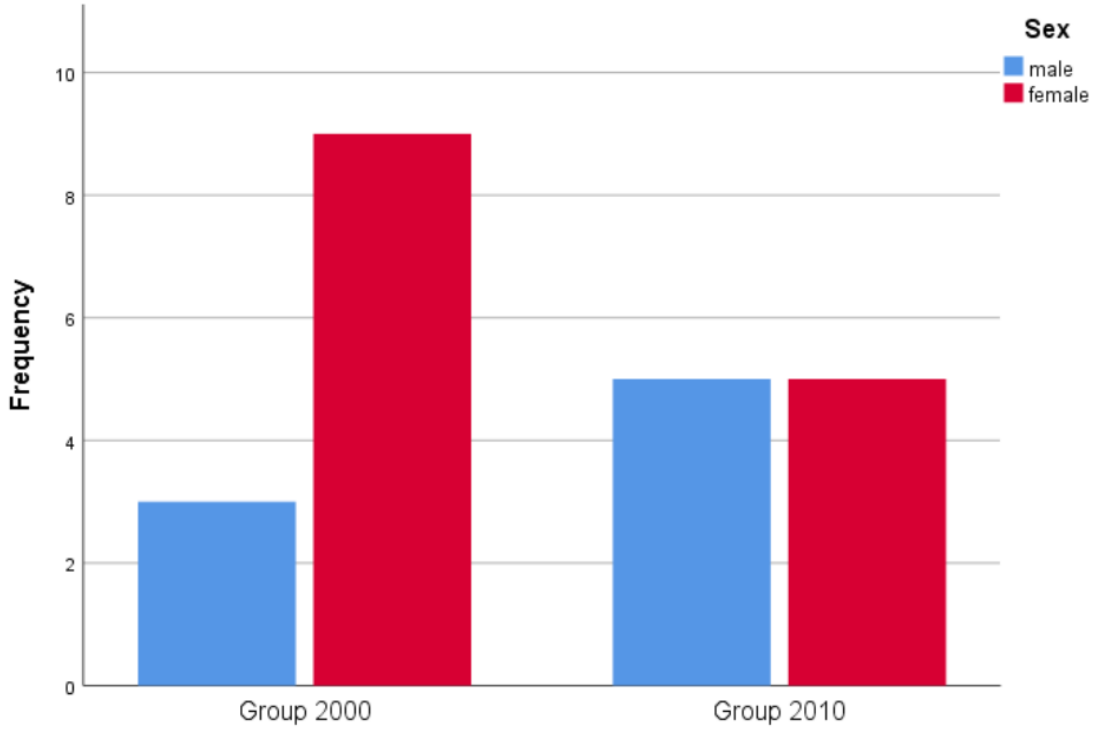

Figure 1: Gender distribution in both groups

Median age of our study population was 2,9 years (IQR 0,2-5,6) with a range from 0 to 17 years. Looking at the age split by groups, we found a median age of 2,9 years (IQR 1,1-6,6) in group 2000 and a median age of 1,6 years (IQR 0,1-4,7; p=0,346) in group 2010 (Figure 2).

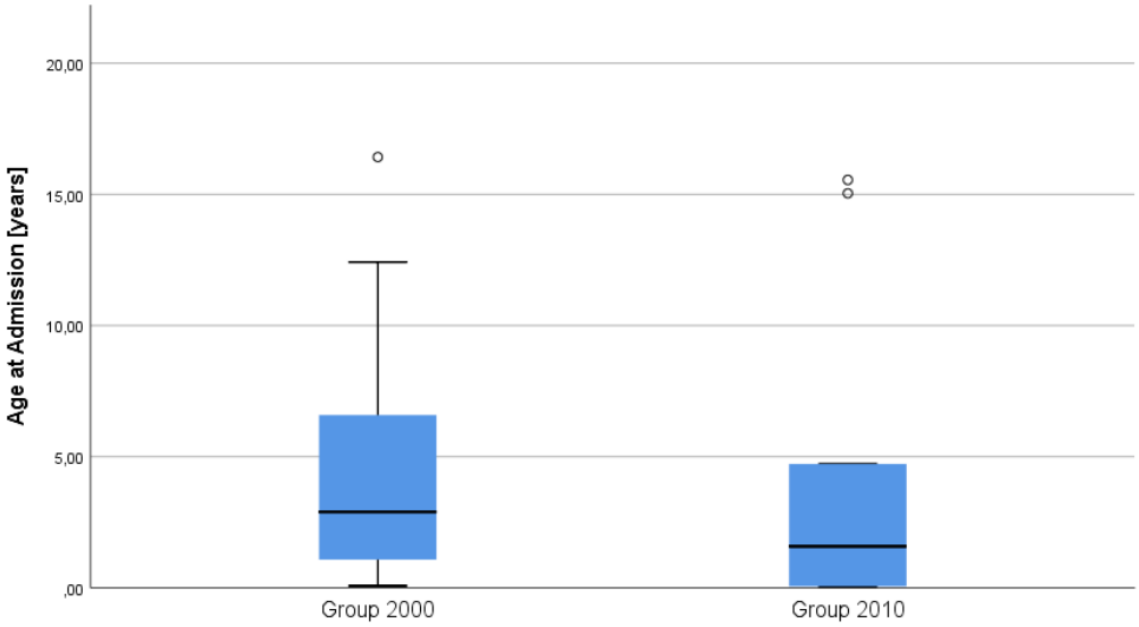

Figure 2: Age distribution in both groups

We identified 5 different bacteria as cause of sepsis in our patients, which were Neisseria meningitidis, Staphylococcus aureus, Streptococcus pneumonia and Streptococci of group A and B. The frequency of cases per pathogen in our patients is presented in Figure 3.

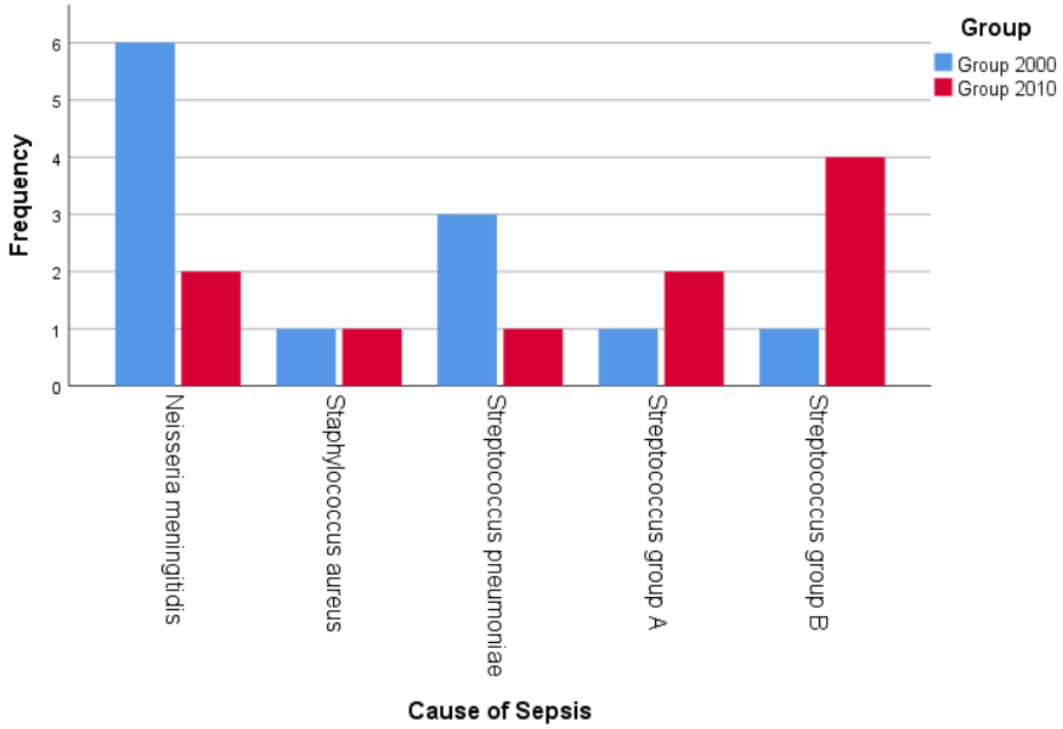

Figure 3: Frequency of different bacterial causes for sepsis

3.2 Initial state of the cardiovascular system

We compared various parameters to assess the patient's initial condition with focus on the cardiovascular system (Table 4). APSC was equal in both groups with a value of 25 (IQR 22-28 in group 2000; IQR 23-30 in group 2010; p=0,674). HR also was similar in both groups with 165/minute (IQR 140-188 in group 2000; IQR 120-190 in group 2010; p=0,821). We found a RR of 59/minute (SD ±22,8) in group 2000 and a RR of 46/minute (SD ±14,3; p=0,151) in group 2010. BP and MAP both were lower in group 2000 with a BP of 76,4 mmHg (SD ±29,78) and a MAP of 53,4 mmHg (SD ±25,93) compared to group 2010 with a BP of 86,5 mmHg (SD ±32,75; p=0,458) and a MAP of 65,4 mmHg (SD ±26,3; p=0,296). CVP accounted for 9 mmHg (IQR 7-11) in group 2000 and 6 mmHg (IQR 5-8; p=0,152) in group 2010. In concordance to these values, we found perfusion pressures of 43,4 mmHg (SD ±23,9) in group 2000 and of 57,5 mmHg (SD ±28,65; p=0,325) in group 2010. Capillary refill time accounted for 5 seconds (IQR 3,5-6,0) in group 2000 and 3,3 seconds (IQR 3,0-4,0; p=0,03) in group 2010. The initial temperature was 38,4°C (SD ±1,89) in group 2000 and 37,0°C (SD ±2,55; p=0,172) in group 2010. The core-peripheral temperature gradient was higher in group 2000 as well with 7,2°C (SD ±3,13) compared to 5,5°C (SD ±3,03; p=0,26) in group 2010. The median SvO_2 value at presentation was 68,0% (IQR 32,0-74,0) in group 2000 and 74,7% (IQR 61,4-82,7; p=0,165) in group 2010. The comparison of $PvaCO_2$ showed values of 4,25 mmHg (IQR 2,55-7,95) in group 2000 and 9,8 mmHg (IQR 2,8-14,5; p=0,573) in group 2010. Lactate accounted for 8,47 mmol/l (SD ±5,58) in group 2000 and for 7,57 mmol/l (SD ±4,87; p=0,7) in group 2010.

3.3 Hospital mortality and PICU length of stay

Overall, 9 out of 22 patients did not survive the septic shock after admission to the PICU. In the group of patients who were admitted between 2000 and 2009, 7 out of 12 died, resulting in a mortality rate of 58,3% for this period (Figure 4). Of those patients admitted between 2010 and 2019, 2 out of 10 patients died, resulting in a mortality rate of 20% (p=0,099). Of the 9 patients who did not survive, 6 died on the first day at PICU and none of them survived more than 8 days.

Median PICU length of stay was 6 days (IQR 1-13) in group 2000 and 10 days (IQR 5-14; p=0,346) in group 2010 (Figure 5). Since most patients who did not survive died at the first day, we also compared PICU length of stay among the surviving

patients (Figure 6). Survivors of group 2000 had a median PICU length of stay of 13 days (IQR 13-20) and those of group 2010 one of 11,5 days (IQR 9-17,5; p=0,284).

Table 4: Comparative analysis of the initial cardiovascular situation

	Group 2000	Group 2010	P-value
APSC	25 (IQR 22-28)	25 (IQR 23-30)	0,674
HR [x/min]	165 (IQR 140-188)	165 (IQR 120-190)	0,821
RR [x/min]	59 (SD ±22,8)	46 (SD ±14,3)	0,151
BP [mmHg]	76,4 (SD ±29,78)	86,5 (SD ±32,75)	0,458
MAP [mmHg]	53,4 (SD ±25,93)	65,4 (SD ±26,30)	0,296
CVP [mmHg]	9 (IQR 7-11)	6 (IQR 5-8)	0,152
Perfusion pressure [mmHg]	43,4 (SD ±23,9)	57,5 (SD ±28,65)	0,325
Capillary refill time [s]	5 (IQR 3,5-6,0)	3,3 (IQR 3,0-4,0)	**0,03**
Temperature [°C]	38,4 (SD ±1,89)	37,0 (SD ±2,55)	0,172
Core-peripheral temperature gradient [°C]	7,2 (SD ±3,13)	5,5 (SD ±3,03)	0,26
SvO_2 [%]	68,0 (IQR 32,0-74,0)	74,7 (IQR 61,4-82,7)	0,165
$PvaCO_2$ [mmHg]	4,25 (IQR 2,55-7,95)	9,8 (IQR 2,8-14,5)	0,573
Lactate [mmol/l]	8,47 (SD ±5,58)	7,57 (SD ±4,87)	0,7

All parameters in this table were measured at admission and are either presented as mean with standard deviation (SD) or as median with interquartile range (IQR)

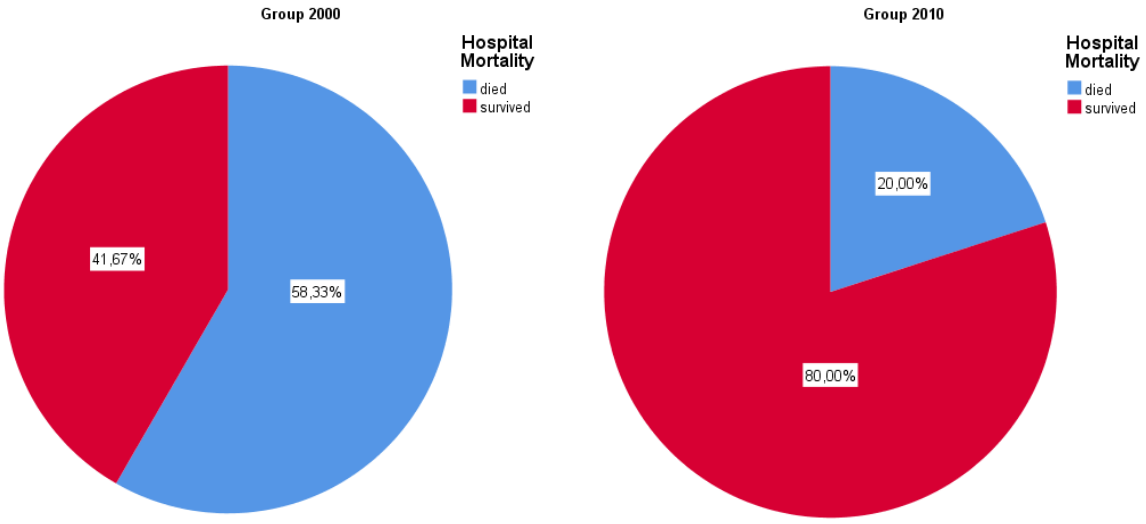

Figure 4: Hospital mortality in group 2000 and group 2010

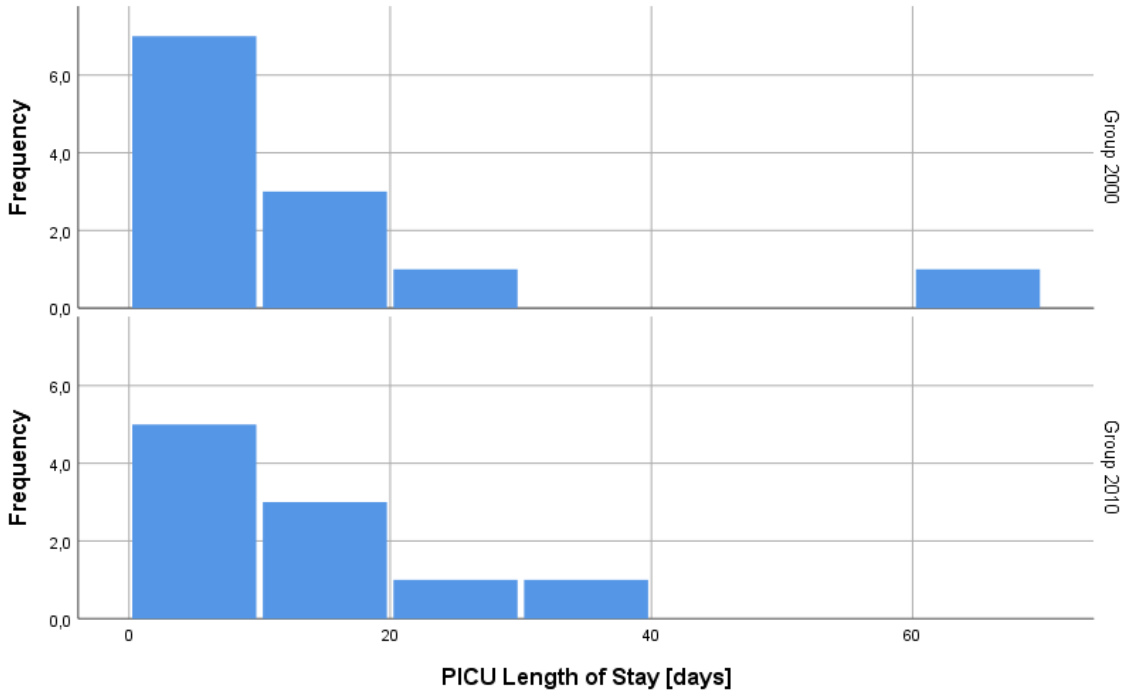

Figure 5: Distribution of PICU length of stay, seperated by group

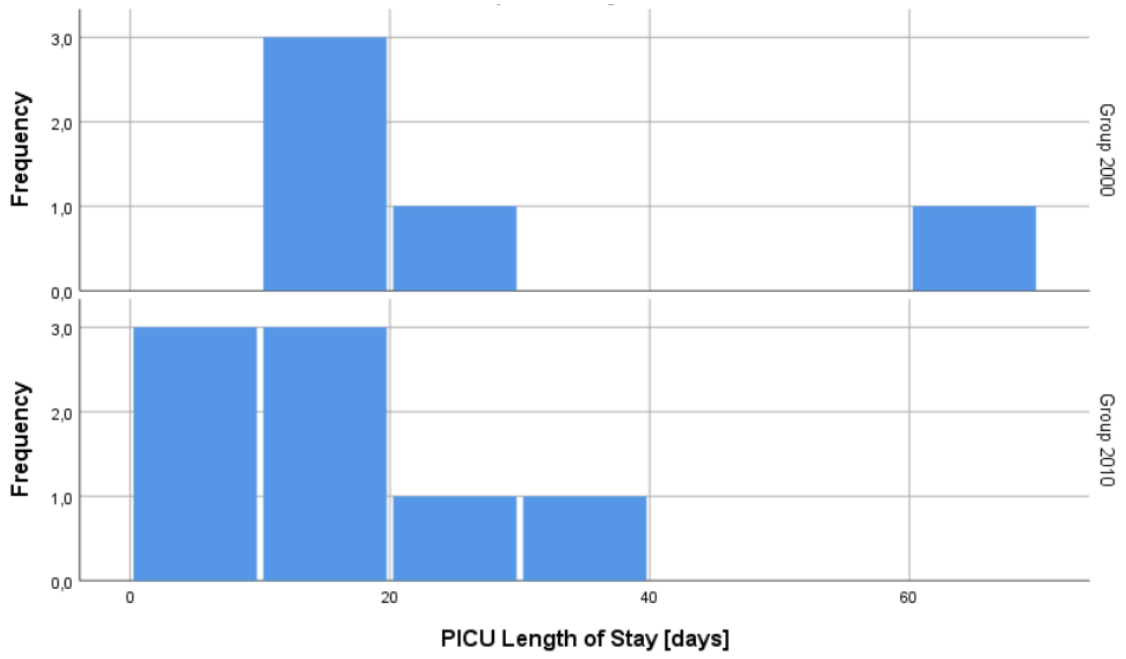

Figure 6: PICU length of stay in dependence of group and hospital mortality (only survivors included)

3.4 Secondary outcomes

3.4.1 Length of intubation

Patients of both groups were intubated for 4 days (IQR 1-6,5 in group 2000; IQR 3-5 in group 2010; p=0,539). This outcome was also investigated a second time among survivors only. Length of intubation among this subgroup was 5 days (IQR 4-10) in group 2000 and 4,5 days (IQR 4-6; p=0,622) in group 2010.

3.4.2 Length of catecholamine use

Catecholamines were used for 3,5 days (IQR 1-6) in group 2000 and for 4 days (IQR 3-5; p=0,346) in group 2010. Again, we investigated length of catecholamine use among survivors only which accounted for 6 days (IQR 6-7) among those who survived in group 2000 and for 4,5 days (IQR 4-6; p=0,354) among those in group 2010. Since we only obtained informations on treatment given throughout the first 7 days after admission, we did not explore duration of catecholamine administration beyond this time. However, only 2 patients received catecholamines for more than 7 days, one of each group. Both of them were included in this analysis with 7 days of catecholamine treatment.

3.4.3 Dosage of catecholamines

Patients in both groups received a number of different catecholamines and vasoactive agents which are characterized by different potencies. To facilitate comparison despite multiple different substances and dosages, we calculated the VIS at four points in time, which were at admission, after 12, 24 and 48 hours (Table 5). Although $VIS_{initial}$, VIS_{12}, VIS_{24} and VIS_{48} were all higher in group 2000 than in group 2010, we could not show any statistically significant differences between the two groups (p>0,05).

Table 5: Vasoactive-inotropic score (VIS) at 4 points in time

	Group 2000	Group 2010	p-value
$VIS_{initial}$	30 (IQR 0-78)	1,25 (IQR 0-21)	0,085
VIS_{12}	39,3 (SD ±28,13)	22,1 (SD ±15,1)	0,122
VIS_{24}	47,4 (SD ±41,25)	23,3 (SD ±11,3)	0,179
VIS_{48}	24,4 (SD ±16,22)	15,6 (SD ±13,02)	0,247

$VIS_{initial}$ is indicated as median with IQR; VIS_{12}, VIS_{24} and VIS_{48} are indicated as mean with standard deviation (SD)

3.4.4 Time to administration of fluids and antibiotics

Investigation of the time elapsed between admission and administration of fluids showed a mean time of 0 hours (IQR 0-0,5 in group 2000; IQR 0-0 in group 2010; p=0,346) in both groups (Figure 7). Regarding the time elapsed until administration of antibiotics, we found a decrease from 0,5 hours (IQR 0-1) in group 2000 to 0,25 hours (IQR 0-1; p=0,739) in group 2010 (Figure 8).

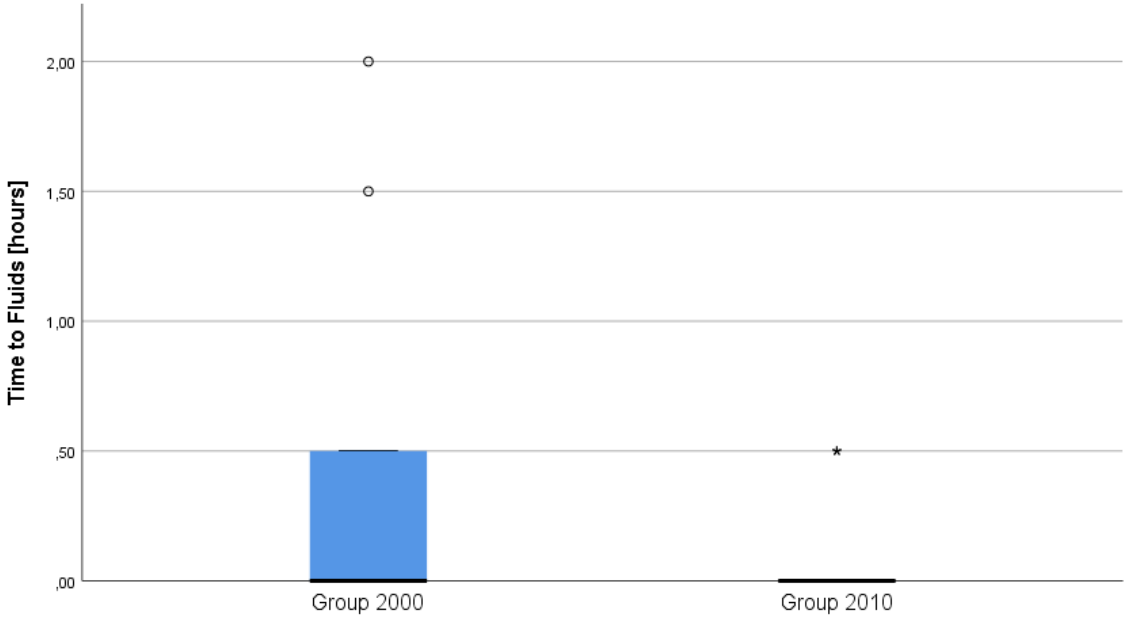

Figure 7: Time elapsed until first administration of fluids

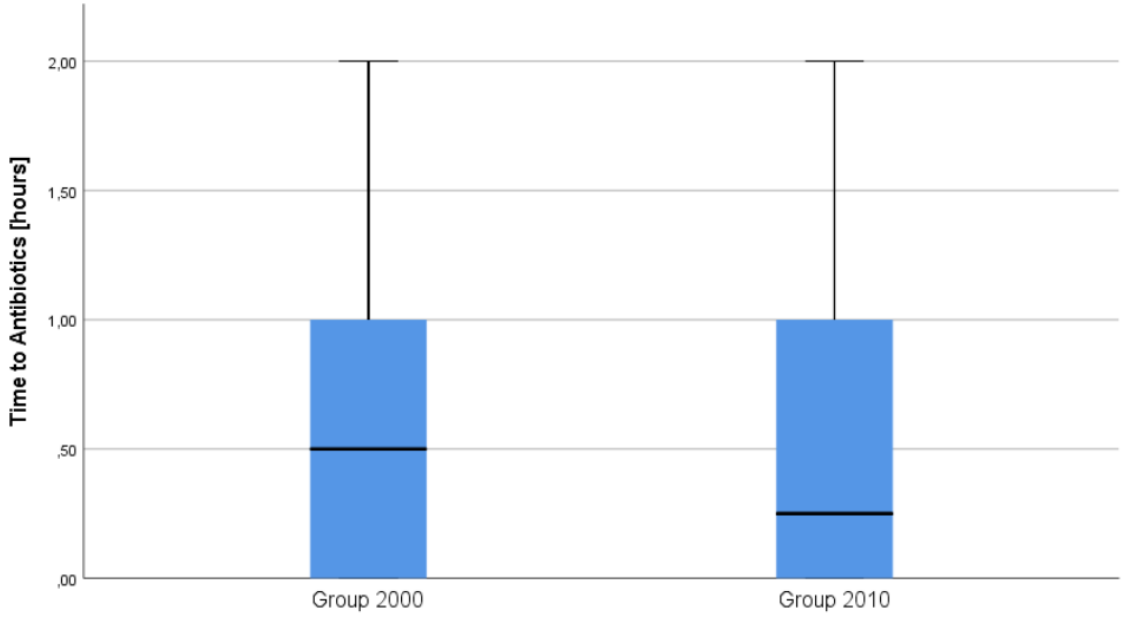

Figure 8: Time elapsed until first administration of antibiotics

3.4.5 Fluids given within the initial 3 hours

Patients in group 2000 averagely received 39,67 ml/kg (SD ±30,584) of fluids within the first 3 hours after admission (Figure 9). In group 2010, this value accounted for 56,62 ml/kg (SD ±35,554; p=0,243). Our calculation of this initial bolus of fluids included crystalloids as well as colloids. We also compared initial rates of crystalloids and colloids separately (Figure 10). As result we found initial crystalloid rates of 2,49 ml/kg/h (IQR 1,62-12,66) in group 2000 and of 4,72 ml/kg/h (IQR 2,56-6,23: p=0,872) in group 2010. Initial rates of colloids were 3,35 ml/kg/h (IQR 0-4,69) in group 2000 and 1,12 ml/kg/h (IQR 0-2,92; p=0,314) in group 2010.

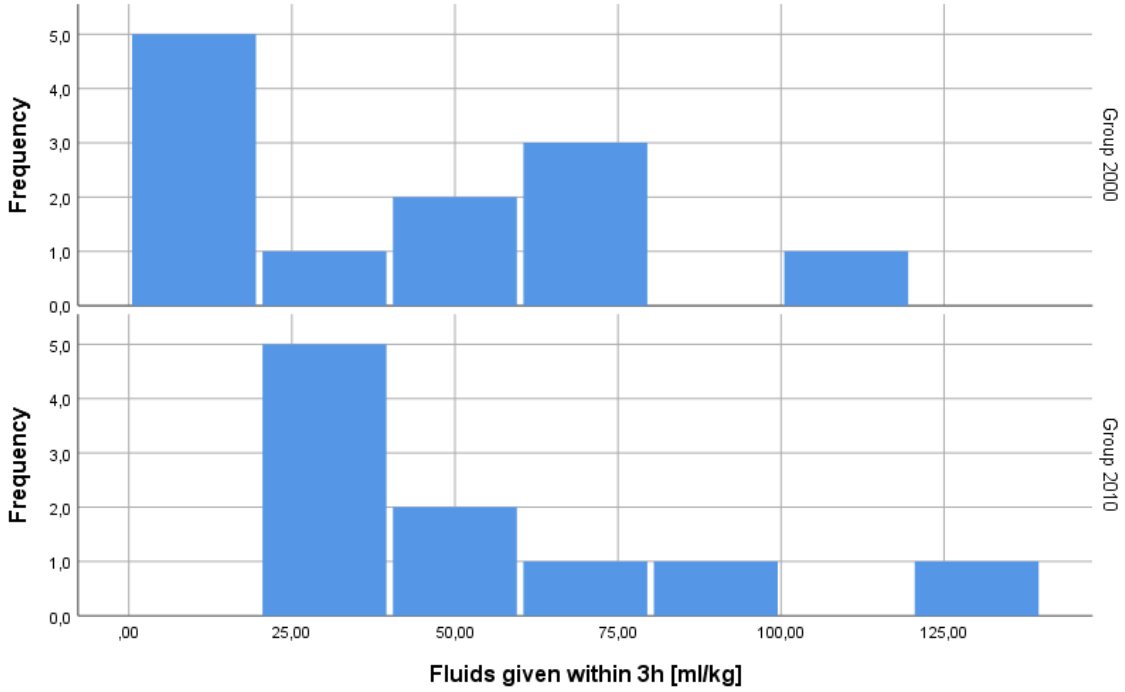

Figure 9: Amount of fluids given during the initial 3 hours after admission

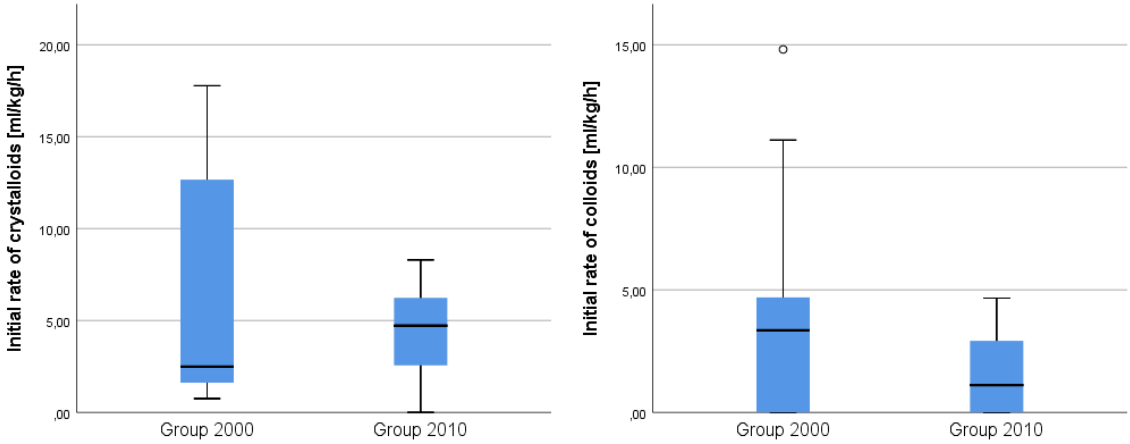

Figure 10: Initial rates of crystalloids (left) and colloids (right)

3.4.6 Administered drugs

Investigating which substances were given, we focused on intravenously administered substances affecting the cardiovascular system, coagulation, acid-base balance and inflammatory response (Table 6). Since all 22 patients received crystalloid fluids, this treatment is not listed in Table 6. Most patients received colloids as well, 75% (n=9) of group 2000 and 100% (n=10; p=0,221) of group 2010. Administration rates of packed red blood cells accounted for 50% (n=6) in group 2000 and for 70% (n=7; p=0,415) in group 2010. Platelet concentrate was given to 33,3% (n=4) in group 2000 and to 40% (n=4; p=1,000) in group 2010.

Among those drugs that specifically affect the cardiovascular system, we found statistically significant difference between the two groups. Epinephrine was administered to 83,3% (n=10) of group 2000 and to 20% (n=2; p=0,008) of group 2010. For dopamine, we found rates of 66,7% (n=8) in group 2000 and 10% (n=1; p=0,011) in group 2010. In contrast to this findings, norepinephrine was given to 41,7% (n=5) of group 2000 and to 90% (n=90; p=0,031) of group 2010. In this group of substances, no statistical significance could be shown for dobutamine (16,7%, n=2 in group 2000; 40%, n=4 in group 2010; p=0,348), phenylephrine (0%, n=0 in group 2000; 30%, n=3 in group 2010; p=0,078), vasopressin (8,3%, n=1 in group 2000; 30%, n=3 in group 2010; p=0,293), levosimendan (8,3%, n=1 in group 2000; 10%, n=1 in group 2010; p=1,000), milrinone (25%, n=3 in group 2000; 30%, n=3 in group 2010; p=1,000) and clonidine (16,7%, n=2 in group 2000; 40%, n=4 in group 2010; p=0,348).

Corticosteroids were used in both groups as well, 66,7% (n=8) of group 2000 and 80% (n=8; p=0,646) of group 2010 received at least one of these substances. We also calculated the hydrocortisone equivalent dosages for all patients and compared two doses that were given: the initial daily dose and the highest daily dose (Figure 11). The initial dose accounted for 0 mg/kg/d (IQR 0-14,115) in group 2000 and for 2 mg/kg/d (IQR 0-7,628; p=0,923) in group 2010. The highest hydrocortisone equivalent dose given was 4,045 mg/kg/d (IQR 0-16,949) in group 2000 and 11,834 mg/kg/d (IQR 4,0-17,002; p=0,381) in group 2010. We investigated length of hydrocortisone use as well which was 1 day (IQR 0-6) in group 2000 and 5,5 days (IQR 2-7; p=0,203) in group 2010. Since hospital mortality might have had an influence on this parameter as well, we also compared duration of hydrocortisone

use amongst survivors only. The result of this comparison was a duration of 7 days (IQR 0-7) in group 2000 and of 6,5 days (IQR 5-7; p=1,000) among those of group 2010.

Buffer solution, including sodium bicarbonate and TRIS, was administered to 91,7% (n=11) of patients in group 2000 and to 60% (n=6; p=0,135) of patients in group 2010. 66,7% (n=8) of group 2000 and 90% (n=9; p=0,323) of group 2010 received diruretics.

In group 2000, heparin was given to 66,7% (n=8) and to 80% (n=8; p=0,646) in group 2010. Antithrombin (AT III) was used in 50% (n=6) of group 2000's cases and in 60% (n=6; p=0,691) of those in group 2010. Thrombolysis with alteplase was conducted 2 times (16,7%) in group 2000 whereas no patient in group 2010 (0%; p=0,481) received this treatment.

Table 6: Administered therapy in both groups

	Group 2000		**Group 2010**		**p-value**
	Frequency	*%*	*Frequency*	*%*	
Colloids given	9	75,0%	10	100,0%	0,221
Packed red blood cells given	6	50,0%	7	70,0%	0,415
Platelet concentrate given	4	33,3%	4	40,0%	1
Epinephrine given	10	83,3%	2	20,0%	**0,008**
Dopamine given	8	66,7%	1	10,0%	**0,011**
Dobutamine given	2	16,7%	4	40,0%	0,348
Norepinephrine given	5	41,7%	9	90,0%	**0,031**
Phenylephrine given	0	0,0%	3	30,0%	0,078
Vasopressin given	1	8,3%	3	30,0%	0,293
Levosimendan given	1	8,3%	1	10,0%	1
Milrinone given	3	25,0%	3	30,0%	1
Clonidine given	2	16,7%	4	40,0%	0,348
Hydrocortisone given	8	66,7%	8	80,0%	0,646
Buffer Solution given	11	91,7%	6	60,0%	0,135
Diuretics given	8	66,7%	9	90,0%	0,323
Heparin given	8	66,7%	8	80,0%	0,646
Antithrombin given	6	50,0%	6	60,0%	0,691
Alteplase given	2	16,7%	0	0,0%	0,481

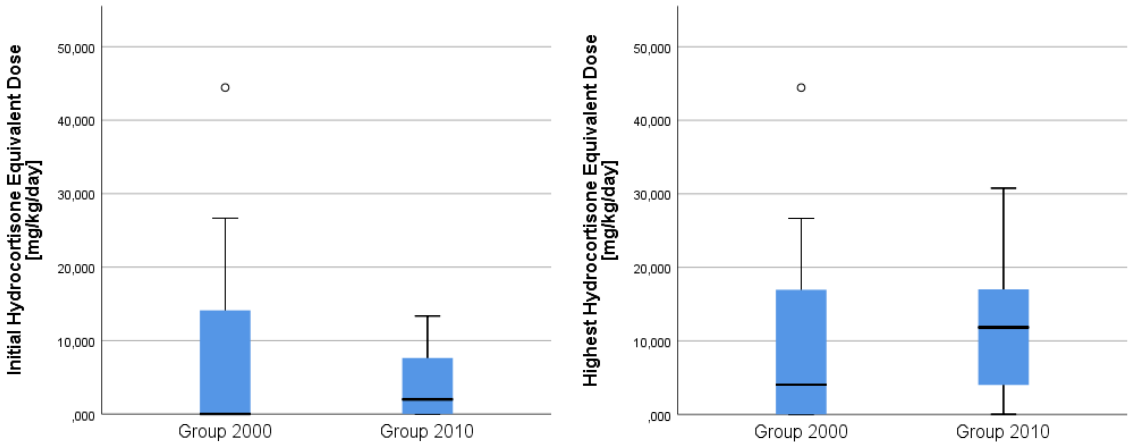

Figure 11: Initial (left) and highest (right) hydrocortisone equivalent dosages given to patients

Furthermore, we also investigated the number of antibiotics that were administered, which antibiotics were used and if there were considerable alterations between both groups. In terms of number of antibiotics given, we found, that patients in group 2000 averagely received 1,6 (SD ±1,17) different antibiotics, whereas patients in group 2010 received 3 (SD ±1,41: p=0,018) different antibiotics (Figure 12).

Being the most commonly used antibiotic in group 2000, ceftriaxone was given to 83,3% (n=10) of this group's patients. All other antibiotics listed in Table 7 were merely given to individual patients or none at all among group 2000, except for ampicillin, which was given to 25% (n=3). In group 2010, we found more variability of used substances. Most frequently used antibiotics in group 2010 were ceftriaxone (given to 50%; n=5), ampicillin (given to 50%; n=5), cefotaxime (given to 40%; n=4), cefuroxime (given to 30%; n=3), meropenem (given to 30%; n=3) and vancomycin (given to 30%; n=3). Comparative analysis showed one statistically significant difference between both groups, which was administration of cefotaxime (0% in group 2000; 40% in group 2010; p=0,029).

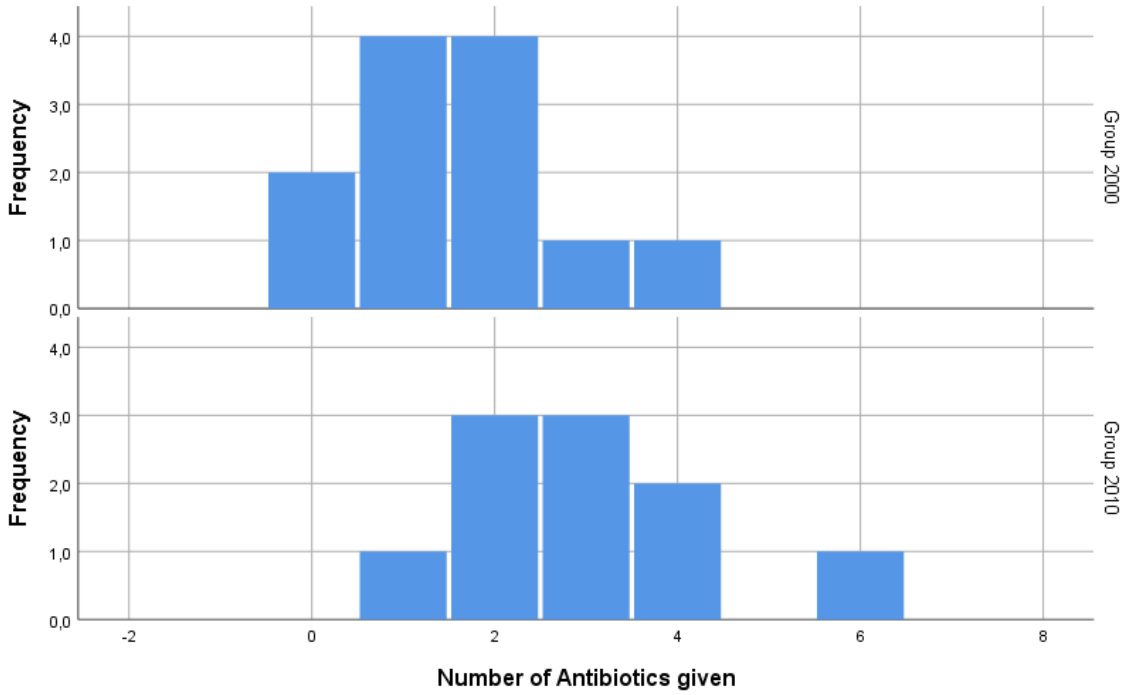

Figure 12: Amount of different antibiotic substances administered

Table 7: Administered antibiotic drugs

	Group 2000		Group 2010		p-value
	Frequency	*%*	*Frequency*	*%*	
Cefuroxime given	1	8,30%	3	30,00%	0,293
Ceftriaxone given	10	83,30%	5	50,00%	0,113
Cefotaxime given	0	0,00%	4	40,00%	**0,029**
Ampicillin given	3	25,00%	5	50,00%	0,379
Piperacillin/Tazobactam given	0	0,00%	1	10,00%	0,455
Flucloxacillin given	1	8,30%	0	0,00%	1
Meropenem given	1	8,30%	3	30,00%	0,293
Imipenem given	0	0,00%	1	10,00%	0,455
Gentamicin given	0	0,00%	1	10,00%	0,455
Clindamycin given	1	8,30%	2	20,00%	0,571
Vancomycin given	0	0,00%	3	30,00%	0,078
Metronidazole given	1	8,30%	0	0,00%	1
Fosfomycin given	1	8,30%	0	0,00%	1
Linezolid given	0	0,00%	1	10,00%	0,455
Rifampicin given	0	0,00%	1	10,00%	0,455

3.5 Correlation

To investigate correlation between catecholamine dosages and hospital mortality as well as PICU length of stay, we used the previously calculated VIS again (Table 5). Analysis of catecholamine dosage and hospital mortality did not show any significant correlation (Table 8). $VIS_{initial}$ (η=0,388; p=0,082) and VIS_{12} (η=0,417; p=0,096) however, did show a moderate correlation with this outcome. Besides, VIS_{12} and PICU length of stay did correlate moderately and significantly (ρ=0,532; p=0,028), whereas $VIS_{initial}$ (ρ=-0,413; p=0,063) and VIS_{24} showed moderate but non-significant correlation with PICU length of stay. While higher $VIS_{initial}$ was associated with greater mortality rates and shorter PICU length of stay, higher VIS_{12} was associated with lower mortality and longer PICU length of stay. Higher VIS_{24} merely was associated with longer PICU length of stay.

Time to administration of fuids as well as the amount of fluids given within 3 hours did not show any appreciable correlations, neither with hospital mortality nor with PICU length of stay. Time to administration of antibiotics showed a non-significant correlation with hospital mortality (η=0,309; p=0,186) and PICU length of stay (ρ=-0,325; p=0,162). Longer time to administration was associated weakly with greater rates of mortality and shorter PICU length of stay.

Evaluating correlation between substances administered and hospital mortality, we found one strong and significant correlation, which was norepinephrine (φ=0,716; p=0,001). While cefotaxime also showed some moderate, not statistically significant correlation (φ=0,392; p=0,066), epinephrine and dopamine did not. Administration of norepinephrine and cefotaxime both were associated with survival of patients. Norepinephrine significantly correlated with PICU length of stay as well (η=0,483; p=0,023). Administration of norepinephrine was associated moderately with longer PICU length of stay. Epinephrine and dopamine did at most correlate weakly or not at all with both outcomes and cefotaxime did not correlate with PICU length of stay either.

The number of different antibiotics did not show any significant correlation with both outcomes. Nevertheless, we found moderate correlation with hospital mortality (η=0,396; p=0,068) and PICU length of stay (η=0,396; p=0,068). Greater number of administered antibiotics was associated with survival and longer PICU length of stay.

Table 8: Correlation of treatment parameters and outcome

	Hospital mortality		PICU length of stay	
	correlation	*p-value*	*correlation*	*p-value*
$VIS_{initial}$	η =0,388	0,082	ρ =-0,413	0,063
VIS_{12}	η =0,417	0,096	**ρ =0,532**	**0,028**
VIS_{24}	η =0,218	0,418	ρ =0,419	0,107
VIS_{48}	η =0,153	0,572	ρ =0,249	0,352
Time to administration of fluids	η =0,008	0,971	ρ =-0,038	0,868
Time to administration of antibiotics	η =0,309	0,186	ρ =-0,325	0,162
Amount of fluids given within 3 hours	η =0,14	0,534	ρ =-0,229	0,306
Epinephrine given	φ =0,203	0,342	η =0,242	0,278
Dopamine given	φ =0,248	0,245	η =0,027	0,903
Norepinephrine given	**φ =0,716**	**0,001**	**η =0,483**	**0,023**
Number of antibiotics	η =0,396	0,068	η =0,396	0,068
Cefotaxime given	φ =0,392	0,066	η =0,019	0,934

η = Eta coefficient, φ = Phi coefficient, ρ = Spearman-Rho correlation coefficient

4 Discussion

Research on sepsis and septic shock has increased over the last years, leading to better comprehension of this deadly disease and improvement of outcome. In 2002, the Surviving Sepsis Campaign (SSC) was launched with the objective to reduce mortality and morbidity. Their widely known guideline, published in 2004, became the base for further research on sepsis and septic shock. This international collaboration of scientists continued to release updated guidelines every few years, taking recent scientific findings into account and pursuing their goal to improve mortality and morbidity. Until 2020 however, when they published the first pediatric guidelines for treatment of septic shock, these guidelines were developed for adults primarily and only included some considerations concerning treatment of children. The first guidelines for hemodynamic support of septic shock in children were published in 2002 by the American College of Critical Care Medicine (ACCM) which were also updated in the following years with the most recent update published in 2017. These guidelines form the main context for the discussion of our results. (4, 9, 46, 61–65)

Our study populations did differ slightly in distribution of gender and age but we did not find any significant difference between the two groups concerning these parameters. For this reason, structural similarity of both groups can be assumed.

As stated in the introduction, normal values for children vary in dependence of age. For the evaluation of the initial situation of the cardiovascular system, we refer to normal values of toddlers since median ages of our groups were 2,9 and 1,6 years, even though all age groups are represented. The HR of 165/minute in both groups was higher than the threshold of 140/minute that was defined by Goldstein et al. for detection of SIRS amongst patients of this age. We also found RR and BP values meeting pediatric SIRS criteria, whereas MAP showed values higher than 5th percentile for the mean age of both groups and therefore would indicate normal cardiovascular function. Due to the limitations of CVP and its obsolete use in terms of assessing the cardiovascular state without considering its temporal progression, it is of less interest when evaluating the initial condition of the patient. Nevertheless, this parameter is required to calculate the perfusion pressure. Perfusion pressure was below the recommended value of 65 mmHg in both groups and worse in group

2000. Capillary refill time was prolonged in both groups and both of them presented with gradients in core-peripheral temperature exceeding 3°C that were defined as threshold for cardiovascular dysfunction. Albeit temperature was slightly elevated in group 2000, it did not meet SIRS criteria in any group. SvO_2 marginally fell below the threshold of 70% in group 2000, whereas it was only just above in group 2010. In contrast to that, the carbon dioxide gap was normal in group 2000 and increased in group 2010. Lactate values of both groups showed extremely elevated levels, indicating tissue hypoperfusion and potential adverse outcome. The comparison of our groups showed slightly worse values for most hemodynamic parameters in group 2000. However, these differences did not show significance, except for capillary refill time. This parameter however, should only be used to get a rough first impression of the patient. For this reason, patients of group 2000 might have been in a slightly worse shape at admission than those of group 2010. This could be due to raised awareness for sepsis and septic shock among physicians and the resulting earlier recognition. APSC, a score to quantify severity of illness, however has been equal in both groups. Therefore, we assumed severity of illness similar in both groups without strong impact on the outcome, although the microcirculatory situation might have been marginally worse in group 2000. (5, 53, 64, 66)

Our primary outcomes were hospital mortality as well as PICU length of stay. Mortality is the most commonly investigated outcome in studies of septic shock and hence frequently reported. Most studies released in the time between 2000 and 2020 stated mortality rates for severe sepsis and septic shock of 6% to 27,8%. The mortality rate we found among patients admitted to PICU between 2000 and 2009 showed a great alteration to that with a mortality of 58,3%. Among patients admitted between 2010 and 2019 on the other hand we observed a rate within this range. Some studies also investigated mortality trends over time and reported a decrease of 6,9-10,9% over a period of 8 years. Our study found a mortality reduction of 38,3% over a period of 20 years. This observed trend in mortality is tremendous, even though we could not prove significance for this outcome. (10, 11, 13, 14, 18, 67, 68)

A less frequently, yet sometimes reported outcome is PICU length of stay. Balamuth et al. and Ruth et al. reported PICU length of stay of 5 days and 7 days, whereas this study found a progression from 6 days to 10 days. Development of new guidelines for septic shock led to improvement of outcomes, including reduction of

PICU length of stay and we also expected to find reduced PICU length of stay in group 2010. As mentioned above, we also found inequal rates of mortality and most patients among nonsurvivors died on the first day after admission. Given this background, we also explored this outcome among survivors only and found a decrease from 13 days to 11,5 days, which is concordant with other study's reports. (11, 13, 69)

The aim of exploring length of intubation and length of catecholamine use was to find potential trends of these parameters, since improvement of therapy might also influence the duration of requirement for these interventions. However, we were unable to indentify any significant divergence over time, neither comparing all patients nor survivors only in both groups.

Regarding dosage of catecholamine, we also were unable find any significant differences. Nevertheless, alterations between both groups were apparent. The VIS was greater in group 2000 at all 4 points in time we analized. This might indicate either a trend towards a more restricted use of catecholamines or, more likely, a worse circulatory situation in group 2000. The highest initial scores could be found among those patients that did not survive the day of admission, additionally pointing towards increased need of catecholamines in those patients in worse cardiovascular shape. This finding however is no surprise since all guidelines recommend escalation of catecholamine dosages in case of refractory shock. (12, 46, 64)

Recently published guidelines including the SSC guidelines for children as well as the ACCM guidelines recommend aggressive early management of septic shock. One of their recommendations is rapid administration of fluids. Both of our groups received immediate fluid management in accordance to these guidelines. Early administration of antibiotics within 1 hour after administration is another recommendation for early management. With a mean time elapsed of 0,5 and 0,25 hours, both groups followed this recommendation as well. (46, 64, 70)

The amount of fluids required to achive stable circulation is quite individual. Therefore, recent guidelines do not recommend specific volume rates but recommend upper limits to avoid overloading of the cardiovascular system. Current recommendations for this upper limit are 40-60ml/kg fluids within 1 hour. Since we evaluated the amount given within 3 hours, comparability to guidelines is not entirely

given. Nevertheless, with values of 39,67 and 56,62 ml/kg, fluid administration did not exceed this advised limit in our groups. Although this alteration was not significant, patients of group 2010 received more fluids than those of group 2000. Due to the slightly worse cardiovascular situation in group 2000, we would have expected the opposite. Furthermore, we could observe a slight, non-significant shift from higher rates of colloids towards higher crystalloid rates. This complies with the latest guidelines, which recommend to preferably use crystalloids for initial therapy. (46, 64)

The evaluation of number of patients treated with colloids, packed red blood cells or platelet transfusion did not show any significant differences between our groups. Furthermore, indications for packed red blood cells and platelet transfusion need to be examined individually for every patient. (64)

Among those substances that affect the cardiovascular system, we found some significant differences between our groups. The goal of maintaining BP was achieved with different substances in our groups while recommendations for this goal also changed over time. Whilst the majority of group 2000 received epinephrine and dopamine, only few of group 2010's patients were treated with these. Norepinephrine on the other hand was significantly more often administered in group 2010. The ACCM guidelines of 2002 recommended dopamine as first-line agent for vasopressor and inotropic therapy, whereas norepinephrine and epinephrine use was only recommended in dopamine-refractory shock. The most recent guideline for pediatric septic shock (SSC 2020) recommends norepinephrine and epinephrine as first-line agents in septic shock. All three substances are catecholamines and therefore have effects on all sympathetic receptors. However, there are differences in receptor affinity. Epinephrine and dopamine both have a strong effect on all sympathetic receptors, increasing CO as well as SVR and therefore are nonselective vasopressor agents. Norepinephrine on the other hand only shows a weak effect on CO and the increase of BP is mainly achieved by vasoconstriction (increase of SVR). Phenylephrine and vasopressin are other substances raising BP by vasoconstriction. Their use also increased over time, statistical significance however could not be proved. These findings led us to the assumption that therapy of septic shock experienced a shift towards a more

selective and hence a more controllable and more physiological inotropic and vasopressor therapy. (9, 64, 71)

The ACCM guidelines of 2002 already recommended hydrocortisone administration to be reserved to those children in fluid and catecholamine refractory shock. This recommendation did not change and the SSC guidelines of 2020 state the same. Since glucocorticoids were used in the majority of our patients, we carried out a more in-depth exploration. Nevertheless, we were unable to show any significant alterations between both groups regarding number of treated patients, dosages and length of use. (9, 64)

With regard to the number of patients treated with buffer solution or diuretics, no difference between our groups was evident. We also could not find any significant alterations in administration of drugs interacting with coagulation (Heparin, AT III) or resolving clots (Alteplase).

Latest SSC guidelines recommend early administration of at least one broad-spectrum antibiotic with subsequent adjustment to specific therapy as soon as a cause of sepsis is identified. The number of antibiotic agents our patients received did show significant difference between group 2000 and group 2010. Patients admitted to PICU between 2010 and 2019 received almost twice as many different agents as those admitted between 2000 and 2009. This development may suggest either more frequent application of combined treatment with several substances or a more frequent adaptation. A closer look at the substances administered shows that group 2010 received a greater variety of antibiotic drugs. However, the different spectrums of activity of the administered antibiotics should also be taken into account to come to a more reliable conclusion. (64, 72, 73)

With regard to the spectrum of activity, two major groups can be distinguished, broad-spectrum and narrow-spectrum antibiotics. As the name indicates, broad-spectrum antibiotics affect a wide range of bacteria, usually covering both gram-positive and gram-negative pathogens. Of the antibiotics given to our patients, ceftriaxone, cefotaxime, ampicillin, piperacillin/tazobactam, meropenem and imipenem belong to this group. Although all of them cover a broad spectrum, they do have their main focuses and weak spots. Furthermore, bacteria can also develop resistences against them. According to recent guidelines, patients in septic shock

should receive an empiric antibiotic treatment with one or more broad-spectrum antibiotics. However, as soon as a pathogen is identified, the antibiotic management should be adjusted to be as narrow as possible. (64, 72, 73)

Narrow-spectrum antibiotics affect less bacteria, in many cases only gram-positive or gram-negative ones. They show strongly deviating spectrums, with some of them only covering individual groups. Although not being counted as broad-spectrum antibiotic, cefuroxime also has a broader spectrum, with a strong effect on many gram-negative pathogens but a weaker effect on gram-positives. Flucloxacillin only affects gram-positive bacteria, in particular staphylococci, also those producing penicillinase. Gentamicin on the other hand only has an effect on gram-negative aerobes, especially on enterobacterales. Clindamycin is the most potent antibiotic against anaerobes, excluding clostridium difficile, but also covers staphylococci, streptococci and pneumococci. Vancomycin only has an effect on gram-positive germs, including anaerobes like clostridium difficile. Another substance against anaerobes is metronidazole, which only affects anaerobes and microaerophiles like helicobacter pylori and campylobacter. Fosfomycin affects staphylococci, streptococci, pneumococci and some gram-negative pathogens. Linezolid only covers gram-positives, including anaerobes and some multiresistant bacteria. As it belongs to the group of antituberculotics, rifampicin covers many mycobacteria like M. tuberculosis and M. leprae, but also affects other gram-negative and gram-positive pathogens. (72, 73)

While we could show a significant increase in administration of one antibiotic substance, which was cefotaxime, we also observed a non-significant decrease in administration of ceftriaxone. Both of them are cephalosporines of the third generation and show a very similar spectrum of activity, which should be kept in mind considering this finding. (73)

Investigating which antibiotic substances were administered, we found that a majority of patients in group 2000 received ceftriaxone as sole broad-spectrum antibiotic, in some cases combined with narrow-spectrum antibiotics, while those of group 2010 mostly received more than one broad-spectrum substance simultaneously. Furthermore, more adjustments of the antibiotic regimen were conducted in group 2010. In most cases, these adjustments were not made towards

a more narrow approach but towards alternative broad-spectrum antibiotics. This may be caused by a variety of factors, including a more individualized and calculated antibiotic approach on the one hand and the increase of antibiotic resistances on the other hand. (74–76)

Observed correlations of dosage of catecholamines with mortality and PICU length of stay showed contradictory results. Higher initial dosage was associated with higher mortality and shorter PICU length of stay, whilst higher catecholamine dosage at later points in time showed association with survival and longer PICU length of stay. This is because patients in poorer initial cardiovascular condition required higher catecholamine rates and the majority of them died on the first day. In contrast, higher catecholamine rates after 12 hours showed an association with a lower mortality rate and longer PICU length of stay, indicating a better outcome with liberal administration of catecholamines.

Our non-significant finding of delayed administration of antibiotics being associatied with an adverse outcome is not surprising, since guidelines recommend rapid administration of at least one broad-spectrum antibiotic following the diagnosis of septic shock. (12, 64, 77)

The strongest correlation we found was between use of norepinephrine and survival. In addition, it was also associated with longer PICU length of stay. This strong association to better outcome emphasizes the potential influence of more selective cardiovascular support on mortality. However, we could not find a correlation between the administration of epinephrine and dopamine with a better or worse outcome.

Albeit the correlation between the number of different antibiotics and outcome was not significant, we were able to show an association. This analysis indicates a better outcome with more antibiotic substances administered. However, the reason for the administration of a greater number of antibiotics in group 2010 is not entirely clear since many factors might have an influence on this finding, as discussed above.

4.1 Limitations

This study comes along with some major limitations. The first and most significant limitation is the study's monocentric approach and the resulting small study population. Due to this small number of patients, coincidental values and findings have a stronger influence on the result of statistical analysis. This issue causes imprecise estimation of confidence intervals, resulting in an increased probability of statistical analysis being unable to recognize significance even though it exists.

Some statistical methods also require a certain number of samples for their calculations and therefore were not applicable in our analysis. Analysing the collected data, we only conducted univariate and bivariate analysis. Treatment of septic shock however is a highly complex issue and improvements can hardly be proven by considering only one variable at a time. Multivariate analysis would be the statistical method required to receive more reliable results and to prove causality of therapy changes causing improvements in outcome. This method however requires a higher number of samples for a reliable result. For this reason, we decided to perform univariate and bivariate analysis. Nevertheless, this limits the reliabily and validity of this study's results.

Furthermore, we did not differentiate between hyper- and hypodynamic septic shock. Since the two types require different management and occur equally frequent in children, comparability between both groups could be limited and our findings may be distorted.

Regarding the patients' initial condition, we assumed no great difference between our groups since most parameters did not show significant difference. Nevertheless, there have been some deviations between the groups and it may be possible that the patient's initial condition may have a stronger influence on our findings than we assumed.

This study was able to show an increase of antibiotic substance in group 2010. However, since we did not include microbiological analyses and antibiotic resistances in our research, we were unable to further investigate their impact on antibiotic management and therefore could not identify the cause for this increase. In consequence, we could not determine whether the switch from one broad-spectrum antibiotic to another was the result of resistances or not.

4.2 Conclusion

This study's main objective was to evaluate a progress in the management of septic shock in children. Although we could show a decrease in mortality and PICU length of stay among survivors, this study was not able to prove significance. Considering it's limitations in terms of statistical analysis, we believe that the finding of higher probability of survival could be significant in larger study populations.

Since we investigated differences in treatment between our groups, we came to the conclusion that this not significant improvement was mainly caused by two factors.

In our opinion, the switch from unselective cardiovascular support towards a more selective approach was the major change. Using norepinephrine instead of dopamine or epinephrine to raise blood pressure is a more physiological approach to cardiovascular support. Furthermore, norepinephrine does not cause potentially adverse effects on the heart due to its predominant effect on vascular muscles. However, as stated before, we did not differentiate between hyper- and hypodynamic septic shock and an increase of systemic vascular resistance will not have beneficial effects in those patients which present with low cardiac output and high vascular resistance.

The second change in treatment we found, was the increasing number of different antibiotic agents. This shift from monotherapy with ceftriaxone towards an antibiotic combination treatment and more frequent adaptation of antibiotic regimen also seems to be beneficial for a positive outcome. Even though we could not identify the reason for the switch from one broad-spectrum antibiotic to another broad-spectrum substance, antibiotic treatment will become of even more importance in the future due to increasing rates of antibiotic resistances.

In conclusion, we have to say that this study shows some major limitations, mainly because of it's small study population. A larger, multicentric implementation of this study would be able to provide more valid and reliable results.

Despite our limitations, the strong association between a more selective approach to cardiovascular support and survival could also be an interesting approach for further research.

5 References

1. Bone RC, Balk RA, Cerra FB, Dellinger P, Fein AM, Knaus WA et al. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992; 20(6):864–74.
2. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M et al. The Third International Consensus Definitionss for Sepsis and Septic Shock (Sepsis-3). JAMA 2016; 315(8):801–10. doi: 10.1001/jama.2016.0287.
3. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A et al. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016; 315(8):762–74. doi: 10.1001/jama.2016.0288.
4. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Crit Care Med 2017; 45(3):486–552. doi: 10.1097/CCM.0000000000002255.
5. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med 2005; 6(1):2–8. doi: 10.1097/01.PCC.0000149131.72248.E6.
6. Schlapbach LJ, Berger C, Aebi C, Agyeman PKA. SIRS in the Time of Sepsis-3: What About the Children? Chest 2018; 153(6):1512. doi: 10.1016/j.chest.2018.02.037.
7. Aneja RK, Carcillo JA. Differences between adult and pediatric septic shock. Minerva Anestesiol 2011; 77(10):986–92.
8. Maisels MJ. Neonatal jaundice. Pediatr Rev 2006; 27(12):443–54. doi: 10.1542/pir.27-12-443.
9. Carcillo JA, Fields AI. Clinical practice parameters for hemodynamic support of pediatric and neonatal patients in septic shock. Crit Care Med 2002; 30(6):1365–78.
10. Weiss SL, Fitzgerald JC, Pappachan J, Wheeler D, Jaramillo-Bustamante JC, Salloo A et al. Global epidemiology of pediatric severe sepsis: the sepsis

prevalence, outcomes, and therapies study. Am J Respir Crit Care Med 2015; 191(10):1147–57. doi: 10.1164/rccm.201412-2323OC.

11. Balamuth F, Weiss SL, Neuman MI, Scott H, Brady PW, Paul R et al. Pediatric severe sepsis in U.S. children's hospitals. Pediatr Crit Care Med 2014; 15(9):798–805. doi: 10.1097/PCC.0000000000000225.
12. Fitzgerald JC, Weiss SL, Kissoon N. 2016 Update for the Rogers' Textbook of Pediatric Intensive Care: Recognition and Initial Management of Shock. Pediatr Crit Care Med 2016; 17(11):1073–9. doi: 10.1097/PCC.0000000000000942.
13. Ruth A, McCracken CE, Fortenberry JD, Hall M, Simon HK, Hebbar KB. Pediatric severe sepsis: current trends and outcomes from the Pediatric Health Information Systems database. Pediatr Crit Care Med 2014; 15(9):828–38. doi: 10.1097/PCC.0000000000000254.
14. Boeddha NP, Schlapbach LJ, Driessen GJ, Herberg JA, Rivero-Calle I, Cebey-López M et al. Mortality and morbidity in community-acquired sepsis in European pediatric intensive care units: a prospective cohort study from the European Childhood Life-threatening Infectious Disease Study (EUCLIDS). Crit Care 2018; 22(1):143. doi: 10.1186/s13054-018-2052-7.
15. Amann-Vesti B, Arnold C, Panzer U, Stahl RAK, Thaiss F, Wenzel U. Klinische Pathophysiologie. 10., vollständig überarbeitete und erweiterte Auflage. Stuttgart, New York: Georg Thieme Verlag; 2018.
16. Parker MM, Shelhamer JH, Natanson C, Alling DW, Parrillo JE. Serial cardiovascular variables in survivors and nonsurvivors of human septic shock: heart rate as an early predictor of prognosis. Crit Care Med 1987; 15(10):923–9. doi: 10.1097/00003246-198710000-00006.
17. Grondman I, Pirvu A, Riza A, Ioana M, Netea MG. Biomarkers of inflammation and the etiology of sepsis. Biochem Soc Trans 2020. doi: 10.1042/BST20190029.
18. Ames SG, Workman JK, Olson JA, Korgenski EK, Masotti S, Knackstedt ED et al. Infectious Etiologies and Patient Outcomes in Pediatric Septic Shock. J Pediatric Infect Dis Soc 2017; 6(1):80–6. doi: 10.1093/jpids/piv108.

19. Levin DL, Morriss FC, Hrsg. Essentials of pediatric intensive care. St. Louis, Mo: Quality Medical Pub; 1990.

20. Hof H, Schlüter D, Hrsg. Medizinische Mikrobiologie. 7. überarbeitete und erweiterte Auflage. Stuttgart: Thieme; 2019. (Duale Reihe).

21. Angus DC, van der Poll T. Severe sepsis and septic shock. N Engl J Med 2013; 369(9):840–51. doi: 10.1056/NEJMra1208623.

22. Vincent J-L, Rello J, Marshall J, Silva E, Anzueto A, Martin CD et al. International study of the prevalence and outcomes of infection in intensive care units. JAMA 2009; 302(21):2323–9. doi: 10.1001/jama.2009.1754.

23. King EG, Bauzá GJ, Mella JR, Remick DG. Pathophysiologic mechanisms in septic shock. Lab Invest 2014; 94(1):4–12. doi: 10.1038/labinvest.2013.110.

24. Kaempfer R. Bacterial Superantigen Toxins, CD28, and Drug Development. Toxins (Basel) 2018; 10(11). doi: 10.3390/toxins10110459.

25. Tang D, Kang R, Coyne CB, Zeh HJ, Lotze MT. PAMPs and DAMPs: signal 0s that spur autophagy and immunity. Immunol Rev 2012; 249(1):158–75. doi: 10.1111/j.1600-065X.2012.01146.x.

26. Murphy KM, Weaver C. Janeway's immunobiology. 9th edition. New York, London: GS Garland Science Taylor & Francis Group; 2017.

27. Russell JA, Rush B, Boyd J. Pathophysiology of Septic Shock. Crit Care Clin 2018; 34(1):43–61. doi: 10.1016/j.ccc.2017.08.005.

28. Camerer E, Kolstø AB, Prydz H. Cell biology of tissue factor, the principal initiator of blood coagulation. Thromb Res 1996; 81(1):1–41. doi: 10.1016/0049-3848(95)00209-x.

29. Okamoto T, Tanigami H, Suzuki K, Shimaoka M. Thrombomodulin: a bifunctional modulator of inflammation and coagulation in sepsis. Crit Care Res Pract 2012; 2012:614545. doi: 10.1155/2012/614545.

30. Fourrier F. Severe sepsis, coagulation, and fibrinolysis: dead end or one way? Crit Care Med 2012; 40(9):2704–8. doi: 10.1097/CCM.0b013e318258ff30.

31. Binette TM, Taylor FB, Peer G, Bajzar L. Thrombin-thrombomodulin connects coagulation and fibrinolysis: more than an in vitro phenomenon. Blood 2007; 110(9):3168–75. doi: 10.1182/blood-2007-03-078824.

32. van Meijer M, Pannekoek H. Structure of plasminogen activator inhibitor 1 (PAI-1) and its function in fibrinolysis: an update. Fibrinolysis 1995; 9(5):263–76. doi: 10.1016/S0268-9499(95)80015-8.

33. Castellino FJ, Ploplis VA. Structure and function of the plasminogen/plasmin system. Thromb Haemost 2005; 93(4):647–54. doi: 10.1160/TH04-12-0842.

34. Levi M, van der Poll T, Schultz M. New insights into pathways that determine the link between infection and thrombosis. Neth J Med 2012; 70(3):114–20.

35. Zeerleder S, Hack CE, Wuillemin WA. Disseminated intravascular coagulation in sepsis. Chest 2005; 128(4):2864–75. doi: 10.1378/chest.128.4.2864.

36. Backer D de, Orbegozo Cortes D, Donadello K, Vincent J-L. Pathophysiology of microcirculatory dysfunction and the pathogenesis of septic shock. Virulence 2014; 5(1):73–9. doi: 10.4161/viru.26482.

37. Backer D de, Creteur J, Dubois M-J, Sakr Y, Koch M, Verdant C et al. The effects of dobutamine on microcirculatory alterations in patients with septic shock are independent of its systemic effects. Crit Care Med 2006; 34(2):403–8. doi: 10.1097/01.ccm.0000198107.61493.5a.

38. Bateman RM, Tokunaga C, Kareco T, Dorscheid DR, Walley KR. Myocardial hypoxia-inducible HIF-1alpha, VEGF, and GLUT1 gene expression is associated with microvascular and ICAM-1 heterogeneity during endotoxemia. Am J Physiol Heart Circ Physiol 2007; 293(1):H448-56. doi: 10.1152/ajpheart.00035.2007.

39. Edul VSK, Enrico C, Laviolle B, Vazquez AR, Ince C, Dubin A. Quantitative assessment of the microcirculation in healthy volunteers and in patients with septic shock. Crit Care Med 2012; 40(5):1443–8. doi: 10.1097/CCM.0b013e31823dae59.

40. Walley KR. Heterogeneity of oxygen delivery impairs oxygen extraction by peripheral tissues: theory. J Appl Physiol 1996; 81(2):885–94. doi: 10.1152/jappl.1996.81.2.885.

41. Goldman D, Bateman RM, Ellis CG. Effect of decreased O2 supply on skeletal muscle oxygenation and O2 consumption during sepsis: role of heterogeneous capillary spacing and blood flow. Am J Physiol Heart Circ Physiol 2006; 290(6):H2277-85. doi: 10.1152/ajpheart.00547.2005.

42. Humer MF, Phang PT, Friesen BP, Allard MF, Goddard CM, Walley KR. Heterogeneity of gut capillary transit times and impaired gut oxygen extraction in endotoxemic pigs. J Appl Physiol 1996; 81(2):895–904. doi: 10.1152/jappl.1996.81.2.895.

43. Eipel C, Bordel R, Nickels RM, Menger MD, Vollmar B. Impact of leukocytes and platelets in mediating hepatocyte apoptosis in a rat model of systemic endotoxemia. Am J Physiol Gastrointest Liver Physiol 2004; 286(5):G769-76. doi: 10.1152/ajpgi.00275.2003.

44. Prowle JR, Kirwan CJ, Bellomo R. Fluid management for the prevention and attenuation of acute kidney injury. Nat Rev Nephrol 2014; 10(1):37–47. doi: 10.1038/nrneph.2013.232.

45. Sato R, Nasu M. A review of sepsis-induced cardiomyopathy. J Intensive Care 2015; 3:48. doi: 10.1186/s40560-015-0112-5.

46. Davis AL, Carcillo JA, Aneja RK, Deymann AJ, Lin JC, Nguyen TC et al. American College of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock. Crit Care Med 2017; 45(6):1061–93. doi: 10.1097/CCM.0000000000002425.

47. Roberts JK, Disselkamp M, Yataco AC. Oxygen Delivery in Septic Shock. Ann Am Thorac Soc 2015; 12(6):952–5. doi: 10.1513/AnnalsATS.201501-069CC.

48. Am Schulte Esch J, Bause H. Anästhesie: Intensivmedizin, Notfallmedizin, Schmerztherapie. 3., vollst. überarb. und erw. Aufl. Stuttgart: Thieme; 2007. (Duale Reihe). Verfügbar unter: http://www.thieme.de/ebooklibrary/inhalte/3131190833/index.html.

49. EDUARDO MEANEY, FELIX ALVA, RAFAEL MOGUEL, ALEJANDRA MEANEY, JUAN ALVA, RICHARD WEBEL. Formula and nomogram for the sphygmomanometric calculation of the mean arterial pressure. Heart 2000; 84(1):64. Verfügbar unter: https://heart.bmj.com/content/84/1/64.full.

50. Bartels K, Esper SA, Thiele RH. Blood Pressure Monitoring for the Anesthesiologist: A Practical Review. Anesth Analg 2016; 122(6):1866–79. doi: 10.1213/ANE.0000000000001340.

51. Striebel HW. Anästhesie - Intensivmedizin - Notfallmedizin: Für Studium und Ausbildung. Mit Video-Download. 9.Aufl. s.l.: Schattauer Verlag; 2017. Verfügbar unter: http://www.content-select.com/index.php?id=bib_view&ean=9783794568178.

52. Beloncle F, Radermacher P, Guerin C, Asfar P. Mean arterial pressure target in patients with septic shock. Minerva Anestesiol 2016; 82(7):777–84.

53. Tibby SM, Hatherill M, Murdoch IA. Capillary refill and core-peripheral temperature gap as indicators of haemodynamic status in paediatric intensive care patients. Arch Dis Child 1999; 80(2):163–6. doi: 10.1136/adc.80.2.163.

54. Backer D de. Detailing the cardiovascular profile in shock patients. Crit Care 2017; 21(Suppl 3):311. doi: 10.1186/s13054-017-1908-6.

55. Scheeren TWL, Wicke JN, Teboul J-L. Understanding the carbon dioxide gaps. Curr Opin Crit Care 2018; 24(3):181–9. doi: 10.1097/MCC.0000000000000493.

56. Rimachi R, Bruzzi de Carvahlo F, Orellano-Jimenez C, Cotton F, Vincent JL, Backer D de. Lactate/pyruvate ratio as a marker of tissue hypoxia in circulatory and septic shock. Anaesth Intensive Care 2012; 40(3):427–32. doi: 10.1177/0310057X1204000307.

57. Zobel G, Kuttnig M, Grubbauer HM, Rödl S. Evaluation of clinical scoring systems in critically ill infants and children. Clin Intensive Care 1990; 1(5):202–6.

58. Levy MM, Evans LE, Rhodes A. The Surviving Sepsis Campaign Bundle: 2018 update. Intensive Care Med 2018; 44(6):925–8. doi: 10.1007/s00134-018-5085-0.

59. McIntosh AM, Tong S, Deakyne SJ, Davidson JA, Scott HF. Validation of the Vasoactive-Inotropic Score in Pediatric Sepsis. Pediatr Crit Care Med 2017; 18(8):750–7. doi: 10.1097/PCC.0000000000001191.

60. Studio G&T, Aktories K, Förstermann U, Hofmann FB, Starke K. Allgemeine und Spezielle Pharmakologie und Toxikologie: Begründet Von W. Forth, D. Henschler, W. Rummel. 12th ed. Philadelphia: Urban & Fischer Verlag GmbH & Co. KG; 2017. Verfügbar unter: https://ebookcentral.proquest.com/lib/gbv/detail.action?docID=5553758.

61. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Intensive Care Med 2004; 30(4):536–55. doi: 10.1007/s00134-004-2210-z.

62. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Intensive Care Med 2008; 34(1):17–60. doi: 10.1007/s00134-007-0934-2.

63. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013; 41(2):580–637. doi: 10.1097/CCM.0b013e31827e83af.

64. Weiss SL, Peters MJ, Alhazzani W, Agus MSD, Flori HR, Inwald DP et al. Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. Intensive Care Med 2020; 46(Suppl 1):10–67. doi: 10.1007/s00134-019-05878-6.

65. Brierley J, Carcillo JA, Choong K, Cornell T, Decaen A, Deymann A et al. Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. Crit Care Med 2009; 37(2):666–88. doi: 10.1097/CCM.0b013e31819323c6.

66. Haque IU, Zaritsky AL. Analysis of the evidence for the lower limit of systolic and mean arterial pressure in children. Pediatr Crit Care Med 2007; 8(2):138–44. doi: 10.1097/01.PCC.0000257039.32593.DC.

67. Kutko MC, Calarco MP, Flaherty MB, Helmrich RF, Ushay HM, Pon S et al. Mortality rates in pediatric septic shock with and without multiple organ system

failure. Pediatr Crit Care Med 2003; 4(3):333–7. doi: 10.1097/01.PCC.0000074266.10576.9B.

68. Menon K, McNally JD, Zimmerman JJ, Agus MSD, O'Hearn K, Watson RS et al. Primary Outcome Measures in Pediatric Septic Shock Trials: A Systematic Review. Pediatr Crit Care Med:e146-e154.

69. Paul R, Neuman MI, Monuteaux MC, Melendez E. Adherence to PALS Sepsis Guidelines and Hospital Length of Stay. Pediatrics 2012; 130(2):e273-80. doi: 10.1542/peds.2012-0094.

70. Biban P, Gaffuri M, Spaggiari S, Zaglia F, Serra A, Santuz P. Early recognition and management of septic shock in children. Pediatr Rep 2012; 4(1):e13. doi: 10.4081/pr.2012.e13.

71. Zanotti Cavazzoni SL, Dellinger RP. Hemodynamic optimization of sepsis-induced tissue hypoperfusion. Crit Care 2006; 10 Suppl 3:S2. doi: 10.1186/cc4829.

72. Lüllmann H, Mohr K, Hein L, Wehling M. Pharmakologie und Toxikologie: Arzneimittelwirkungen verstehen - Medikamente gezielt einsetzen : ein Lehrbuch für Studierende der Medizin, der Pharmazie und der Biowissenschaften, eine Informationsquelle für Ärzte, Apotheker und Gesundheitspolitiker. 18. vollständig überarbeitete Auflage. Stuttgart, New York: Georg Thieme Verlag; 2016.

73. Graefe K-H, Lutz W, Bönisch H. Pharmakologie und Toxikologie. 2. Aufl. s.l.: Georg Thieme Verlag KG; 2016. (Duale Reihe).

74. Martínez JL, Baquero F. Emergence and spread of antibiotic resistance: setting a parameter space. Ups J Med Sci 2014; 119(2):68–77. doi: 10.3109/03009734.2014.901444.

75. Dodds DR. Antibiotic resistance: A current epilogue. Biochem Pharmacol 2017; 134:139–46. doi: 10.1016/j.bcp.2016.12.005.

76. McGough SF, MacFadden DR, Hattab MW, Mølbak K, Santillana M. Rates of increase of antibiotic resistance and ambient temperature in Europe: a cross-national analysis of 28 countries between 2000 and 2016. Euro Surveill 2020; 25(45). doi: 10.2807/1560-7917.ES.2020.25.45.1900414.

77. Milano PK, Desai SA, Eiting EA, Hofmann EF, Lam CN, Menchine M. Sepsis Bundle Adherence Is Associated with Improved Survival in Severe Sepsis or Septic Shock. West J Emerg Med 2018; 19(5):774–81. doi: 10.5811/westjem.2018.7.37651.