‘My mission in life is not merely

to survive but to thrive’

- MAYA ANGELOU

STORY OF SEPSIS

PREFACE

Greetings to you and your family

With humbled heart I thank my wife, parents, teachers and almighty who has given power to pen about the most widespread and most important medical condition SEPSIS. Almost 30 million people are affected and 3 million deaths happen every year because of sepsis. According to WHOs (World Health Organization) Global Report on Epidemiology and Burden of Sepsis report 2020, half of the sepsis cases are affecting the children.

The aim of writing this book is to give quick understanding regarding SEPSIS and its PROGNOSIS for Undergraduate, Post graduate trainees and Faculty of medicine in a simple language. The book gives a novelistic go-through so that all about Sepsis can be learnt like a story rather than academic exercise.

The book goes through various aspects of SEPSIS, right from the understanding of the pathophysiology, brief History, evolution of definition, derangement in homeostasis, various protocols adapted, Clinical trials conducted and prognostication of sepsis patients.

In modern day life context, TIME is having an immense value. Patients and their loved ones expect healthcare professionals to provide best available care and be able to clear all the doubts, bring down the anxiety and provide care with assurance. Every clinician aspires to see smile on the face of the patients and their family members. May this book empower all those aspiring for this.

I hope this book can give an in-sight about SEPSIS and its PROGNOSIS.

Thank You

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ABBREVATIONS & ACRONYMS

A

AKI - acute kidney injury
Ang - angiopoietin
APPs - Acute-phase proteins
ARDS- acute respiratory distress syndrome
ATP - Adenosine triphosphate

B

BBB- Blood brain barrier
BCE – Before Common Era
Bpm- beats per minute

C

CD- Cluster of differentiation
CDPV- Carotid doppler peak velocity
CE- Common Era
CNS- Central nervous system
CRP- C reactive protein
CVP- central venous pressure

D

DAMPs= damage-associated molecular patterns
DIC- disseminated intravascular coagulation
Dl – decilitre
DNA- Deoxyribose nucleic acid

E

ECMO- extracorporeal membrane oxygenation
EGDT- Early Goal-Directed Therapy
EGF- Epidermal growth factor
ESR- Erythrocyte Sedimentation Rate
ET- endothelin
ETCO2-End tidal carbondioxide

F

FiO2 - Fraction of inspired oxygen

G

GCS- Glasgow coma scale

H

HFNO- high-flow nasal oxygenation

I

ICAM - intercellular adhesion molecule
ICU- Intensive care unit

IL- Interleukin

J

K

Kg- Kilogram
Kpa- Kilo pascals

L

LBP- Lipopolysaccharide-Binding Protein

LMWH- low molecular weight heparin

M

m- meter
MAP- Mean arterial Pressure
mEq- milli equivalent
Mg – milligram
min- minute
mL- milli litre
Mm Hg – millimeter of mercury
mmol- milli mol
MRSA- methicillin-resistant *Staphylococcus aureus*
mtDNA- mitochondrial DNA
MV- Mechanical ventilation
µL- microlitre

N

NGAL-Neutrophil Gelatinase-Associated Lipocalin
NIV- non-invasive ventilation
NMBA- neuromuscular blocking agents
NO- Nitric oxide
NOD - nucleotide-binding oligomerization domain
NOS-Nitrix oxide synthase

O
P

PaCo2- Partial pressure of arterial Carbondioxide
PAI- plasminogen activator inhibitor
PAMPs- pathogen-associated molecular patterns
PaO2- Partial pressure of arterial Oxygen
PBR- protocol-based resuscitation
PCT- procalcitonin
PEDF- Pigment Epithelium-Derived Factor
PEEP- positive end expiratory pressure
PLR- Passive Leg Raise
POCUS-Point of Care Ultrasound
PPV- Pulse pressure variation

Q

qSOFA- Quick Sequential Organ Failure assesment

R

RCT- randomized controlled trials
RIG - retinoic acid inducible gene
ROS- reactive oxygen species
RRT- renal replacement therapy

S

SBP- Systolic blood pressure
ScvO2- central venous oxygen saturation
SD- standard deviation
SIRS – Systemic Inflammatory Response Syndrome
SOFA- Sequential Organ failure assessment
SSC- Surviving sepsis campaign
sTREM1- Soluble Triggering Receptor Expressed on Myeloid Cells-1
SV- stoke volume
SVV- Stroke volume variation

T

Tie- Tyrosine kinase with immunoglobulin-like and Epidermal growth factor-like

TLR- toll-like receptors
TNF- Tumor necrosis factor

U

UFH- Unfractioned heparin

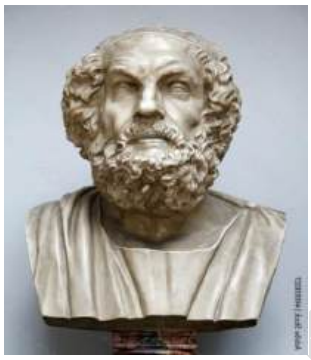
V

VCAM- vascular cell adhesion molecule
VTi- Velocity time integral

W
X
Y
Z

CHAPTER 1 : HISTORY OF SEPSIS

1.1 Homer :



Thy song men liken to the sea
With all the notes of music in its tone,
With tides that wash the dim dominion
Of Hades, and light waves that laugh in glee
Around the isles enchanted; nay, to me
Thy verse seems as the River of source unknown
That glasses Egypt's temples overthrown
In his sky-nurtured stream, eternally

- Homer

It all commenced approximately 2,700 years ago when the illustrious poet Homer eloquently articulated the profound and intricate nature of human suffering within the compelling verses of his timeless and venerable poetic compositions.

The Greek term "σηψιζ," which can be intricately defined as the biochemical process of decomposition involving the breakdown of animal, vegetable, or organic matter facilitated by the presence and activity of various bacteria, serves as the etymological foundation from which the contemporary medical term "SEPSIS" has emerged and evolved.

The lexeme "sepo" (σηπω), which translates to "I rot," is unequivocally the principal source and direct linguistic lineage of the term "sepsis" as it is utilized in modern medical vernacular. Homer is widely recognized as the presumed author of the illustrious epic poems known as the ***Iliad*** and the ***Odyssey***, which are regarded as profoundly influential literary works that have left a lasting impact on the cultural and literary heritage of ancient Greece.

The contemporary comprehension of the pathophysiological mechanisms underlying sepsis first became manifest in the detailed and insightful account provided by Schottmuller, who meticulously described septicemia as a critical state characterized by the invasion of microbial entities into the bloodstream, resulting in the manifestation of various clinical signs indicative of systemic illness.

Schottmuller's description of septicemia, which is a term largely associated with his work in the early 20th century, emphasized the presence of bacteria in the bloodstream as a critical component of the condition. He made a substantial contribution to our knowledge of how bacterial infections move throughout the bloodstream to cause septicemia (sepsis), which can have potentially fatal implications and systemic inflammation. His research contributed to the understanding of the significance of treating bacterial infections as soon as possible in order to stop the development of septicemia and septic shock.

In his Corpus Hippocraticum, the renowned physician and philosopher Hippocrates (c. 400 BCE) included references to the phrase.

1.2 Hippocrates: Theory of Dysregulated Humors

Hippocrates, who is widely regarded as a seminal figure in the annals of ancient Greek philosophy and medicinal practice, was born in the region of Greece approximately around the year 460 BC, a time marked by significant intellectual and cultural developments in the Mediterranean world.

His contributions to the field of medicine are highly esteemed, as he is most notably recognized for pioneering advancements that have profoundly influenced the medical profession. In addition to his remarkable achievements, he established the Hippocratic School of Medicine, which served as a foundational institution for medical education, and his extensive body of work

facilitated the transformation of medicine into a rational and empirical scientific discipline, thereby distinguishing it from the more speculative nature of philosophy.

At the core of Hippocrates' medical philosophy was the significant concept known as the "Theory of the Four Humours," which articulated the belief that the human body was composed of four distinct and essential fluids, referred to as "humours," that were pivotal in determining health and disease. These four humours include:

Blood,

Phlegm,

Yellow bile, and

Black bile.

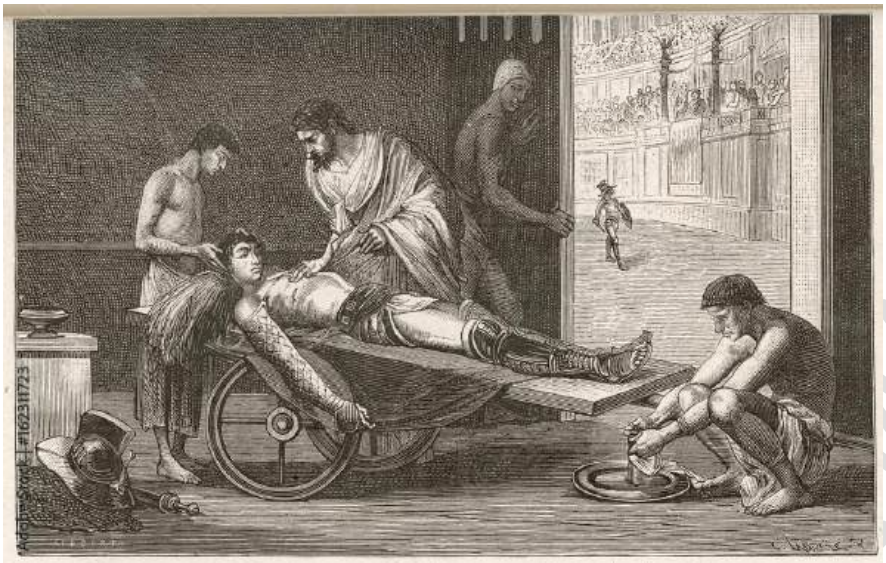
The prevailing notion posited by Hippocrates was that any disorder or imbalance among these humours could lead to the manifestation of illness, and thus, to restore health, it was imperative to administer treatments that possessed properties opposite to those of the humours, thereby achieving a state of equilibrium once more.

According to the teachings and observations of Hippocrates, sepsis was characterized as a potentially lethal condition involving a foul-smelling biological decomposition of bodily tissues, which was indicative of a severe underlying pathology.

Furthermore, it was widely theorized during Hippocrates' time that the "dangerous principles" resulting from this biological degradation, particularly within the confines of the colon, could lead to a state of "autointoxication," whereby the body effectively poisoned itself due to the release of harmful substances.

In his extensive studies, Hippocrates hypothesized that various body fluids, namely phlegm, yellow bile, black bile, and red fluids, could serve as potential sources of illness, thereby underscoring the complexity of human health and the intricate interplay of bodily humours in the manifestation of disease.[1]

1.3 Galen



Claudius Galen, Greek physician working in Italy treats gladiators wounded in the arena at PERGAMON; Date : 2nd Century stock photo

Another esteemed historical figure in the exploration of sepsis theories was Galen (129–199 CE). He was esteemed as a specialist in medicine due to his acute observational aptitudes.

Galen was the inaugural physician to utilize the pulse as an indicator of malady. He enhanced the discipline and application of pharmacological agents in therapeutics.

The comprehension and management of sepsis were not thoroughly documented during the era of Claudius Galen, a renowned physician in ancient Rome, as the contemporary conception of sepsis had not yet been fully formulated.

Nevertheless, Galen did render a considerable contribution to medicine as a whole, particularly in the domains of anatomy, physiology, and pharmacology. He emphasized the significance of systematic experimentation and meticulous observation, both of which established the foundation for the progress of medical knowledge.

Galen would have encountered infections and their ramifications in his medical endeavors, which would have influenced sepsis. He endorsed the theory that the equilibrium or disequilibrium of the humors—blood, phlegm, yellow bile, and black bile—could exert an influence on one's health.

Four Temperaments of Galen :

These four distinct classifications that were delineated by Galen correspond to the temperamental categories that he aptly designated as "sanguine," "choleric," "melancholic," and "phlegmatic," and these terms were derived from his theoretical framework surrounding the bodily humours,

which were believed to influence human disposition and personality traits. Each of these temperaments emerged as a consequence of an overabundance of one particular humour, which consequently led to an imbalance in the inherent paired qualities that characterize human emotional and psychological states.

His comprehensive "apotheca," which can be understood as a meticulously curated collection of medicinal substances, not only served as a foundational model for contemporary pharmacies but also reflected the extensive knowledge and practices of the time regarding the preparation and administration of medicinal compounds. Among his most renowned pharmaceutical innovations was theriac, an intricate concoction that comprised more than seventy diverse ingredients, which underscored both the complexity and the ambition of his medicinal formulations.

It is crucial to acknowledge that the conceptualization of sepsis as a profound and systemic inflammatory response to infectious agents did not emerge until a considerably later period, and this understanding was significantly enhanced by the groundbreaking contributions of modern medical research along with clinical observations that took place throughout the 19th and 20th centuries.

Consequently, while it is indisputable that Galen's contributions to the field of medicine are both extensive and foundational, it is equally important to recognize that his direct impact on the contemporary understanding of sepsis, as we define this condition in today's medical lexicon, was not explicitly articulated or documented within the corpus of his writings.

1.4 Antonie Van Leeuwenhoek :

The remarkable advancement and subsequent establishment of germ theory, which fundamentally transformed our understanding of infectious diseases, was made feasible through the pioneering and groundbreaking initial observations, detailed descriptions, and intricate illustrations provided by the eminent scientist Antonie van Leeuwenhoek, who, in the year 1674, meticulously documented and characterized what he referred to as "animacules," a term he used to describe microscopic life forms that encompassed a diverse array of shapes, including but not limited to spherical entities, rod-like structures, and spiral configurations, which in contemporary scientific nomenclature correspond to the classifications of cocci, bacilli, and spirochetes, respectively.

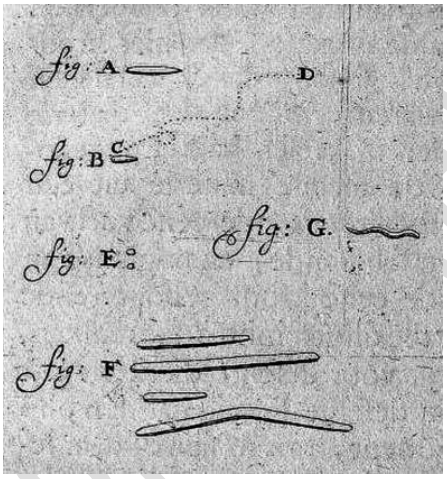


Image Courtesy: Funk, Duane & Parrillo, Joseph & Kumar, Anand. (2009). Sepsis and Septic Shock: A History. Critical care clinics. 25. 83-101, viii. 10.1016/j.ccc.2008.12.003.

1.5 Role of Germ theory in Understanding and management of sepsis

Louis pasteur

The advancement and acknowledgment of germ theory fundamentally transformed the comprehension and administration of sepsis. Germ theory, which attained prominence in the 19th century through the contributions of scholars such as Louis Pasteur and Robert Koch, asserted that numerous ailments are instigated by microorganisms including bacteria, viruses, fungi, and parasites.

Herein lies how germ theory specifically facilitated the understanding and management of sepsis:

Identification of Infectious Agents: Germ theory furnished a framework for discerning the particular microorganisms accountable for inducing infections. Prior to the establishment of germ theory, the notion that imperceptible, microscopic entities could incite diseases such as sepsis was not broadly endorsed. With the emergence of germ theory, investigators succeeded in identifying bacteria such as Staphylococcus aureus and Streptococcus pyogenes as prevalent etiological agents of sepsis.

Understanding Transmission: Germ theory underscored that infectious maladies could be conveyed from individual to individual, via contaminated objects, or through vectors (such as mosquitoes or fleas). (Little more description is required) This comprehension was pivotal in thwarting the proliferation of infections that could culminate in sepsis, including wound infections or infections related to childbirth.

Improvements in Hygiene and Sterilization: Germ theory incited significant enhancements in hygienic practices within medical environments. Sterilization of surgical instruments, disinfection of hands and surfaces, and maintenance of cleanliness in hospitals became standard protocols to avert the introduction of deleterious bacteria into wounds or the bloodstream, thereby diminishing the prevalence of sepsis.

Development of Antibiotics: The discovery and advancement of antibiotics in the mid-20th century were directly influenced by germ theory. (How it is influenced in shortly)Antibiotics are efficacious in treating bacterial infections, including those that could precipitate sepsis. Pharmaceuticals such as penicillin and subsequent antibiotics revolutionized the management of infections, significantly lowering mortality rates associated with sepsis.

Advances in Immunology: Germ theory also catalyzed progress in the elucidation of the immune system's reaction to infections. This insight is crucial in the management of sepsis, as an exaggerated immune response (severe sepsis and septic shock) can result in organ dysfunction and mortality. Comprehending the foundational immunological mechanisms has prompted targeted interventions and enhanced supportive care for patients afflicted with sepsis.

Why there is sudden jump to handwashing? Flow is interrupted.

1.6 Ignaz Philipp Semmelweis: Hand washing

Ignaz Philipp Semmelweis, a physician and scientist of Hungarian origin with German ancestry, emerged as a seminal figure in the realm of medical science, particularly recognized for his pioneering efforts in the implementation of antiseptic procedures, which ultimately earned him

the esteemed title of the "savior of mothers," reflecting the profound impact of his contributions on maternal health.

During the mid-19th century, while engaged in his medical practice in Vienna, Philipp Semmelweis made remarkable strides that significantly advanced the understanding and

systematic practice of hand hygiene within medical environments. His groundbreaking work was instrumental in drastically decreasing the prevalence of puerperal fever, a lethal condition that afflicts women in the immediate aftermath of childbirth, thereby transforming obstetric care.

The following delineates the pivotal contributions of Philipp Semmelweis to the field of handwashing:

Observational Study and Hypothesis: Through meticulous observation, Semmelweis discerned that the rate of puerperal fever was disproportionately elevated in maternity wards that were manned by medical students and physicians, who frequently transitioned directly from conducting autopsies, in stark contrast to those wards that were staffed by midwives. This alarming discrepancy prompted him to formulate the hypothesis that some unidentified "cadaverous particles," which were inadvertently transported from autopsy procedures, were the culprits behind the infections afflicting new mothers.

Introduction of Handwashing Protocols: In a concerted effort to empirically validate his hypothesis, Semmelweis took the initiative to institute a rigorous handwashing protocol that mandated the use of a chlorinated lime solution for all medical personnel prior to their involvement in childbirth. This seemingly straightforward yet profoundly effective intervention was designed to mitigate the transmission of infectious agents from the hands of physicians and medical students to the vulnerable women in labor, thereby safeguarding maternal health.

Demonstration of Effectiveness: Following the implementation of the handwashing protocol, Semmelweis meticulously monitored the outcomes and observed an astonishing decline in the rates of puerperal fever within the maternity ward where the handwashing practice was enforced. The compelling results stemming from his intervention provided irrefutable evidence that adherence to hand hygiene could significantly curtail the propagation of infectious diseases within medical establishments.(Reference article)

Challenges and Resistance: Notwithstanding the unequivocal evidence derived from his rigorous observations and the data he compiled, Semmelweis encountered formidable resistance and skepticism from the medical fraternity of his era. The revolutionary nature of his ideas, which fundamentally contradicted the entrenched medical theories and practices of the time, resulted in widespread rejection and criticism, further complicating the dissemination of his findings.

Legacy and Impact: The groundbreaking work of Semmelweis established a vital foundation for contemporary antiseptic methodologies and infection control protocols within healthcare environments. His fervent advocacy for hand hygiene was ultimately corroborated by the later advent of germ theory and the widespread acceptance of the concept of microbial transmission of diseases. In contemporary healthcare settings around the globe, the practice of handwashing prior to patient interaction remains an essential protocol, significantly reducing the incidence of infections and enhancing patient outcomes.

It was only after one of his colleagues inadvertently inflicted a wound upon himself during an autopsy that Semmelweis was able to establish a connection among the practices of autopsies, the occurrence of puerperal sepsis, and the deliveries conducted by medical students, thereby illuminating a critical link in the understanding of infection transmission.

In the year 1847, he put forth a proposal advocating for the practice of handwashing with chlorinated lime solutions at the First Obstetrical Clinic of the Vienna General Hospital, where the mortality rates among patients attended to by doctors were found to be threefold higher than those under the care of midwives, highlighting the urgent need for reform in clinical practices.

As a direct consequence of his innovative interventions, the maternal mortality rate experienced a dramatic decline from 18% to an astonishingly low figure of less than 2%, and in 1861, he published a comprehensive account of his findings in a seminal work entitled "Etiology, Concept, and Prophylaxis of Childbed Fever," contributing significantly to the medical literature of the time.

Semmelweis poignantly articulated the gravity of the situation, stating: “The fingers and hands of students and doctors, soiled by recent dissections, carry those death-dealing cadaver's poisons into the genital organs of women in childbirth,” [2]thereby underscoring the critical importance of hand hygiene in preventing maternal morbidity and mortality.

1.7 Joseph Lister

Joseph Lister, a prominent figure in the field of medicine who lived from 1827 to 1912, made significant advancements in surgical practices by discovering an effective methodology that successfully prevented the onset of infections in wounds both during surgical procedures and in the subsequent postoperative period. He notably distinguished himself as the pioneering individual to implement the scientific principles derived from Germ Theory within the realm of

surgical operations, thus revolutionizing the approach to surgical hygiene and patient care. The antiseptic system developed by Lister laid the foundational framework upon which contemporary infection control protocols are constructed, highlighting his lasting influence on the medical field.

In his pursuit of knowledge and understanding of antiseptic techniques, Lister engaged in self-experimentation, a practice that was not uncommon among many scientists of his era who sought empirical evidence to support their theories and hypotheses. His extensive research endeavors were primarily concentrated on the identification and determination of the optimal concentration of carbolic acid that should be utilized in surgical dressings, ensuring that these dressings would effectively inhibit the occurrence of sepsis while simultaneously being gentle enough not to cause undue irritation or damage to the skin, an important consideration that affected both the surgical instruments employed during procedures and the healing process of the wounds themselves.

1.8 THE DISCOVERY OF THE ROLE OF ENDOTOXIN

Ludwig Brieger

The heat sensitive toxins isolated by **Ludwig Brieger** (1849–1919) in the culture

supernatant of diphtheria were the first true exotoxins to be discovered.[3]

Ludwig Brieger (1849-1919) was a German chemist known for his contributions to biochemistry and medicine. While he did not specifically focus on sepsis, his work in chemistry and toxicology laid some foundational knowledge that indirectly contributed to the understanding and management of sepsis. Here are a few aspects of Brieger's work that relate to sepsis:

1. **Toxin Research**: Brieger studied toxins produced by bacteria, including toxins produced by pathogens involved in sepsis. His research helped in identifying and characterizing bacterial toxins, which are critical in understanding the pathogenesis of sepsis.
2. **Chemical Analysis**: Brieger developed methods for chemical analysis, which were important in identifying and isolating substances produced by bacteria that could cause harmful effects in the body, contributing indirectly to the understanding of septic processes.
3. **Contributions to Pharmacology**: Brieger's work contributed to the field of pharmacology, which later played a crucial role in developing antibiotics and other medications used in the treatment of infections that can lead to sepsis

1.9 Richard Pfeiffer:

Richard Pfeiffer, who is widely recognized as one of the early pioneers in the field of bacteriology and who also served as an esteemed assistant to the renowned microbiologist Robert Koch, received the distinguished honor of being elected as a Foreign Member of the Royal Society in the year 1928, an impressive achievement that occurred when he had reached the age of 70 years, thereby marking a significant milestone in his illustrious career.

Richard Pfeiffer, whose lifespan spanned from 1858 to 1955, dedicated his research efforts to meticulously investigating the intricate mechanisms underlying cholera pathogenesis, specifically through the study of Vibrio cholerae; however, despite his diligent endeavors, he was unable to identify the characteristic exotoxin that had been previously documented in various other pathogenic organisms.

Subsequently, the Italian pathologist Eugenio Centanni made a groundbreaking discovery regarding the correlation between Pfeiffer's endotoxin and its role in the capacity of certain bacteria to induce fever in hosts; through his extensive research, he ascertained that these particular substances were fundamentally chemically inseparable from the structural composition of the bacterial cell wall, and in recognition of their unique properties, he aptly designated this material as pyrotoxin, deriving the term from the Greek word that translates to 'fire.'

Further advancements and research conducted in the twentieth century by notable scientists Osborn and Nikaido have provided compelling evidence that elucidates the diverse array of bacterial species that employ endotoxin as a crucial mediator in their pathogenic processes, thereby contributing significantly to the understanding of bacterial virulence mechanisms within the broader context of microbiological research.

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CHAPTER 2

DEFINITION & PATHOPHYSIOLOGY OF SEPSIS

2.1 Evolution of Sepsis Definition:

1991

a) Systemic inflammatory response syndrome (SIRS)[1]

SIRS criteria
• **Temperature <36ºC or >38ºC** • **Heart rate >90 bpm** • **Respiratory rate >20/minute or $PaCO_2$ (partial pressure of arterial carbon dioxide) below 4.3kpa 32 mm Hg** • **White blood cell counts of >12,000 or <4,000 per cu mm or >10% immature (band) forms**

(Reference number to be mentioned)

Sepsis is a systemic response to infection, manifested by two or more of the SIRS criteria as a result of infection.

Severe sepsis: Sepsis associated with organ dysfunction, hypo perfusion, or hypotension;

Hypo perfusion and perfusion abnormalities may include, but not limited to, Lactic acidosis,

Oliguria, or an acute alteration in mental status

Septic shock: Sepsis-induced hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but not limited to, lactic acidosis, oliguria, or an acute alteration in mental status.[2]

b) 2001

Sepsis 2001: Suspected or documented infection with some of the following abnormalities.[2]

a) General parameters
b) Inflammatory parameters
c) Hemodynamic parameters
d) Organ dysfunction parameters
e) Tissue perfusion parameters

General parameters:

a. Fever (core temperature > 38.3°C); hypothermia (core temperature < 36°C);
b. Heart rate > 90 beats per min or > 2 SD above the normal value for age;
c. Tachypnea: respiratory rate > 30 breaths per min;
d. Altered mental status; significant edema or positive fluid balance >20 mL kg−1 over 24 h
e. Hyperglycemia (plasma glucose > 110 mg dL−1 or 7.7 mM L−1) in the absence of diabetes

Inflammatory parameters:

a. Leukocytosis : white blood cell count > 12,000/μL;
b. Leukopenia : white blood cell count < 4000/μL;
c. Normal white blood cell count with > 10% immature forms;
d. Plasma C-reactive protein > 2 SD above the normal value
e. Plasma procalcitonin > 2 SD above the normal value

Hemodynamic parameters:

a. Arterial hypotension (systolic blood pressure < 90 mmHg, MAP < 70 mmHg, or

b. Systolic blood pressure decrease > 40 mmHg in adults or < 2 SD below normal for age
c. Mixed venous oxygen saturation > 70%, cardiac index > 3.5 L min^{-1} m^{-2})

Organ dysfunction parameters:

a. Arterial hypoxemia : PaO2/FIO2 < 300;
b. Acute oliguria : Urine output (< 0.5 mL kg−1 h−1 or 45 mM L−1 for at least 2h);

Creatinine increase ⩾ 0.5 mg dL−1;

c. Coagulation abnormalities

(INR > 1.5 or activated partial thromboplastin time > 60 s);

Thrombocytopenia (platelet count < 100,000 μL−1)

d. Hyperbilirubinemia (plasma total bilirubin > 4 mg dL−1 or 70 mmol L−1)

Tissue perfusion parameters:

a. Hyperlactatemia (>3 mmol L−1);
b. Decreased capillary refill or mottling

C)2016

Sepsis 2016 to Present

Sepsis is a life-threatening organ dysfunction caused by dysregulated host response to infection.[3]

Clinical criteria for sepsis:

Suspected or documented infection and an acute increase of ⩾2 SOFA points

[*The task force considered that positive qSOFA (quick SOFA) criteria should also Prompt consideration of possible infection in patients not previously recognized as infected]*

qSOFA criteria:

Quick SOFA (qSOFA)
• **Respiratory rate ≥ 22 breaths/min** • **Altered mental state (GCS score <15)** • **Systolic blood pressure ≤100 mmHg**

Box 2. (from Singer et al, 2016).

Septic shock is defined as a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality.

Septic shock can be identified with a clinical construct of sepsis with persisting hypotension, requiring vasopressor therapy to elevate MAP ⩾ 65 mm of Hg and Lactate > 2 mmol L−1 (18 mg dL−1) despite adequate fluid resuscitation.

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2.2PATHOPHYSIOLOGY OF SEPSIS

At cellular level sepsis is characterized by changes in the function of

a) Endothelium which forms the inner surface of blood vessel
b) Coagulation process and
c) Blood flow

The pathophysiology of sepsis is complex and results from the effects of circulating bacterial products, mediated by cytokine release and sustained bacteremia.

Cytokines are primarily responsible for the clinically observable effects of the bacteremia in the host The substances, which include short-lived regulatory proteins known as cytokines interact with endothelium causing injury to the endothelium and possibly death of the cells. (Please provide reference) These interactions lead to the activation of coagulation factors.

In very small blood vessels, the coagulation response, in combination with endothelial damage, may impede blood flow leading to blood vessels becoming leaky and clot formation.As fluid and microorganisms escape into the surrounding tissues, the tissues begin to swell in the lungs that can lead to pulmonary edema manifesting as shortness of breath. (Need to rewrite with proper referencing)

a. Innate immunity and inflammatory mediators

Our knowledge of the molecular pathobiology and immunology of sepsis has significantly advan ced.It was previously believed that the hyperimmune host response to a specific infection was m ostly responsible for the hemodynamic signs of sepsis.[1]

The initial phase of the host response to the pathogen involves the activation of innate immune c ells, which are mostly composed of natural killer cells, neutrophils, macrophages, and monocytes .[2]

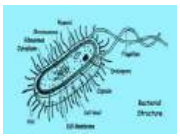
The activation of innate immune system occurs via binding of pathogen-associated molecular patterns (PAMPs) such as endotoxins from bacteria and β-glucans from fungi to specific pattern

recognition receptors on immune cells.Similar interaction happens when damage-associated molecular patterns (DAMPs) bind to specific receptors of immune cells.

Damage-associated molecular patterns (DAMPs) may be intracellular material or molecules released from dead or damaged host cells. They bind to specific receptors present on monocytes and macrophages like toll-like receptors (TLRs), C-type leptin receptors, NOD-like receptors (nucleotide-binding oligomerization domain) and RIG-1 like receptors (retinoic acid inducible gene 1)

This results in the activation of intracellular signal transduction pathways that cause the transcription and release of proinflammatory cytokines like TNFα, IL-1, and IL-6.

Furthermore, a few pattern recognition receptors, like the NODlike receptor group, have the abili ty to group together to form larger protein complexes known as inflammasomes, which are invol ved in the production of important cytokines like IL1β and IL18 as well as caspases, which are in volved in the process of programmed cell death.



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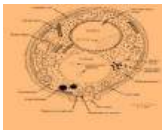


FUNGI

ENDOTOXIN

B-GLUCAN

PATHOGEN ASSOCIATED MOLECULAR PROTEIN

PATTERN RECOGNITION RECEPTOR

(RECEPTOR OF IMMUNE CELL- MACROPHAGE, MONOCYTE, NK CELL, NEUTROPHILS)

DEAD/DAMAGED HOST CELL

DAMAGE ASSOCIATED MOLECULAR PROTEIN

(ATP, MITOCHONDRIA DNA)

TLR's

C TYPE LEPTIN

NOD

RIG-1

NOD AGGREGATES

INFLAMMOSOME

IL-1B , IL-1 γ

ACTIVATION OF INTRACELLULAR SIGNAL

TRANSCRIPTION

Proinflammatory cytokines cause :

a) activation and proliferation of leukocytes,
b) activation of the complement system,
c) upregulation of endothelial adhesion molecules and chemokine expression,
d) tissue factor production, and
e) induction of hepatic acute phase reactants.

In sepsis, there is an exaggeration of the above immune response resulting in collateral damage and death of host cells and tissues.

b. Dysregulation of hemostasis

Sepsis is characterized by the simultaneous activation of the coagulation and inflammatory casca des, as well as the crossing of the hemostatic and inflammatory pathways. The spectrum of this interaction can vary from mild thrombocytopenia to fulminant disseminated intravascular coagulation (DIC).

The release of tissue factor from damaged endothelium cells is assumed to be the primary cause of sepsis's hypercoagulability. Additional sources include monocytes and polymorphonuclear cel ls.[3]

Following the systemic activation of the coagulation cascade by tissue factor, thrombin is produc ed, platelets are activated, and platelet-fibrin clots are formed.
These microthrombi have the potential to induce tissue hypoxia and organ failure due to local per fusion abnormalities.

In vitro experimental models of endotoxemia and bacteremia have shown a complete inhibition of inflammation-induced thrombin production with the blockade of tissue factor.[4]

Apart from the previously mentioned procoagulant impact, there is also a reduction in the anticoa gulant properties of protein C and antithrombin, which typically moderate the coagulation cascad e.Thrombomodulin, which is activated by thrombin, transforms protein C into its active version,

known as activated protein C.After that, activated protein C degrades factors Va and VIIIa, whic h work along with activated protein S to produce an anticoagulant effect.

It is also known to have strong antiinflammatory properties through reducing neutrophil and mon ocyte adherence to endothelium and inhibiting TNFα, IL-1β, and IL-6. (Please explain this statement)

Patients experiencing significant systemic inflammation, such those suffering from sepsis, have r educed amounts of protein C in their plasma, downregulated thrombomodulin, and low levels of protein S. These factors contribute to the uncontrolled spread of the coagulation cascade.[5]

In addition to the hypercoagulability described above, a reduction of fibrinolysis is also observed as a result of sepsis.[6]

As TNFα and IL-1β levels increase, tissue plasminogen activators are released from vascular endothelial cells. The resultant increase in activation of plasmin is blunted by the sustained increase in plasminogen activator inhibitor type 1 (PAI-1). The net effect is diminished fibrinolysis and fibrin removal, which contributes to the perpetuation of microvascular thrombosis.

c. Immunosuppression

Remarkably, a prolonged state of immunosuppression frequently precedes the acute proinflamma tory condition of sepsis.Apoptosis and a diminished sensitivity to inflammatory cytokines result i n a reduction in the quantity of T lymphocytes (helper and cytotoxic).[7]

Additionally, two studies have shown that endotoxins reduce the synthesis of essential cytokines including TNF and IL-6.[8,]

According to the aforementioned research, a septic person's immune system is unable to mount a successful defense against subsequent bacterial, viral, or fungal illnesses.

It has been hypothesized that early lymphopenia can function as a biomarker for immunosuppres sion in sepsis based on a study that demonstrated that a low lymphocyte count early in sepsis (da y 4 of diagnosis) is predictive of both 28-day and 1-year mortality.[10] (Mention the name of study)

d) Cellular, tissue, and organ dysfunction

The underlying mechanism behind tissue and organ dysfunction in sepsis is the decreased delivery to and utilization of oxygen by cells as a result of hypoperfusion. Hypoperfusion occurs due to the cardiovascular dysfunction that is seen in sepsis.[11]

According to several researchstudies, the incidence of septic cardiomyopathy ranges from 18% t o 60%. It is believed to be connected to circulating cytokines, including TNFα and IL-1β, which can depress cardiac myocytes and interfere with their ability to perform mitochondrial functions. (Referencing)

The two most important features of septic cardiomyopathy is that

a) It is acute in onset and reversible.
b) The low left ventricular ejection fraction is accompanied by normal or low left ventricular filling pressures unlike in cardiogenic shock where there is increased left ventricular compliance.[12]

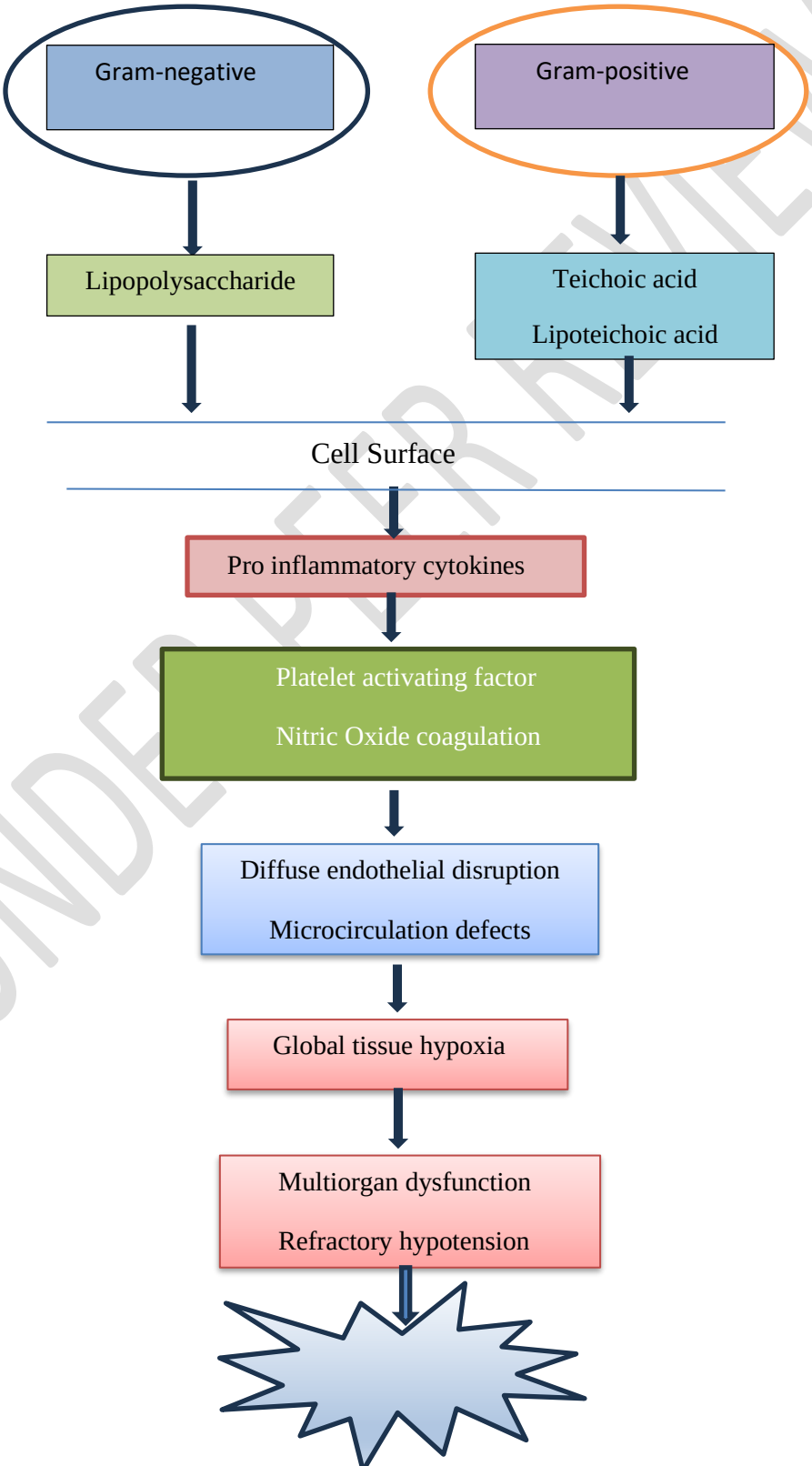
Many research studies have shown that both systolic and diastolic dysfunction happens with decreased stroke volumes and increased end-diastolic and end-systolic volumes in sepsis.[13,14]

However, there is currently no proof that cardiac depression has a specific impact on mortality.S epsis also causes a state of hypotension and distributive shock due to the venous and arterial dilat ation caused by inflammatory mediators and resulting decreased venous return.

All three of the microvasculature's components—venules, capillaries, and arterioles—are dilated.This is made worse by intravascular fluid seeping into the interstitial space due to cha nges in endothelial cadherin and tight junctions, which lead to a loss of endothelial barrier functi on.

Tissue and organ hypoperfusion may arise from the combination of microvascular thrombosis (al ready discussed) and all of the aforementioned alterations in the body's hemodynamics.

Illustration of Bacterial Sepsis leading to Septic Shock



SEPTIC SHOCK

(Is flow chart self-made or referred from somewhere? If referred mention the reference)

As a result, cells produce more lactic acid as a result of enhanced anaerobic glycolysis. Furthermore, the inflammatory response's production of reactive oxygen species (ROS) results in mitochondrial dysfunction and a decrease in ATP levels.

Cell damage is the result of these pathways.A large portion of the morbidity and mortality of sep sis is caused by the more general changes to the tissue and organs that are detailed below.

There are significant alterations to the endothelium with disruption of its barrier function, vasodilation, increased leukocyte adhesion, and the creation of a procoagulant state. This results in accumulation of edema fluid in the interstitial spaces, body cavities, and subcutaneous tissue. In the lungs, there is disruption of the alveolar–endothelial barrier with accumulation of protein-rich fluid in the interstitial lung spaces and alveoli. This can cause a ventilation–perfusion mismatch, hypoxia, and decreased lung compliance producing acute respiratory distress syndrome (ARDS) in extreme cases.

Acute kidney injury occurs in different degrees in the kidneys due to a combination of diminishe d renal perfusion, acute tubular necrosis, and more subtle abnormalities in the tubules and microv asculature.Increased mucosal lining permeability in the gastrointestinal tract leads to both lumina l enzyme autodigestion of the bowel and bacterial translocation across the bowel well.

In the liver, there is a suppression of bilirubin clearance producing cholestasis. Altered mentation is commonly noted in sepsis and is indicative of CNS dysfunction. The endothelial changes undermine the blood–brain barrier, causing the entry of toxins, inflammatory cells, and cytokines.

The ensuing changes of cerebral edema, neurotransmitter disruption, oxidative stress, and white matter damage give rise to a clinical spectrum of septic encephalopathy that varies from mild confusion to delirium and coma.

Sepsis is known to produce a catabolic state. There is a rapid and significant breakdown of muscle to produce amino acids for gluconeogenesis that will fuel the immune cells. In addition, increased insulin resistance can result in a state of hyperglycemia.

(Metabolic changes in sepsis can be included)

Lactic acidosis in Sepsis is due to

a) impaired regional microvascular blood flow & autoregulation

b) mitochondrial dysfunction with impaired pyruvate oxidation

c) excess catecholamines may impair hepatic lactate extraction (by reducing regional hepatic blood flow)

d) lactate clearance is decreased because pyruvate dehydrogenase activity is reduced in both skeletal muscle and liver.[15,16]

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CHAPTER 3

END ORGAN DAMAGE

The underlying mechanism behind tissue and organ dysfunction in sepsis is the decreased delivery to and utilization of oxygen by cells as a result of hypoperfusion.[1]

Hypoperfusion occurs due to the cardiovascular dysfunction that is seen in sepsis.

septic cardiomyopathy varies from 18% to 60% in various studies. It is thought to be related to circulating cytokines, such as TNFα and IL-1β among others, which can cause depression of cardiac myocytes and an interference with their mitochondrial function.

The most important feature of septic cardiomyopathy is that

a) It is acute in onset and reversible.
b) Second, the low left ventricular ejection fraction is accompanied by normal or low left ventricular filling pressures unlike in cardiogenic shock with increased left ventricular compliance .[2]

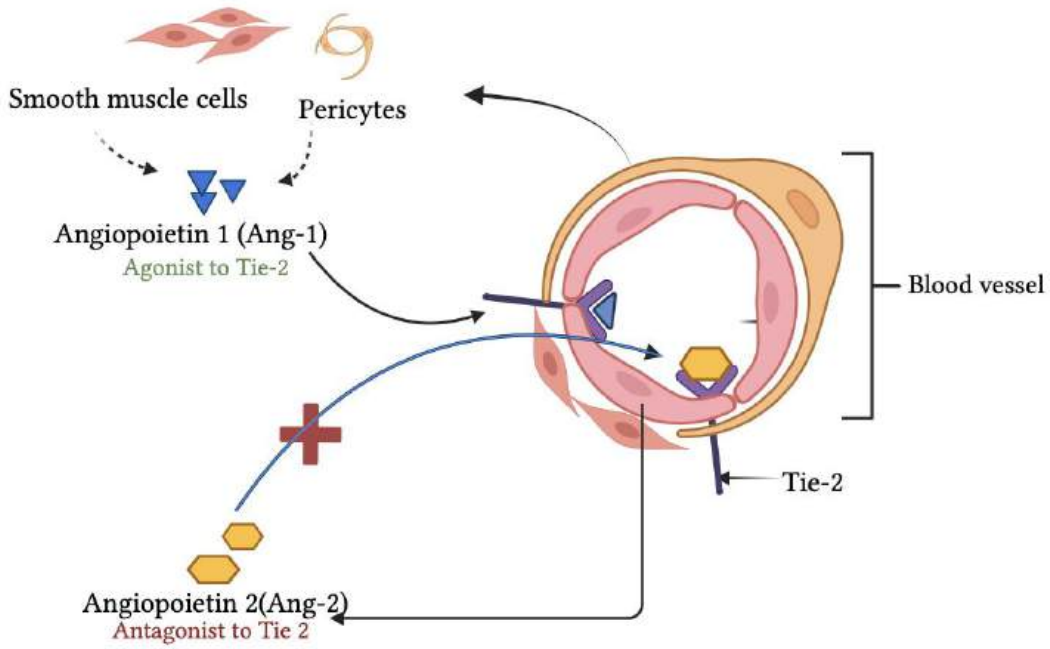
Multiple research studies have shown both systolic and diastolic dysfunction with decreased stroke volumes and increased end-diastolic and end-systolic volumes in sepsis.[3,4]

3.1 Vascular Dysfunction

Sepsis patients have a number of concurrent alterations in the systemic vascular bed, with a growing body of research emphasizing the significance of microcirculatory dysfunction and damage.[5] Increased capillary permeability jeopardizes systemic perfusion by reducing the effective vascular volume. Diffuse endothelial damage and dysfunction, mediated by proinflammatory chemicals, appear to be the origin of this paracellular leakage.[6]

Recent studies, in particular, highlight the critical role that the immunoglobulin-like loop epidermal growth factor domain ligand-receptor system (Ang-Tie) plays in the imbalance of angiopoietin-tyrosine kinase in sepsis patients. Tissue edema is brought on by increased Ang-2 expression and decreased Ang-1 expression, which block the Tie-2 receptor and enhance vascular permeability.[7]Its prognostic value has been demonstrated in clinical studies where high serum Ang-2/Ang-1 ratio was associated with increased severity of organ dysfunction and higher mortality, even in early sepsis.[8,9]

Angiopoietin-Tyrosine kinase receptor (Tie2) system



what is Ang-Tie System ?

Angiopoietin receptor system

A family of growth factors known as angiopoietins consists of the glycoproteins angiopoietins 1 and 2, as well as their orthologs 3 (found in mice) and 4 (found in humans). The receptors, which comprise Tie1 and Tie2, are tyrosine kinases.

Smooth muscle cells and pericytes generate angiopoietin 1, which binds to endothelial cells' Tie2 receptors. ***Angiopoietin 1 is thought to be essential for smooth muscle cell and pericyte recruitment, vascular wall remodeling, and endothelial sprouting.***

Additionally, endothelial cells produce angiopoietin 2, which binds to the Tie2 receptor and functions as an antagonistic factor without activating the receptor.

What is the ang TIE-2 pathway?

A vascular endothelial signaling axis, the Angiopoietin-Tie2 pathway, may mediate the abrupt transition from microvascular integrity to pathological disruption. Tonically activated Tie2 promotes vascular quiescence.

While a successful resuscitation combined with a reasonable and sufficient vascular volume expansion can usually counteract these volume distribution abnormalities[10], some patients still have a concurrent persistent vasodilatory state that prevents them from receiving enough blood flow even after reaching a euvolemic state. Sepsis's most severe expression, septic shock, is what this clinical situation is known as. When neurohormonal stimulus is not able to cause vascular smooth muscle to contract, systemic arterial and venous vasodilation occurs.[11,12] This lowers the pressure gradient needed for venous return, which in turn lowers cardiac output. Inducible nitric oxide synthase (iNOS) over-expression appears to be linked to inflammation-induced endothelial dysfunction, despite the fact that the processes behind this severe vascular dysfunction are still poorly understood.[13]

The overproduction of nitric oxide (NO) causes the smooth muscle cells in the arteries to relax and become hyperpolarized. This prevents the smooth muscle cells from responding to vasoconstrictors, which keeps the blood pressure from rising.[14]Septic shock has also been linked to a vasopressin shortage and the paradoxical simultaneous downregulation of vasoconstrictive receptors; however, the exact mechanism underlying this in humans is still unknown, and attempts to directly reverse these maladaptive mechanisms with therapy have not proven successful.[15-18]

3.2 Cardiac Dysfunction

Contractile dysfunction is the main characteristic of cardiac dysfunction in sepsis, and it manifests as

- Biventricular dilatation,
- Reversible decrease in ejection fraction,
- Diminished blood pressure response to intravenous fluid resuscitation, and
- Inability to improve cardiac output despite high levels of circulating catecholamines

The three main mechanisms involved in sepsis leading to cardiac dysfunction are

1. Myocardial Ischemia
2. Direct myocardial depression
3. Mitochondrial dysfunction

1. **Myocardial ischemia** :

One of the most significant mechanisms of cardiac dysfunction generated by sepsis is decreased blood supply to the myocardium. Myocardial depression, which is reversible, has been linked to the idea of myocardial hibernation in sepsis. This adaptive response to ischemia and hypoxia was suggested as a frequent sign of myocardial dysfunction in sepsis [19]. Despite this defence mechanism, individuals with severe sepsis may experience a significant exacerbation of septic myocardial dysfunction due to cardiac muscle ischemia. The level of intravascular fluid has a significant impact on cardiac function. Hemodynamic instability in sepsis patients is primarily caused by the loss of vascular tone resulting from arterial vasodilation.

What is Myocardial hibernation ?

Hibernating myocardium occurs when a region of heart muscle stops working because there's not enough blood flow. It goes to "sleep" and stops contracting. This process of hibernation can happen over months and even years.

In this state, heart muscle switches from using fatty acids to glucose for contraction keep the cells alive which exhausts quickly. so a hibernating muscle can't help the heart pump blood.

2. **Direct Myocardial depression**

The direct myocardial depression happens mainly because of three reasons

a. Downregulation of β-adrenergic receptor
b. Cardiac myocyte Injury / death
c. Apoptosis

a. Downregulation of β-adrenergic receptors

The initial biochemical mechanism behind direct myocardial depression is a reduction in the components of β-adrenergic receptors, which impedes the adrenergic response at the cardiomyocyte level. This process is mediated by a variety of pro-inflammatory chemicals, mostly nitric oxide [NO] and cytokines.

Cytokines are peptides occasionally produced locally from both somatic cells (endothelial, epithelial, fibroblasts) and immune cells (neutrophils, lymphocytes, macrophages) in response to stress or challenges due to surgical insults, trauma, ischemia, or sepsis, and their signal serves as a means of communication among challenged cells.(20)Cytokines induce production of other inflammatory mediators like NO , Prostanoids and so on. (Please complete the statement/content)

Tumor necrosis factor (TNF)-α and interleukin (IL)-1β are the most common pro-inflammatory cytokines. They are released by macrophages in sepsis and have demonstrated significant cardiac contractility depression. While TNF-α and IL-1β are considered to be the most important components of the inflammatory mechanism (21), NO and oxygen-free radicals are regarded as second-degree factors in the process of septic myocardial depression

in response to TNF-α, IL-1 depresses cardiac contractility by stimulating NO synthase (NOS) [22]. Therefore, inhibitors of IL-1 such as IL-1 receptor antagonist could be a good choice to reduce the morbidity of septic cardiomyopathy patients and to improve their survival, but this finding lacks enough supporting evidence.

Nitric oxide

Expressed in the vascular endothelium, NO is a potential mediator of septic cardiomyopathy and has a wide range of physiological effects in the cardiovascular system.NO is produced by Nitric oxide synthase(NOS). The three isoforms of NOS are NOS1, NOS2 and NOS3.

NOS 1 and 3 were shown as potential players in early septic cardiomyopathy, while NOS 2 was identified as a possible cause of contractile depression in late sepsis.(23) (Can be included in above text)

Prostanoids

Elevated levels of thromboxane, prostacyclin, and other prostanoids have been found in the serum of septic patients. Prostanoids have been proven to have the potential to alter coronary endothelial function.

NOTE :Prostanoid inhibition by nonsteroid anti-inflammatory drugs, mainly ibuprofen and lornoxicam, has also been proposed as a treatment option, but neither drug was efficient in improving survival in clinical studies

Endothelin-1

High levels of endothelin-1 (ET-1) were found to be able to trigger the release of inflammatory cytokines.

Intracellular adhesion molecules

The increased expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) was observed in coronary endothelium and in cardiomyocytes after LPS and TNF-α stimulation. The blockade of VCAM-1 prevented myocardial dysfunction and decreased myocardial neutrophil accumulation.(24)

Complement system

Sepsis is characterized by an activation of the humoral immune response that sets off a cascade of complement proteins, including C5a, a potent pro-inflammatory agent that increases the release of granular enzymes, the creation of cytokines, neutrophil chemotaxis, and reactive oxygen species (ROS). Furthermore, the infusion of anti-C5a antibody can restore C5a-induced cardiodepression, which is mediated via the production of C5aR in cardiomyocytes.(25)

Other mediators

The evidence for more myocardial depressant substances is still emerging, with many new endogenous substances being identified as potential causes of septic myocardial depression. These include estrogenic compounds, histamine, eicosanoids/ prostaglandins, and leukocyte lysozyme (26)

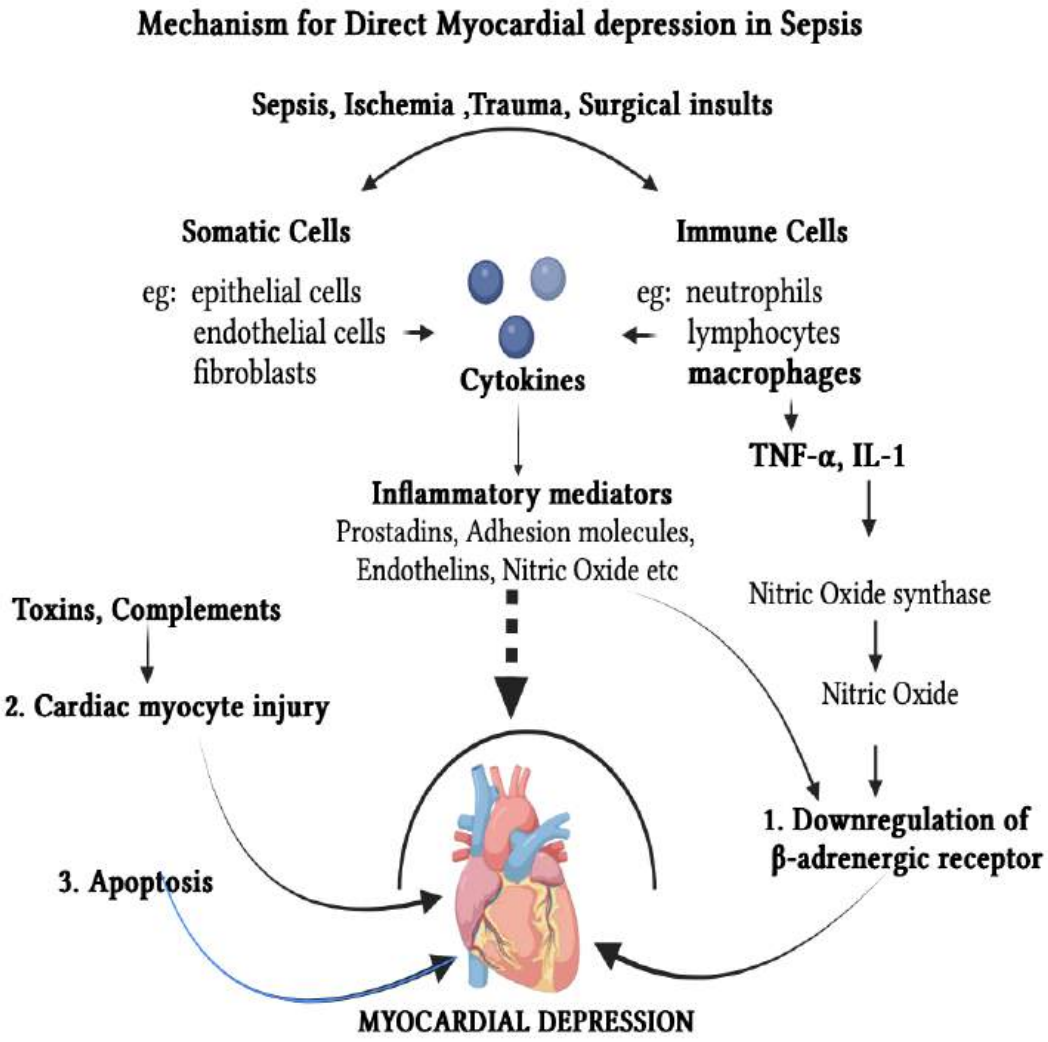
Both B-type natriuretic peptide and atrial natriuretic peptide were significantly elevated in septic patients when compared to controls(27)

b. Cardiac myocyte Injury or death

The second mechanism is characterized by cardiomyocyte injury and/or death caused by toxins, complements, DAMPs, and other myocardial depressants.(28)

c. Apoptosis

Apoptosis of cardiomyocytes is among the leading causes of myocardial depression and sepsis-induced multiple organ dysfunction. When not treated early, myocardial dysfunction often progresses with apoptosis of cardiomyocytes, followed by downregulation of β-adrenoceptors and impairment of myofibril function due to the disruption of calcium liberation



3. Mitochondrial dysfunction

Metabolic dysfuction

While the exact processes behind mitochondrial failure in sepsis remain unclear, multiple investigations have verified that mitochondrial dysfunction plays a pivotal role in energy depletion-induced septic cardiomyopathy.(29)

The heart is likely to be affected by sepsis-induced mitochondrial dysfunction due to its strong dependence on high adenosine triphosphate (ATP) levels to maintain its contraction and diastolic function. With the aim of finding options of restoring mitochondrial function.

Mitochondrial oxidative stress and injury

Because of mitochondrial dysfunction in sepsis, there is an increase in reactive oxygen species (ROS) such as superoxide, which can cause oxidative injury and ongoing harm to cells and organs. In the septic heart, an imbalanced generation of reactive oxygen species (ROS) and reactive nitrogen species hinders oxidative phosphorylation(30)

This directly prevents mitochondria from respiring and harms a number of subcellular elements, including mitochondrial proteins, which frequently results in mitochondrial apoptosis. Oxidative stress results in mitochondrial dysfunction and has been strongly associated with organ failure in sepsis models and reported in septic patients(31)

Other involved biochemical pathways include mitochondria Ca^{2+} flux, mitochondrial DNA (mtDNA) in sepsis, mitochondrial dynamics, mitochondrial biogenesis, and mitochondrial autophagy.

3.3 Pulmonary dysfunction

Acute respiratory distress syndrome (ARDS) is most frequently caused by sepsis[32], and it affects 40% of patients who have sepsis or septic shock.[33]
Acute respiratory failure with diffuse pulmonary infiltrates brought on by alveolar damage and in creased pulmonary vascular permeability to proteinrich fluid are the hallmarks of acute respirator y distress syndrome (ARDS).

Studies have demonstrated that proinflammatory cytokines, such as tumor necrosis factor alpha (TNF-
α) or IL1β, widespread endothelial barrier dysfunction, platelet activation with microthrombi for mation, and neutrophil extracellular trap formation, are the mechanisms underlying this alveolar barrier injury, even though the exact cause of the damage is still unknown.[34-36]
Severe hypoxemia and hypercapnia are brought on by the increased physiological dead space cau sed by the edema and alveolar injury.[37]

Finally,there is disruption of the alveolar–endothelial barrier with accumulation of protein-rich fluid in the interstitial lung spaces and alveoli. This can cause a ventilation–perfusion mismatch, hypoxia, and decreased lung compliance producing acute respiratory distress syndrome (ARDS) in extreme cases

3.4 Renal / Kidney dysfunction

Another prominent target of this gradual organ deterioration is the renal system.
More than half of patients with sepsis or septic shock experience acute kidney damage (AKI)[38,39] , with sepsis being the most common contributory factor in critically sick patients.[40]
Serum creatinine elevation of > 0.3 mg/dl in 48 hours, 50% increase from baseline in 7 days, or u rine output < 0.5 ml/kg/h for more than 6 hours are the criteria used to establish AKI.[41]
Compared to patients with sepsis without AKI[42] and patients with non-
sepsis linked AKI[43], patients with sepsis-associated AKI have a 62% and 36% higher risk of in-hospital mortality, respectively.

The fundamental underpinnings of sepsis
associated AKI remain unclear despite its high frequency.
The traditional model has been renal hypoperfusion resulting in acute tubular necrosis; however, recent research indicates that the local microcirculation and inflammatory signals—
such as ischemia-reperfusion damage, oxidative stress, and tubular apoptosis—
may play an even more significant role.[44,45]
Additionally, the use of nephrotoxic medications and excessive or less-
physiological fluid resuscitation during sepsis treatment can potentially lead to AKI.
Increased intracapsular pressure, decreased glomerular filtration rate, and subsequent organ edem a are caused by volume overload, which also raises central venous pressure and renal vascular pr essure.[46,47]

The part that resuscitation fluid selection plays in the development of AKI linked to sepsis has ga rnered attention recently.
Evidence suggests that the high chloride content in normal saline (0.9% sodium chloride) may be related with lower renal outcomes and survival when compared to balanced crystalloids (e.g., la ctated Ringer's solution).[48-52]

3.5 Coagulation dysfunction

Proinflammatory cytokines also promote platelet adhesion and coagulation cascade activation by increasing endothelial luminal expression and serum circulation of intercellular adhesion molecu le-1 (ICAM-1) and VCAM-1.

Furthermore, the same proinflammatory cytokines downregulate the anticoagulant pathways. A potent anticoagulant with fibrinolytic qualities, Protein C, is less activated when endothelial sy nthesis of thrombomodulin, a glycoprotein that binds thrombin to prevent fibrinogen from conve rting to fibrin, is significantly reduced.[53,54]

It's interesting to note that neutrophil extracellular traps appear to be the mechanism behind this, as they cause fibrin clot formation, thrombin synthesis, and platelet aggregation.[55] Subsequently, microthrombi formation in small vessels exacerbates the impairment of oxygen su pply and perfusion, leading to damage and malfunction of the organs.

Overall, this procoagulant over-
expression results in platelet consumption and coagulation factor depletion, which causes overt d isseminated intravascular coagulation (DIC) and classical sepsis-
associated thrombocytopenia. This is particularly true when tissue factor is expressed and von W illebrand factor is secreted when endothelial cells and monocytes are activated to the point of cyt okine release after injury.[56]
Up to 55% and 61% of individuals with sepsis and septic shock, respectively, develop thrombocy topenia and/or DIC.[57,58]

Worse outcomes, including an increased risk of major bleeding events and death, are linked to bo th of these diseases.[58-62]
The prevention and management of significant bleeding events is the current approach to treating these coagulation abnormalities[63], whereas attempts to intervene in the pathophysiology of this s yndrome have proven fruitless.[64-66]

3.6 Hepatic /Liver dysfunction

The liver is a target of the host response and a regulator of the inflammatory process, therefore it is by no means an innocent bystander in sepsis. Kupffer cells release more IL-1β, IL-6, and TNF-α when they are exposed to lipopolysaccharides.[67,68] Acute-
phase proteins (APPs), which have broad pro- and anti-
inflammatory activities, are released into the systemic circulation by hepatocytes in response to p

ro-inflammatory cytokines.[69]
Thus, it has been postulated that hepatocytes, through APPs, play a crucial part in maintaining im munological homeostasis during sepsis by averting a too inflammatory or immunosuppressive st ate .Given that concurrent hepatic impairment affects up to 46% of patients with sepsis[70] and has been linked to a greater 28-day death rate[71], this regulatory role becomes increasingly important.

Hypoxic hepatitis and sepsisinduced cholestasis are two main processes that appear to account fo r the liver damage and consequent dysfunction in sepsis.

A clinical setting that results in decreased oxygen delivery or utilization by the liver (such as car diac, respiratory, or circulatory failure) and at least 20 times the upper limit of normal serum ami notransferase levels, without additional potential causes of liver injury, is commonly referred to a s hypoxic hepatitis.[72,73]

Deep hemodynamic changes, the development of microthrombi, sinusoidal blockage, and endoth elial dysfunction all contribute to sepsis and reduce liver perfusion, which in turn causes damage and hypoxic hepatitis .
Sepsis was the second most common predisposing factor for hypoxic hepatitis in a recent study t hat included 1116 critically ill patients with this illness.[74] With an in-
hospital mortality of 53 percent, only behind cardiac failure

However, there is a lack of standardization in the classification of sepsis-
induced cholestasis, its origin remains unclear, and its prognostic significance is uncertain.
The diagnosis of sepsis-
induced cholestasis is typically based on an elevation of total serum bilirubin greater than 2 mg/d l and aminotransferases greater than at least 2-
fold the upper normal limit.[75] This condition is defined as impaired bile formation and defective f low caused by a non-obstructive intrahepatic insult .
According to animal models, proinflammatory cytokines change the expression of bile acid trans porters on hepatocytes, which reverses the normal flow of bile acids into the blood.
Additionally, by preventing cholangiocyte secretion, pro-
inflammatory cytokines and NO cause ductular cholestasis.[76,77]

3.7 Central Nervous System dysfunction

Central nervous system (CNS) dysfunction in sepsis patients is a multifaceted process influenced by systemic inflammation, neuroinflammation, and direct and indirect effects of infection on the brain. Understanding the pathophysiology involves examining how sepsis-related factors disrupt normal CNS function and lead to neurological complications.

BBB Disruption in Sepsis:

The Blood-Brain Barrier (BBB) is a highly selective semipermeable barrier that separates the circulating blood from the brain extracellular fluid in the central nervous system (CNS). Its main function is to protect the brain from harmful substances circulating in the bloodstream while allowing essential nutrients and molecules to pass through to maintain proper brain function.

1. **Systemic Inflammation:**
    - **Cytokine Release:** During sepsis, the body mounts a systemic inflammatory response to the infection. This response involves the release of pro-inflammatory cytokines such as Tumor Necrosis Factor-alpha (TNF-α), Interleukin-1 beta (IL-1β), and Interleukin-6 (IL-6).
    - **Impact on Endothelial Cells:** These cytokines can act on endothelial cells that form the BBB. TNF-α and IL-1β, in particular, can disrupt the integrity of tight junctions between endothelial cells of the BBB.
2. **Tight Junction Disruption:**
    - **Role of Tight Junctions:** Tight junctions are complex protein structures that seal the intercellular space between endothelial cells, preventing large molecules and pathogens from crossing into the brain.
    - **Effect of Cytokines:** In sepsis, cytokines induce the phosphorylation and internalization of tight junction proteins such as occludin and claudins. This process weakens the tight junctions, leading to increased permeability of the BBB.
3. **Increased Permeability:**
    - **Leakage of Substances:** As the BBB becomes more permeable, circulating pathogens, inflammatory mediators, and immune cells can cross into the brain parenchyma.
    - **Neuroinflammation:** The entry of these substances triggers a localized inflammatory response within the brain, termed neuroinflammation, which exacerbates neuronal injury and dysfunction.
4. **Direct Effects of Pathogens and Toxins:**
    - **Microbial Products:** Some pathogens produce toxins (e.g., lipopolysaccharide in gram-negative bacteria) that directly affect BBB permeability.
    - **Activation of Glial Cells:** Toxins and microbial products can activate microglia and astrocytes, leading to further release of inflammatory cytokines and perpetuating BBB disruption.
5. **Clinical Implications:**
    - **Neurological Complications:** BBB dysfunction in sepsis contributes to the development of CNS complications such as delirium, encephalopathy, seizures, and stroke.
    - **Therapeutic Challenges:** The increased permeability of the BBB complicates the delivery of therapeutic agents to the brain, as many drugs cannot effectively cross the compromised barrier.

Sepsis-associated encephalopathy affects up to 70% of critically sick patients with sepsis.[78] Beyond direct infections of the brain and its surrounding tissues (such as meningitis or encephalitis), sepsis damages the central nervous system through a variety of methods, one of which is the critical mismatch between systemic perfusion and metabolic demands.
Critical brain ischemia injuries can result from significant systemic hemodynamic instability, which can override the central nervous system's finely tuned perfusion regulation systems.[79] Furthermore, sepsis-induced coagulopathy and the development of cardiac arrhythmias may help to explain why patients with sepsis are more likely to experience ischemic and hemorrhagic strokes.[80-83]

However, the pronounced inflammatory response leads to blood-brain barrier rupture and microcirculatory failure, which permits the entry of neurotoxins and inflammatory mediators into brain tissue.[84] Crucially, the elevated NO diffuses even past the blood-brain barrier that is still intact, resulting in oxidative stress and neuronal dysfunction as well as death.[85]

This acute brain dysfunction, which can range from delirium to convulsions and coma[84], is also significantly influenced by the disruption of cholinergic and dopaminergic neurotransmission.[86,87] Furthermore, the autonomic dysfunction is worsened when these insults affect vital organs, such as the brainstem, which prolongs hemodynamic instability and raises the risk of death.[88]

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CHAPTER 4
LANDMARK CLINICAL TRIALS

4.1 RIVERS 2001

This table provides a detailed explanation of the purpose, clinical intervention, outcomes, and conclusions of the RIVERS 2001 trial, highlighting its significance in critical care management for severe sepsis and septic shock.

Aspect	Description
Purpose	The RIVERS (Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock) trial aimed to assess the effectiveness of early, goal-directed therapy (EGDT) compared to standard therapy in managing severe sepsis and septic shock. Severe sepsis and septic shock are critical conditions where prompt and appropriate treatment is crucial to improve patient outcomes.
Clinical Intervention	The trial's intervention involved implementing EGDT within the first 6 hours of patient presentation in the EGDT group. This approach required achieving and maintaining specific physiological targets: central venous pressure (CVP), mean arterial pressure (MAP), and central venous oxygen saturation (ScvO2). Standard therapy was based on usual clinical practices at the participating centers.
Outcome	The primary outcome measured was mortality within 90 days after enrollment. The trial found a significant reduction in mortality among patients who received EGDT compared to those who received standard therapy alone. This outcome demonstrated the potential benefits of early, goal-directed therapy in improving survival rates for patients with severe sepsis and septic shock.
Conclusion	The RIVERS trial concluded that implementing EGDT as specified (targeting CVP, MAP, and ScvO2 goals early in the course of treatment) led to improved outcomes, particularly lower mortality rates, compared to standard therapy alone. These findings supported the adoption of EGDT protocols in the initial management of severe sepsis and septic shock patients, emphasizing the importance of early intervention and targeted therapeutic goals.

Early goal-directed therapy in the treatment of severe sepsis and septic shock Rivers. NEJM 2001; 345:1368-1377. doi:10.1056/NEJMoa010307

4.2 SOAP II 2010

Aspect	Description
Purpose	The SOAP II trial aimed to evaluate the effectiveness of protocol-based resuscitation (PBR) compared to usual care in the management of patients with septic shock. The trial sought to determine if PBR, which includes specific hemodynamic and oxygen delivery targets, would improve outcomes in terms of mortality and organ dysfunction.
Clinical Intervention	Patients in the PBR group received intensive monitoring and management according to predefined hemodynamic and oxygen delivery goals. These goals included maintaining central venous pressure (CVP), mean arterial pressure (MAP), and mixed venous oxygen saturation (SvO2) within specified ranges using fluids, vasopressors, and inotropic agents as needed. Standard care patients received treatment as per the discretion of the treating clinicians.
Outcome	The primary outcome measured was mortality at 28 days after randomization. Secondary outcomes included organ dysfunction and other markers of morbidity. The trial found no significant difference in mortality between the PBR and standard care groups, indicating that PBR did not confer a survival benefit over usual care in patients with septic shock.
Conclusion	The SOAP II trial concluded that protocol-based resuscitation, as implemented in the study, did not result in lower mortality rates compared to standard care for patients with septic shock. While PBR aimed to optimize hemodynamic parameters and oxygen delivery, it did not demonstrate superiority over usual care in improving survival outcomes or reducing organ dysfunction in this patient population.

This table provides a comprehensive overview of the purpose, clinical intervention, outcomes, and conclusions drawn from the SOAP II 2010 trial, highlighting its findings in the context of managing septic shock with protocol-based resuscitation.

De Backer D, Biston P, Devriendt J, Madl C, Chochrad D, Aldecoa C, Brasseur A, Defrance P, Gottignies P, Vincent JL; SOAP II Investigators. Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med. 2010 Mar 4;362(9):779-89. doi: 10.1056/NEJMoa0907118. PMID: 20200382.

4.3 ProCESS 2014

Aspect	Description
Purpose	In adult patients with sepsis, does protocol-based care compared to usual care reduce death within 60 days ?
Clinical Intervention	▪ Early goal-directed therapy (EGDT) group: strict protocolised care (based on Rivers study) for 6 hours with dedicated doctor, nurse and research assistant that provided prompts ▪ Protocol-based standard therapy group: relaxed protocolised care (based upon published expert opinions) for 6 hours with dedicated doctor, nurse and research assistant that provided prompts
Outcome	The primary outcome measured was mortality at 60 days and secondary outcome was all cause in hospital mortality at 90 days.
Conclusion	No significant advantage, with respect to mortality or morbidity, of protocol-based resuscitation over bedside care that was provided according to the treating physician's judgement.

This table provides a detailed overview of the purpose, clinical intervention, outcomes, and conclusions drawn from the ProCESS 2014 trial, emphasizing its findings regarding protocolized care in the management of septic shock.

ProCESS Investigators; Yealy DM, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, Pike F, Terndrup T, Wang HE, Hou PC, LoVecchio F, Filbin MR, Shapiro NI, Angus DC. A randomized trial of protocol-based care for early septic shock. N Engl J Med. 2014 May 1;370(18):1683-93. doi: 10.1056/NEJMoa1401602. Epub 2014 Mar 18. PMID: 24635773; PMCID: PMC4101700.

4.4 ARISE 2014

Aspect	Description
Purpose	The ARISE trial aimed to evaluate the effectiveness of early goal-directed therapy (EGDT) compared to usual care in the management of patients presenting to the emergency department with early septic shock. The trial sought to determine if EGDT would improve outcomes such as mortality and organ dysfunction.
Clinical Intervention	Patients in the EGDT group received a structured resuscitation protocol involving aggressive fluid resuscitation, vasopressor therapy to achieve target mean arterial pressure (MAP), and blood transfusion if hemoglobin levels dropped below specified thresholds. Standard care patients received treatment based on clinical judgment and usual practices at the participating centers.
Outcome	The primary outcome was mortality from any cause within 90 days after randomization. Secondary outcomes included organ dysfunction and health-related quality of life. The trial found no significant difference in mortality between the EGDT and standard care groups, indicating that EGDT did not confer a survival benefit over usual care in patients with early septic shock.
Conclusion	The ARISE trial concluded that early goal-directed therapy, as implemented in the study, did not result in lower mortality rates compared to standard care for patients presenting with early septic shock in the emergency department. The findings suggested that adherence to a specific EGDT protocol did not improve survival outcomes or reduce organ dysfunction in this patient population.

This table provides a detailed overview of the purpose, clinical intervention, outcomes, and conclusions drawn from the ARISE 2014 trial, highlighting its findings regarding early goal-directed therapy in the management of septic shock in the emergency department setting.

Australasian Resuscitation In Sepsis Evaluation Randomised Controlled Trial ARISE Investigators. NEJM Oct 1 2014 (ePub); DOI: 10.1056/NEJMoa1404380

4.5 ProMISe 2015

Aspect	Description
Purpose	The ProMISe trial aimed to assess the effectiveness of protocolised management (PM) compared to usual care in the early management of patients with sepsis admitted through emergency departments. The trial aimed to determine if PM, which involved standardized protocols for fluid resuscitation, hemodynamic support, and infection control, would improve clinical outcomes including mortality and organ dysfunction.
Clinical Intervention	Patients in the PM group were managed according to a protocol that included early aggressive fluid resuscitation targeting predefined hemodynamic goals (e.g., central venous pressure and mean arterial pressure), timely administration of antibiotics, and other supportive measures. This approach aimed to achieve and maintain hemodynamic stability and optimize tissue perfusion early in the course of sepsis. Standard care patients received treatment based on the discretion of the treating clinicians, which typically followed usual clinical practices.
Outcome	The primary outcome measure was mortality from any cause at 90 days after randomization. Secondary outcomes included the development of organ dysfunction and health-related quality of life. The trial reported no statistically significant difference in mortality between the PM and standard care groups, indicating that PM did not confer a survival advantage over usual care in patients with sepsis.
Conclusion	The ProMISe trial concluded that protocolised management, as implemented in the study, did not lead to improved mortality rates compared to standard care for patients presenting with sepsis in the emergency department. The findings suggested that adherence to a specific protocol for early sepsis management did not demonstrate superiority in reducing mortality or organ dysfunction in this patient population.

ProMISe Trial Investigators. 2015; published on line published on March 17
DOI: 10.1056/NEJMoa1500896

4.6 CLASSIC 2022

Aspect	Description
Purpose	The CLASSIC trial aimed to find out if restrictive approach to fluid therapy compared to a standard care result in fewer deaths at day 90 in adult patients in ICU with septic shock.
Clinical Intervention	**Restrictive Group:** Patients managed with a restrictive fluid strategy. **Indications for Fluid Administration:** • **Severe Hypoperfusion:** Defined by lactate > 4 mmol/L, MAP < 50 mmHg (with or without vasopressors/inotropes), mottling beyond the kneecap, or urine output < 0.1 ml/kg within the first 2 hours post randomization. • **Overt Losses:** Fluids allowed to correct for losses (e.g., diarrhea and vomiting) but not for volume expansion. • **Electrolyte Derangements:** IV fluids permissible if oral or enteral routes are contraindicated, aiming for 1L/24 hours total intake to correct electrolyte imbalances. **Fluid Administration Protocol:** • Administer 250-500 ml bolus of crystalloid if any severe hypoperfusion criteria are met, followed by re-evaluation. • Fluids used for medications and nutrition are included in total intake; minimize volume for medication administration.
Outcome	The primary outcome measure was mortality from any cause at 90 days after randomization. Restrictive group had 42.3% mortality vs 42.1% among Standard treatment group.
Conclusion	The CLASSIC 2022 trial concluded that in adult ICU patients with septic shock, IV fluid restriction did not result in fewer deaths at 90 days compared to standard IV fluid therapy

The above summary outlines the criteria for fluid administration in a restrictive manner, focusing on correction of specific indications of severe hypoperfusion and electrolyte imbalances while avoiding fluid overload.

Meyhoff TS, Hjortrup PB, Wetterslev J, Sivapalan P, Laake JH, Cronhjort M, Jakob SM, Cecconi M, Nalos M, Ostermann M, Malbrain M, Pettilä V, Møller MH, Kjær MN, Lange T, Overgaard-Steensen C, Brand BA, Winther-Olesen M, White JO, Quist L, Westergaard B, Jonsson AB, Hjortsø CJS, Meier N, Jensen TS, Engstrøm J, Nebrich L, Andersen-Ranberg NC, Jensen JV, Joseph NA, Poulsen LM, Herløv LS, Sølling CG, Pedersen SK, Knudsen KK, Straarup TS, Vang ML, Bundgaard H, Rasmussen BS, Aagaard SR, Hildebrandt T, Russell L, Bestle MH, Schønemann-Lund M, Brøchner AC, Elvander CF, Hoffmann SKL, Rasmussen ML, Martin YK, Friberg FF, Seter H, Aslam TN, Ådnøy S, Seidel P, Strand K, Johnstad B, Joelsson-Alm E, Christensen J, Ahlstedt C, Pfortmueller CA, Siegemund M, Greco M, Raděj J, Kříž M, Gould DW, Rowan KM, Mouncey PR, Perner A; CLASSIC Trial Group. Restriction of Intravenous Fluid in ICU Patients with Septic Shock. N Engl J Med. 2022 Jun 30;386(26):2459-2470. doi: 10.1056/NEJMoa2202707. Epub 2022 Jun 17. PMID: 35709019.

(Correct the referencing)

4.7 CLOVERS 2023

Aspect	Description
Purpose	To determine whether a restrictive fluid strategy, coupled with early vasopressor use, compared to a liberal fluid strategy, influences mortality in patients with sepsis-induced hypotension before discharge by day 90.
Clinical Intervention	**Restrictive group :** • Criteria for fluid cessation: SBP < 100 mmHg or MAP < 65 mmHg after receiving 1 – 3L crystalloid. • Cease all bolus and maintenance fluids. • Up to 2L fluid boluses allowed (including pre-randomization) at clinician's discretion. • If MAP < 65 mmHg or SBP < 90 mmHg: Initiate titration of norepinephrine ± second vasopressor to achieve MAP > 65 mmHg. • Once MAP target achieved, limit fluids to keep vein open (KVO), medications, and nutrition. • Rescue fluids (500 ml bolus) recommended for severe or refractory hypotension, lactate > 4 mmol/L with increasing trend, sinus heart rate > 130 bpm for 15 mins, echocardiographic or hemodynamic signs of extreme hypovolemia, or clinician's discretion.
Outcome	The primary outcome was mortality before discharge home by day 90.Secondary outcomes may include hemodynamic stability, organ dysfunction, and other clinical parameters. Conclusion is drawn based on mortality data between the restrictive and liberal fluid strategy groups
Conclusion	The study found that implementing a restrictive fluid strategy with early vasopressor usage did not result in significantly lower or higher mortality rates compared to a liberal fluid strategy in patients with sepsis-induced hypotension.

National Heart, Lung, and Blood Institute Prevention and Early Treatment of Acute Lung Injury Clinical Trials Network; Shapiro NI, Douglas IS, Brower RG, Brown SM, Exline MC, Ginde AA, Gong MN, Grissom CK, Hayden D, Hough CL, Huang W, Iwashyna TJ, Jones AE, Khan A, Lai P, Liu KD, Miller CD, Oldmixon K, Park PK, Rice TW, Ringwood N, Semler MW, Steingrub JS, Talmor D, Thompson BT, Yealy DM, Self WH. Early Restrictive or Liberal Fluid Management for Sepsis-Induced Hypotension. N Engl J Med. 2023 Feb 9;388(6):499-510. doi: 10.1056/NEJMoa2212663. Epub 2023 Jan 21. PMID: 36688507; PMCID: PMC10685906.

CHAPTER 5

TREATMENT PROTOCOLS

5.1 SEPSIS GUIDELINES – SURVIVING SEPSIS CAMPAIGN 2021

The 2021 Surviving Sepsis Campaign Guidelines presented a comprehensive set of evidence-based recommendations tailored for adult patients diagnosed with sepsis and septic shock. This version of the guidelines prioritized a multifaceted, international perspective, as well as the long-term consequences of sepsis as experienced by both patients and their families.

The guidelines included the subsequent sections:

1) Screening and prompt intervention;

2) Infectious etiologies;

3) Hemodynamic optimization;

4) Respiratory support;

5) Adjunctive therapies; and

6) Care objectives and long-term prognoses.

Despite significant progress in the rapid identification and resuscitation of affected individuals, sepsis remains a major factor contributing to morbidity and mortality worldwide, underscoring the necessity for sustained investigation, educational endeavors, and the propagation of knowledge.[1,2]

5.1.1 Screening and early treatment

a) Sepsis screening

The development of sepsis screening tools has evolved significantly over time, beginning with basic clinical criteria and advancing to more sophisticated scoring systems. Early tools focused on identifying systemic inflammatory response syndrome (SIRS) criteria, which were later

supplemented by more comprehensive systems like the Sequential Organ Failure Assessment (SOFA) and its derivatives. These tools have been refined to improve sensitivity and specificity in detecting sepsis, particularly in emergency and critical care settings. The evolution of these tools reflects ongoing efforts to enhance early recognition and treatment of sepsis, thereby reducing associated morbidity and mortality.

Sepsis represents a potentially life-threatening organ dysfunction due to dysregulated response to infection, and hospital mortality in septic shock often
exceeds 40%.[2] The goal of early detection and treatment is to lower morbidity and death.The Gui delines strongly advised utilizing performance improvement programs, which include sepsis scre ening and standard operating procedures for treatment, in order to facilitate early detection.

Early Sepsis Screening Tools

- **SIRS Criteria**: Initially, sepsis was identified using SIRS criteria, which included parameters like body temperature, heart rate, respiratory rate, and white blood cell count. However, these criteria were not specific to sepsis and could be triggered by other conditions

- **SOFA and qSOFA**: The SOFA score was developed to assess organ dysfunction and predict sepsis outcomes. The quick SOFA (qSOFA) was later introduced for rapid assessment in non-intensive care settings, focusing on altered mental status, systolic blood pressure, and respiratory rate

The quick Sequential (Sepsis-related) Organ Failure Assessment (qSOFA), which has been widely used since the release of the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), is one of the instruments used for sepsis screening**.**[3]

Latest Screening Tools

NEWS2 Score

The NEWS2 (National Early Warning Score 2) is an updated version of the original NEWS, developed to improve the detection and response to clinical deterioration, including sepsis. It is widely used in healthcare settings to standardize the assessment of acutely ill patients.

Components of NEWS2

1. Respiratory Rate: Measures the number of breaths per minute.
2. Oxygen Saturation: Assesses blood oxygen levels.
3. Temperature: Measures body temperature.
4. Systolic Blood Pressure: Assesses blood pressure.

5. Heart Rate: Measures the number of heart beats per minute.
6. Level of Consciousness (AVPU): Assesses the patient's alertness, response to voice, pain, or unresponsiveness.

Each parameter is scored from 0 to 3, with the total NEWS2 score ranging from 0 to 20. Higher scores indicate a higher risk of clinical deterioration.

Interpretation

- Low Score: Indicates stable condition.
- Moderate Score: Suggests the need for closer monitoring.
- High Score: Indicates a high risk of clinical deterioration and the need for urgent intervention.

LIP Score

The LIP score is a sepsis screening tool that incorporates three key biomarkers:

Lymphocyte count (Lym),

International Normalized Ratio (INR), and

Procalcitonin (PCT) levels.

It was developed to provide a simple and effective method for identifying sepsis, especially in settings with limited resources. Each component is scored, and the total LIP score ranges from 0 to 3. A **LIP score of 3 or higher** indicates a high likelihood of sepsis

LIP **Score ≤ 2**: Low risk of sepsis.

LIP **Score ≥ 3**: High risk of sepsis, suggesting the need for immediate evaluation and potential intervention[4]

Risk Stratification tools

REDS score

The REDS score is a clinical tool designed to risk-stratify patients with suspected sepsis in the emergency department (ED). It aims to identify patients at high risk of mortality and guide decisions regarding their management and need for intensive care. The score is derived from a combination of clinical parameters and has been shown to perform comparably or better than other existing sepsis scoring systems.

The REDS score is calculated from a combination of the following components:

- qSOFA score
- sMISSED score
- Refractory hypotension (RH)
- Lactate

The REDS score ranges from 0 to 12, with a score of 3 or more indicating a high risk of mortality[5]

Current Trends

Combining existing screening tools with blood investigations like Lactate and C-Reactive protein is though to be more effective in recognising sepsis. A high blood lactate level is linked to negative outcomes in a number of conditions, despite having a low predictive value when used alone. Measuring lactate levels during sepsis screening is not strongly advised by the SSC Guidelines; however, an increased lactate level should initiate a comprehensive clinical assessment of the patient.

Screening tools are being developed based on machine learning and AI technologies. However the clinical application is yet to be tested and validated

b) **Initial resuscitation**

Early and appropriate fluid resuscitation has been a pillar in the treatment of sepsis. However, controversy existed regarding what constitutes an “adequate” volume of fluids in the initial phase. Previous iterations of the SSC Guidelines issued a strong recommendation to use a fixed volume of 30 ml/kg in the first 3 hours.

Notwithstanding, the 2021 SSC Guidelines reclassified this intervention as a weak recommendation due to the inadequate quality of evidence that supports this practice. The panel reviewed three substantial randomized controlled trials (RCTs) focused on early-goal directed therapy in the context of sepsis.[6,7,8]

While not explicitly outlined in the study protocol, a majority of the participants received approximately 30 ml/kg of intravenous fluids prior to the randomization process, indicating that this may be regarded as "standard care" across various clinical environments.[9]

Furthermore, one RCT conducted within a resource-constrained setting revealed inferior outcomes associated with a sepsis protocol that utilized a greater volume of fluids when juxtaposed with standard care practices.[10]

Finally, retrospective analyses concerning the subset of patients afflicted with congestive heart failure and end-stage renal disease—who may be presumed to exhibit poorer outcomes with increased fluid volumes—revealed that these patients actually exhibited improved outcomes when they received adequate intravenous (IV) resuscitation within the initial three hours of their clinical presentation.[11]

Subsequent to the initial resuscitation phase, the approach to fluid administration develops into a more intricate challenge, as the potential for fluid overload intensifies, a condition associated with unfavorable outcomes which necessitates a more thoughtful strategy.

There are various static and dynamic measures which may be helpful in day to day practice.

Static Measures

i) Central Venous Pressure

ii) Pulmonary Capillary Wedge Pressure

iii) Blood Pressure

iv) Urine Output

v) IVC(Inferior vena cava) diameter

Static measures are parameters that remain relatively constant and are measured at a single point in time. They include:

i)Central Venous Pressure (CVP): Reflects the pressure in the thoracic vena cava near the right atrium.

Central venous pressure (CVP) measurement is a critical tool in fluid resuscitation, particularly in managing critically ill patients. CVP provides an estimate of circulatory filling and cardiac preload, which are essential for guiding fluid therapy. However, its use is not without limitations and should be considered alongside other clinical parameters. The following sections explore the importance and application of CVP in fluid resuscitation.

Importance of CVP in Fluid Resuscitation

- CVP is a direct measurement of venous pressure within the vena cava or right atrium, providing insights into the relationship between venous return and right heart function.[12]

  12. Xi, Xiang. Central Venous Pressure Monitoring. (2023).191-205. doi: 10.1002/9781119581154.ch15

- In hypovolemic shock, CVP measurement can guide fluid therapy by indicating the need for fluid administration or cessation.

Limitations and Considerations

- CVP should not be used as the sole parameter for determining fluid status, as it does not directly reflect intravascular volume.[12]
- Changes in CVP should be interpreted alongside cardiac output (CO) to avoid misleading conclusions about fluid responsiveness(Mallat & Reddi, 2018).[13]
- Non-invasive methods, such as measuring the superior vena cava (SVC) diameter and collapsibility, offer alternative ways to estimate CVP, though they have varying sensitivity and specificity.[14]

While CVP remains a valuable tool in fluid resuscitation, its limitations necessitate a comprehensive approach that includes other hemodynamic parameters. Non-invasive methods like ultrasonography offer promising alternatives but require careful interpretation and further research to establish their efficacy in clinical practice.

ii)Pulmonary Capillary Wedge Pressure (PCWP): Estimates left atrial pressure

To calculate the **Pulmonary Capillary Wedge Pressure (PCWP)**, you typically need to use a **Swan-Ganz catheter** and follow these steps:

1. **Insert the Catheter**: Insert a balloon-tipped, multi-lumen catheter (Swan-Ganz catheter) into a peripheral vein (e.g., jugular or femoral vein).
2. **Advance the Catheter**: Advance the catheter into the right atrium, right ventricle, and then into a branch of the pulmonary artery.
3. **Measure Pulmonary Artery Pressure**: Inflate the balloon to occlude the branch of the pulmonary artery. The pressure measured distal to the balloon approximates the left atrial pressure (PCWP)

4. **Record the Pressure**: The pressure recorded during balloon inflation is the PCWP. It fluctuates during the cardiac cycle and normally shows a, c, and v waves similar to the right atrial pressure tracing

Interpretation of PCWP Values

Normal Range:**8-12 mm Hg**: Indicative of normal left atrial pressure and adequate fluid status.

Low PCWP:**<8 mm Hg**: May suggest hypovolemia (low blood volume) or dehydration. In such cases, fluid resuscitation is typically needed to restore adequate blood volume and improve tissue perfusion.

High PCWP:**>12 mm Hg**: Indicates elevated left atrial pressure, which can result from fluid overload, heart failure, or pulmonary edema. Care must be taken to avoid excessive fluid administration, and diuretics or inotropes may be considered to manage fluid status and support cardiac function.

Application in Fluid Resuscitation

- **Initial Assessment**: Use PCWP to determine the patient's baseline fluid status before initiating fluid resuscitation.
- **Monitoring**: Continuously monitor PCWP during fluid therapy to assess the patient's response and adjust fluid administration accordingly.
- **Avoiding Complications**: High PCWP values indicate a risk of fluid overload, which can lead to pulmonary edema and worsen patient outcomes. Careful monitoring helps prevent such complications.

Limitations of measuring PCWP in fluid resuscitation

While measuring **Pulmonary Capillary Wedge Pressure (PCWP)** is valuable in fluid resuscitation, it does have some limitations:

1. **Invasiveness**: The procedure requires the insertion of a Swan-Ganz catheter, which is invasive and carries risks such as infection, bleeding, and arrhythmias.
2. **Technical Skill**: Proper placement and interpretation of PCWP require significant clinical expertise and experience.
3. **Patient Condition**: PCWP measurements can be less accurate in patients with certain conditions, such as pulmonary hypertension or right heart failure.
4. **Dynamic Changes**: PCWP is a static measure and may not always reflect real-time changes in fluid responsiveness, especially in rapidly changing clinical situations.

5. **Resource Intensive**: The equipment and expertise needed for PCWP measurement may not be available in all healthcare settings, limiting its widespread use.

By interpreting PCWP accurately, healthcare providers can make informed decisions about fluid therapy, ensuring optimal patient outcomes while avoiding potential complications related to fluid overload.

iii)Blood Pressure: Measures systemic arterial pressure.

For sepsis patients, the target blood pressure is typically focused on maintaining an adequate **Mean Arterial Pressure (MAP)**. Here are the general targets:

- **MAP - 65 mm Hg** is the standard target for most sepsis patients. This helps ensure adequate perfusion to vital organs.
- **Higher MAP for Specific Cases**: In patients with a history of arterial hypertension or those at risk of acute kidney injury, a higher MAP target of **75-85 mm Hg** may be beneficial.[15]

iv)Urine Output: Indicates kidney perfusion and function.

The target urine output for sepsis patients is typically **0.5 to 1 mL/kg/hour**. This range helps ensure adequate kidney perfusion and function while avoiding fluid overload. Monitoring urine output is crucial in guiding fluid resuscitation and assessing the patient's response to treatment.

iv)IVC Diameter

- IVC Diameter < 1.5 cm: Indicates volume depletion or hypovolemia. This suggests that the patient may need fluid resuscitation.
- IVC Diameter 1.5 - 2.5 cm: Considered normal and indicates adequate fluid status.
- IVC Diameter > 2.5 cm: Suggests volume overload or hypervolemia. This may indicate the need to reduce fluid administration or consider diuretics.

Dynamic Measures

Dynamic measures assess the heart's response to physiological changes and are more sensitive indicators of fluid responsiveness. They include:

i) Passive Leg Raise
ii) IVC Collapsibility Index

iii) IVC Distensibility Index
iv) Pulse Pressure Variation
v) Stroke Volume Variation
vi) End Expiratory Occlusion Test
vii) Velocity Time Integral
viii) Carotid Doppler Peak Velocity
ix) Change in ETCO2

i) Passive Leg Raise

The passive leg raise (PLR) test is a valuable tool for assessing fluid responsiveness in sepsis patients, offering a non-invasive and dynamic method to predict the need for fluid resuscitation. This technique involves temporarily increasing venous return by elevating the patient's legs, which can help determine if a patient will benefit from additional fluid administration. The PLR test is particularly useful in critically ill patients, such as those with sepsis, where both fluid overload and insufficiency can lead to adverse outcomes.

PLR has been validated as a reliable method for evaluating fluid responsiveness, with studies showing its accuracy and specificity in critically ill patients.[16]

In a study comparing PLR with rapid fluid challenge (RFC), PLR demonstrated moderate agreement in predicting fluid responsiveness, with positive and negative predictive values of 70.6% and 72.0%, respectively, based on cardiac output changes.[17]

ii) IVC Collapsibility Index

The inferior vena cava collapsibility index (IVC-CI) is a non-invasive ultrasound measure used to predict fluid responsiveness in sepsis patients. It assesses the variation in IVC diameter with respiration, which can indicate the patient's volume status and guide fluid therapy.

Effectiveness of IVC-CI in Predicting Fluid Responsiveness

- A study on septic cancer patients found that changes in IVC-CI during the first hour of fluid therapy could predict fluid responsiveness with moderate accuracy. A change of ≥6.3% in IVC-CI after one hour had a sensitivity of 79.3% and specificity of 72.7% for predicting positive fluid responsiveness(Gaafar et al., 2024).[18]

- In mechanically ventilated patients with septic shock, the transhepatic approach for measuring IVC distensibility showed good accuracy in predicting fluid responsiveness, comparable to the subxiphoid approach(Hasanin et al., 2023).[19]
- Another study compared (rephrase) IVC respiratory variation with the end-expiratory occlusion test, finding that IVC variation had better predictive values for fluid responsiveness in mechanically ventilated sepsis patients, with a sensitivity of 91.3% and specificity of 100%(Abdelmaksoud et al., 2023).[20]

Advantages of IVC-CI

- IVC-CI is a non-invasive method, reducing the risk associated with invasive procedures and allowing for repeated assessments with low inter-operator variability.
- It can help prevent fluid overload, as demonstrated in a study where ultrasound-guided fluid therapy led to a significantly lower positive fluid balance compared to usual care in septic shock patients.

While IVC-CI is a valuable tool for assessing fluid responsiveness, it is not without limitations. The baseline value of IVC-CI was not predictive of responsiveness in some studies, indicating that changes over time are more informative. Additionally, the method's accuracy can vary based on the approach used and patient conditions, such as mechanical ventilation.Therefore, it is often used in conjunction with other monitoring techniques to provide a comprehensive assessment of fluid status in sepsis patients.

iii) IVC Distensibility Index

IVC Distensibility Index in Fluid Responsiveness

- Non-Invasive and Practical: The IVC Distensibility Index is favored for its non-invasive approach, making it a practical choice in the ICU setting. It does not require extensive training, unlike other invasive methods such as central venous pressure measurement.
- Predictive Accuracy: In cancer patients with sepsis, a change in IVC collapsibility index during the first hour of fluid therapy predicted fluid responsiveness with moderate accuracy, showing a sensitivity of 72.4% and specificity of 63.6% for a 3.4% change, and improved metrics for a 6.3% change.[18]
- Spontaneously Breathing Patients: In spontaneously breathing septic patients, the IVC collapsibility index demonstrated a high predictive value with a sensitivity of 95.8% and specificity of 93.7% in a study by (Elsaeed et al)

Limitations and Considerations

While the IVC Distensibility Index is a useful tool, it is not without limitations. Its predictive accuracy can vary based on patient conditions, such as mechanical ventilation status and underlying health issues. Additionally, while it provides a non-invasive alternative, it may not replace more comprehensive hemodynamic monitoring in all clinical scenarios.

iv) Pulse Pressure Variation (PPV):

Assesses changes in pulse pressure during the respiratory cycle.Pulse pressure variation (PPV) is a way to predict fluid responsiveness in septic shock patients:
To calculate PPV, compare the highest pulse pressure at the end of exhalation to the lowest at the end of inhalation. The PPV is the difference between the two values.

A PPV of 13% or higher indicates fluid responsiveness. A ΔRESPPP of 10% or higher is also considered a good cut-off point.

Measure Pulse Pressure Variation (PPV): Record the systolic blood pressure at the end of expiration (end-expiratory SBP) and at the end of inspiration (end-inspiratory SBP). Calculate the pulse pressure (PP) by subtracting the end-expiratory SBP from the end-inspiratory SBP.

v) Stroke Volume Variation (SVV):

Measures changes in stroke volume during the respiratory cycle.

Steps to Measure SVV Using POCUS

Patient Positioning: Position the patient in the supine position with a slight left lateral decubitus position to bring the heart closer to the chest wall.

Probe Selection: Use a low-frequency curvilinear or phased-array probe for better penetration.

Probe Placement: Place the probe in the subxiphoid area, just below the xiphoid process, and slide it caudally towards the liver to obtain a clear view of the left ventricle.

Measure Left Ventricular Outflow Tract (LVOT) Diameter: Identify the LVOT in the parasternal long-axis view and measure its diameter.

Measure LVOT Velocity Time Integral (VTI): Use pulse wave Doppler to measure the velocity of blood flow through the LVOT and calculate the VTI.

Calculate Stroke Volume (SV): Multiply the LVOT diameter squared by the VTI and a constant (0.785) to calculate the stroke volume.

Calculate SVV:

$$\mathbf{SVV\ (\%) = (SV_{max} - SV_{min})/SV_{mean}}$$

- **SVmax**: is the mean of the four highest SV values during a 30-second period
- **SVmin**: is the mean of the four lowest SV values during a 30-second period
- **SVmean**: is the average SV value during the 30-second period

Interpretation of SVV

- **SVV > 13%**: Indicates a high likelihood of fluid responsiveness. The patient may benefit from additional fluid administration.
- **SVV ≤ 13%**: Suggests that the patient is less likely to be fluid responsive. Caution should be exercised with further fluid administration.

Using POCUS to measure SVV provides a non-invasive, rapid, and accurate method to assess fluid responsiveness in septic shock patients, helping guide fluid therapy and improve patient outcomes.

vi) End-Expiratory Occlusion Test (EEOT):

Measures the change in pulse pressure or cardiac output when the expiratory phase of ventilation is occluded**.**The end-expiratory occlusion (EEO) test is a method used to assess fluid responsiveness in septic patients, particularly those who are mechanically ventilated. This test involves temporarily halting mechanical ventilation at the end of expiration to observe changes in cardiac output (COP) or other hemodynamic parameters.

The EEO test may not be feasible in all patients, particularly those with spontaneous breathing activity or arrhythmias, as these conditions can interfere with the test's accuracy.[21]

Variations in blood pressure in response to changes in positive end-expiratory pressure do not reliably reflect fluid responsiveness, indicating that the EEO test should be used cautiously and in conjunction with other assessments.[22]

vii) Velocity Time Integral

Velocity Time Integral (VTI) measurement using ultrasound is a valuable tool for assessing fluid responsiveness in critically ill patients, including those with sepsis. Here's how to measure VTI and use it to assess fluid responsiveness:

Steps to Measure VTI Using Ultrasound

Patient Positioning: Position the patient in the supine position with a slight left lateral decubitus position to bring the heart closer to the chest wall.

Probe Selection: Use a low-frequency phased-array or curvilinear probe.

Probe Placement: Place the probe in the parasternal long-axis view to visualize the left ventricular outflow tract (LVOT).

Obtain Apical View: Adjust the probe to get an apical 5-chamber or 3-chamber view to visualize the LVOT.

Measure LVOT Diameter: Measure the LVOT diameter in the parasternal long-axis view at the level of the aortic annulus.

Place Doppler Cursor: Place the pulse wave Doppler cursor just below the aortic valve in the LVOT.

Obtain Doppler Waveform: Record the Doppler waveform for at least 3 cardiac cycles. The VTI is the area under the curve of the Doppler velocity waveform.

Calculate Stroke Volume (SV): Use the formula:

$$SV = LVOT^2_{diameter} \times VTI \times 0.785$$

Assess Fluid Responsiveness: Measure the change in VTI before and after a fluid challenge (e.g., a bolus of IV fluids) or a passive leg raise (PLR). An increase in VTI of 10-15% or more indicates fluid responsiveness.

Interpretation

- Increase in VTI by 10-15% or more: Indicates fluid responsiveness, suggesting that the patient may benefit from additional fluid administration.
- Minimal or no change in VTI: Suggests that the patient is less likely to be fluid responsive, and further fluid administration may not be beneficial.

Measuring VTI using ultrasound provides a non-invasive and reliable method to assess fluid responsiveness, helping to guide fluid therapy and optimize patient outcomes in septic shock patients.

viii) Carotid Doppler Peak Velocity

Carotid Doppler peak velocity (CDPV) is a non-invasive method that has been explored for assessing fluid responsiveness in septic shock patients. The method involves measuring changes in blood flow velocity in the carotid artery, which can reflect changes in cardiac output following fluid administration. This approach is particularly useful when traditional cardiac index (CI) monitoring is unavailable or challenging. However, the effectiveness and reliability of CDPV in predicting fluid responsiveness have been debated across various studies.

Correlation with Cardiac Output

- CDPV changes during an end-expiratory occlusion test (EEOt) have shown a significant correlation with changes in CI, with a correlation coefficient of 0.51, indicating a moderate relationship (D'Arrigo et al., 2023).[23]
- In a systematic review, CDPV demonstrated a sensitivity of 72% and specificity of 87% for predicting fluid responsiveness, suggesting moderate accuracy(Walker et al., 2024).[24]

Comparison with Other Methods

- CDPV was found to be more precise than the inferior vena cava collapsibility index (ΔD-IVC) in predicting fluid responsiveness, with a sensitivity of 81% and specificity of 66.7%(Soliman et al., 2022).
- Other studies have shown that respiratory variability of mitral and tricuspid annular peak systolic velocity could also serve as reliable indicators, with higher sensitivity and specificity values compared to CDPV(Magda & Erchuan, 2023).[25]

While CDPV offers a non-invasive alternative for assessing fluid responsiveness, its moderate accuracy and the presence of a large gray zone limit its standalone utility. Other methods, such as respiratory variability of valvular velocities, may provide more reliable predictions. Further research and consistent methodologies are needed to enhance the reliability of CDPV in clinical settings.

ix) Change in ETCO2:

The change in end-tidal carbon dioxide (ETCO2) is a valuable parameter for assessing fluid responsiveness in sepsis patients. ETCO2 changes can reflect alterations in cardiac output and perfusion, making it a useful non-invasive marker in fluid management strategies. Studies have shown that ETCO2 changes after fluid challenges or passive leg raising tests can predict fluid responsiveness with varying degrees of accuracy

C) Admission to intensive care unit

Finally, it was recognized that the admission of critically ill patients in general, and specifically those with sepsis, within 6 hours to the ICU leads to better outcomes.[25,26]

D) Timing of antimicrobials

In light of the recognized link between the expedient provision of appropriate antimicrobials and mortality rates in sepsis, specifically in individuals encountering septic shock, the protocols for initiating antimicrobials were established according to the likelihood of sepsis and the status of shock.

a. For patients diagnosed with confirmed or probable sepsis, the 2021 Guidelines articulated a robust recommendation advocating for the initiation of empiric **antimicrobials within a 1-hour timeframe**.

b. In clinical situations where sepsis is a relevant consideration, although not definitively or probably diagnosed, patients presenting with shock should be administered antimicrobials **within 1 hour** (in line with the principle of being 'too sick to miss'), whereas patients without shock should be subjected to an expedited assessment to distinguish between infectious and non-infectious causes of acute illness, with the intent of identifying and providing antimicrobials (if deemed suitable) **within a 3-hour timeframe**.

c. In circumstances where patients exhibit a low probability of infection and lack any indicators of shock, the 2021 Guidelines promulgated a tentative recommendation advocating for sustained observation and monitoring for potential signs of sepsis, while refraining from the initiation of empiric antimicrobials.

E) Biomarkers to start antibiotics

The 2021 Guidelines recommended to obtain microbiologic cultures before starting antimicrobials, so long as it does not substantially delay the initiation of antimicrobials.

The Guidelines included a **weak recommendation against adding procalcitonin** to a standard clinical evaluation, given a lack of benefit demonstrated in RCTs.

F) Antimicrobial choice

The 2021 Guidelines advocated for assessing the patient's risk of infection and individualizing the choices for each patient based on the most likely organism and local antimicrobial resistance patters.

For example, for patients at a high risk for methicillin-resistant *Staphylococcus aureus* (MRSA) infection, clinicians should use empiric MRSA coverage (strong recommendation). The full Guidelines present risk factors for the above mentioned infections that should prompt empiric coverage.

G) Delivery of antimicrobials, pharmacokinetics, and pharmacodynamics

The administration of antimicrobials must be conducted in a way that enhances their therapeutic potential while simultaneously alleviating their related toxicity. Extended infusions of β-lactams, which prolong the therapeutic window, have been correlated with moderate-quality evidence indicating a possible decrease in mortality rates. Consequently, this approach received a suboptimal endorsement in the 2021 Guidelines, which recognized that its implementation may require additional resources and could prove impractical across various clinical environments.

H) Source control

The comprehensive 2021 Guidelines incorporated a series of best practice statements that delineate the imperative need for the immediate implementation of emergent source control measures in patients who are diagnosed with sepsis or experiencing septic shock, which should be executed as swiftly as possible to optimize patient outcomes; furthermore, it is essential to ensure the prompt and efficient removal of any intravascular access devices that are deemed to be a potential or probable source of infection, thereby mitigating the risk of further complications associated with the patient's clinical condition.

I) De-escalation and discontinuation of antimicrobials

The guidelines established in the year 2021 explicitly acknowledged that the evidence presented was of an extremely low quality, yet it nonetheless suggested a potential correlation between the practice of antimicrobial de-escalation and the occurrence of shorter hospital stays,

as well as a reduction in short-term mortality rates; consequently, the guidelines incorporated a rather weak recommendation advocating for the implementation of a daily review process concerning the practice of antimicrobial de-escalation.

Moreover, the practice of de-escalation might contribute to a reduction in healthcare costs as well as mitigate the development of antibiotic resistance, and within the framework of the guidelines, there was a moderate suggestion that clinicians consider administering shorter durations of antimicrobial therapy for patients who exhibit adequate source control, instead of opting for prolonged durations of treatment; however, it is noteworthy that the guidelines did not explicitly address or provide detailed recommendations regarding the length of treatment required for any specific individual case.

In instances where it remains ambiguous what constitutes the optimal duration of antimicrobial therapy, despite the presence of adequate source control, the guidelines incorporated a rather weak recommendation proposing the utilization of procalcitonin level measurements in conjunction with clinical evaluations, which could serve as criteria for determining the discontinuation of antibiotics; this recommendation was based on low-quality evidence indicating that employing this combined approach may lead to a decrease in mortality rates when compared to reliance solely on bedside clinical evaluations.

This recommendation is in stark contrast to the weak suggestion made against the use of procalcitonin levels as a guiding factor for the initiation of antibiotic therapy in the first instance.

5.1.2 Hemodynamic management

a) Fluid management

There has been substantial development of the evidence base for fluid choice in sepsis. The 2021 Guidelines included a strong recommendation for using crystalloids as first-choice fluids in resuscitation, a strong recommendation against using starches, and a weak recommendation against using gelatins.

There are numerous crystalloid solutions available, usually classified into

a. “balanced” (eg, Ringer’s lactate) and
b. “nonbalanced” (eg, 0.9% normal saline).

Several trials compared balanced and nonbalanced crystalloids, and low-quality evidence suggests that balanced crystalloids may reduce mortality in septic patients.

Given the similar cost and convenience of both types of crystalloids, the Guidelines included a weak recommendation for using balanced solutions over saline.

The role of albumin remains controversial; while there is some evidence that it may improve patient outcomes, this remains uncertain, and given its higher cost, the Guidelines suggested its use only in patients who have received large volumes of crystalloids but require further fluid resuscitation.

In critically ill individuals, balanced solutions and normal saline have been evaluated in two substantial trials that have emerged since the publication of the Guidelines.[27,28]

The aggregation of existing evidence to this point continues to endorse a marginal recommendation for the utilization of balanced crystalloids in preference to saline, notwithstanding the fact that further investigations specifically addressing fluid selection in the context of sepsis are currently underway at the time of this recommendation.

The panel acknowledged the lack of sufficient evidence to formulate a recommendation regarding restrictive versus liberal fluid strategies during the initial 24 hours of resuscitation in patients suffering from sepsis, asserting that fluids should typically be administered solely to those exhibiting indications of hypoperfusion.

The later dissemination of the CLASSIC (Conservative vs Liberal Fluid Therapy in Septic Shock) trial, which assessed restrictive versus standard intravenous fluid therapy in individuals with septic shock, did not reveal any significant differences in patient mortality or adverse events over a period of up to 90 days.[29]

This indicates that both strategies remain justifiable, and the panel's recommendation to administer fluids exclusively to patients demonstrating signs of hypoperfusion persists as a sound approach to the continuation of fluid therapy.

b)Vasoactive agents and inotropes

The 2021 Guidelines continued to recommend the use of norepinephrine over other vasopressors including dopamine (high-quality evidence), vasopressin (moderate-quality evidence), epinephrine (low-quality evidence), selepressin (low-quality evidence), and angiotensin II (very low-quality evidence).

The panel noted that norepinephrine is not readily available in all regions, and that in such cases epinephrine or dopamine would be a reasonable alternative despite the higher risk of arrhythmia—but also encouraged efforts to improve the availability of norepinephrine.

In patients on norepinephrine who continue to have inadequate MAP, the Guidelines included a weak recommendation for adding vasopressin, without a specific dose at which it should be initiated. For practical purposes, the panel noted this is often done when the dosing is in the range of 0.25−0.5 μg/kg/min.

The 2021 Guidelines examined the utilization of inotropic agents in individuals exhibiting cardiac dysfunction accompanied by sustained hypoperfusion, despite maintaining adequate volume status and blood pressure. Two alternative approaches were proposed.

a. At first, the suggestion to add dobutamine was put forth (consistent with the foundational goal-directed therapy trials); on the other hand, a transition from norepinephrine to epinephrine could be evaluated, considering its improved β-agonist functions.
b. A weak recommendation was issued against the use of levosimendan; this calcium-sensitizing agent appears to exhibit no superior efficacy compared to dobutamine in septic patients and may hinder weaning while leading to an increased incidence of tachyarrhythmias.

c)Monitoring and intravenous access

The 2021 Guidelines included a weak recommendation to start peripheral vasopressors to restore MAP, rather than delaying vasopressors until central access is obtained.

Despite very low quality of evidence, persistent hypoperfusion can be dangerous, even though observational evidence suggests that short (<6 hours) durations of peripheral vasopressors, in **veins at or proximal to the antecubital fossa**, are associated with a low risk of complications.

Ventilation

High-flow nasal cannula and non-invasive ventilation

Sepsis has the potential to cause multiple organ dysfunction, one of which may manifest as respiratory failure. The 2021 Guidelines have reassessed and refined several prior recommendations concerning the management of hypoxemic respiratory failure in individuals afflicted with sepsis, while also introducing two novel recommendations.

a. Initially, drawing from low-quality evidence, a tentative recommendation was proposed endorsing the use of high-flow nasal oxygenation (HFNO) over non-invasive ventilation (NIV) for patients experiencing sepsis-related hypoxemic respiratory failure. This statement was supported by a randomized controlled trial (RCT) that contrasted HFNO with NIV in septic patients afflicted with hypoxemic respiratory failure. The findings revealed minimal differences in intubation rates; however, HFNO was associated with improved survival rates at 90 days and an increase in ventilator-free days at 28 days when compared to NIV.[30]

b. Consistent with earlier versions of the Surviving Sepsis Campaign (SSC) Guidelines, no explicit recommendation was rendered regarding the use of NIV in contrast to invasive mechanical ventilation in the treatment of patients with sepsis-related respiratory failure.

Extracorporeal membrane oxygenation

The recent guideline focused on the application of veno-venous extracorporeal membrane oxygenation (VV-ECMO) for individuals suffering from sepsis-related severe acute respiratory distress syndrome (ARDS).

A meta-analysis encompassing two randomized controlled trials (RCTs) involving critically ill patients exhibiting severe ARDS unresponsive to standard therapeutic approaches indicated a significant decrease in mortality rates among those receiving VV-ECMO at specialized medical facilities.[31]

Accordingly, the Guidelines included a weak recommendation for using VV-ECMO for sepsis-induced severe ARDS when conventional mechanical ventilation fails, in centers with appropriate infrastructure and experience.

Neuromuscular blocking agents

Due to emerging evidence, revisions were implemented in the guidance concerning the application of neuromuscular blocking agents (NMBAs) in individuals experiencing sepsis-induced moderate-to-severe ARDS.

Sustained NMBA administration demonstrated a reduction in mortality rates when juxtaposed with profound sedation lacking continuous neuromuscular blockade; however, it exhibited minimal to no differences when compared to a light sedation approach utilizing intermittent boluses.

Therefore, the 2021 Guidelines included a weak recommendation for using intermittent NMBA boluses over a continuous infusion in patients with sepsis-induced moderate-to-severe ARDS.

Oxygenation targets

The panel was unable to issue a recommendation on the oxygenation targets in patients with sepsis-induced hypoxemic respiratory failure.

Although 3 RCTs were included in the meta-analyses, there was little to no difference in mortality, ventilator-free days, or the length of ICU stay. While meta-analyses of RCTs in patients in other clinical settings were identified, the panel judged these to be too indirect to formulate recommendations.[32]

Lung protective ventilation and proning

Many recommendations remained unchanged from the 2016 Guidelines.

These include recommendations on using

a. low tidal volume ventilation in adults with sepsis-induced ARDS (strong recommendation) and in septic patients without ARDS (weak recommendation).

Recommendations on ventilatory parameters in septic patients with moderate-to-severe ARDS remained the same, including

a. recommendations to target plateau pressures of 30 cm H_2O or less (strong recommendation),

b. use higher positive end expiratory pressure (PEEP) (weak recommendation), and

c. use prone ventilation for at least 12 hours per 24-hour period (strong recommendation).

- **Recruitment maneuvers**

The 2021 Guidelines included 2 additional RCTs on the use of recruitment maneuvers in the updated meta-analysis.

Therefore, the 2021 Guidelines suggested using traditional recruitment manoeuvres, but **recommended against using an incremental PEEP titration strategy in adults with sepsis-induced moderate-to-severe ARDS.**

5.1.3 Additional therapies

The additional therapy section of the SSC Guidelines focused on supportive therapies, whether directly related to sepsis or complications of sepsis-related critical illness.

a.Corticosteroids

Corticosteroids have been included in the SSC Guidelines since their first edition in 2004. The findings from a meta-analysis concerning corticosteroid administration in cases of septic shock have elevated the evidence quality from low to moderate.[33]

Evidence suggests that the use of corticosteroids promotes a swifter resolution of shock, albeit potentially increasing the likelihood of neuromuscular weakness, while the relationship with mortality rates is still not definitively established.

The 2021 Guidelines featured a tentative recommendation for the administration of corticosteroids in adult patients experiencing septic shock who are concurrently receiving vasopressor therapy, despite having undergone sufficient fluid resuscitation. It was suggested to administer 200 mg/day of hydrocortisone, either in 6-hour divided doses or through a continuous infusion.

b.Vitamin C

The 2021 Guidelines issued a new weak recommendation against the use of intravenous vitamin C for sepsis or septic shock.

c.Bicarbonate

As in the 2016 Guidelines, the panel issued a weak recommendation against the routine use of bicarbonate therapy in sepsis-induced lactic acidosis;

However, it may be reasonable to use bicarbonate therapy in septic patients with metabolic acidosis (pH $\leq$7.2) and acute kidney injury. This weak recommendation was primarily driven by a subgroup analysis of an RCT in which these populations showed a large treatment effect.[34]

d.Blood purification techniques

In previous versions, the SSC Guidelines refrained from providing a recommendation regarding the application of hemoperfusion therapies in cases of sepsis. Nonetheless, the 2021 Guidelines incorporated an advisory against the utilization of polymyxin B hemoperfusion for the management of sepsis or septic shock.

A recent randomized controlled trial contributed to an updated meta-analysis that indicated potential harm.[35]

e.Red blood cell transfusion targets and immunoglobulin

Regarding red blood cell transfusion targets, although the quality of evidence was downgraded to moderate based on the inclusion of a new RCT, the 2021 Guidelines included a strong

recommendation for restrictive over liberal strategies (typically defined as a trigger of 7.0 g/dl, in addition to clinical status)

f.Stress ulcer prophylaxis

The 2021 Guidelines included a single recommendation for stress ulcer prophylaxis in patients with risk factors, and pointed to a higher quality of evidence (upgraded to moderate) but a weaker level of recommendation due to possible adverse effects.

g. Venous thromboembolism prophylaxis

The recommendations concerning pharmacologic prophylaxis have remained consistent, with the singular exception that a previously feeble suggestion advocating for the combination of mechanical prophylaxis with pharmacologic approaches has been revised to a recommendation that dissuades the addition of mechanical prophylaxis to pharmacologic measures, as supported by recent evidence.[36]

h.Renal replacement therapy

Regarding renal replacement therapy (RRT), a previous weak recommendation for either continuous or intermittent RRT did not change.

Evidence is against the use of early RRT in patients with acute kidney injury but no definitive indications was strengthened to moderate with the addition of 2 new RCTs, supporting a weak recommendation for the initiation guided by standard dialysis indications.[37,38]

i.Glucose control

The 2021 Guidelines approached questions related to glycemic control from a different perspective, asking at what threshold insulin therapy should be initiated. The Guidelines added a recommendation to **start insulin when blood glucose levels in 2 consecutive measurements were higher than 10 mmol/l or 180 mg/dl,** based upon a network meta-analysis suggesting a lower risk of hypoglycemia when this threshold was used.

j.Nutrition

The 2021 Guidelines included only a single weak recommendation for early (within 72 hours) initiation of enteral nutrition.

5.1.4 Long-term outcomes and goals of care

The 2021 Guidelines introduced a novel segment addressing long-term outcomes and the overarching objectives of care. Conversely, in the 2016 Guidelines, the objectives of care and palliative care were encompassed as singular recommendations.

Numerous recommendations were pertinent to the initial stages of sepsis management. Pertaining to discussions surrounding the goals of care, wherein healthcare providers deliberate on care preferences and available treatment modalities with patients and/or their families, the 2021 Guidelines included a best practice statement aimed at ensuring that patients receive care that aligns with their values.

Evidence of low quality indicated that initiating discussions early (within 48 hours of ICU admission) might enhance perceptions regarding the quality of communication, the patient-centered nature of care, and potentially shorten the duration of ICU stays, possibly attributable to the avoidance of unwanted invasive interventions.

The review of the literature did not reveal any clinical triggers for goals of care discussions that consistently surpassed routine discussions in effectiveness. Rather, the Guidelines advocated for early discussions regarding goals of care upon ICU admission, with additional discussions ideally prompted by patient or family requests and clinical developments likely affecting patient morbidity and mortality, including the necessity for further treatments.

Notably, the application of routine, structured palliative care consultations did not yield uniformly positive results and, in some cases, revealed negative implications for the mental health outcomes of families.[39]

Given that symptom management and comprehensive care are vital to the care experience for patients and their families, the panel issued a best practice statement advocating for the integration of palliative care principles to address patient symptoms and distress, along with formal palliative care consultations when expert input is deemed necessary.

A multitude of recommendations within this section sought to enhance long-term patient outcomes following the initial resuscitative phase of sepsis. Acknowledging that survivors of sepsis frequently experience substantial cognitive impairment, early cognitive therapy within the ICU setting has been investigated as a preventive intervention. Nonetheless, the evidence was inadequate to formulate a definitive recommendation regarding cognitive therapy.[40]

The 2021 Guidelines incorporated a best practice statement to assess and facilitate suitable referrals for patients with sepsis and their families for economic and social support, predicated on evidence demonstrating that individuals lacking such community supports encounter poorer outcomes.

The 2021 Guidelines placed significant emphasis on the risks encountered by patients during transitions of care, such as from the ICU to the general ward or from the ward to home, including a best practice statement advocating for the involvement of patients and their families in shared decision-making processes concerning post-ICU care and discharge planning.

There was minimal quality evidence suggesting that a critical care transition program (for example, follow-up by ICU nurses or physicians in the ward post-ICU stay) might mitigate readmission rates or mortality. The 2021 Guidelines encompassed best practice statements regarding medication reconciliation at the time of ICU and hospital discharge, as well as providing patients and families with information related to sepsis, including its diagnosis, treatment options, and long-term outcomes, as integral components of the discharge plan.

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5.1.5 Latest Update :2023

Treatment pearls

Antimicrobials	**- Culture samples are required before administration of antimicrobials;** **- Treatments should be based on clinical/epidemiological criteria and promptly started;** **- Frequent re-assessments of patients' condition and PCT levels are advisable for an adequate reduction strategy;** **- Short courses of antimicrobial treatments may be indicated.**
Fluids	- Balanced crystalloids are the fluid of choice; - Individualized resuscitation strategies based on FT and FR are preferable; - Approaches based on small and repeated boluses (250–500 mL) of crystalloids with continuous hemodynamic monitoring are advised.
Vasoactive Agents	- Vasopressors are required if a patient's MAP is <65 mmHg despite fluid replacement; - Norepinephrine at a dose of 0.1–1.2mcg/kg/min is the drug of choice for septic patients; - Early administration of NE could prevent fluid overload, thereby reducing mortality; - Vasopressin at a dose of 0.25–0.5mcg/kg/min may be combined with NE if target MAP is not achieved.
Oxygenation and Ventilation Support	- Oxygenation should be started at 15 L/min via a reservoir mask; - The target values for titration should be SpO2 94–98% or SpO2 88–92% if the patient is at risk of hypercapnic respiratory failure; - If NIV/MV is needed, a low tidal volume (6 mL/kg) is advisable; - HFNC may be used in septic patients with hypoxic respiratory failure.
Other Treatments	**1)Heparin** - LMWH rather than UFH should be used to prevent VTE; - Mechanical prophylaxis is advised for patients unsuitable for heparin treatment. **(2) Insulin** - The use of insulin is advisable to achieve a glucose target between 144–180 mg/dL. **(3) Proton Pump Inhibitors** - PPI treatment may be necessary to prevent stress ulcers.

	(4) Renal Replacement Therapy - Although AKI is a common complication of sepsis, RRT may only be indicated in some subsets of patients. **(5) Steroids** - Hydrocortisone may be considered in patients with vasopressor-resistant, inadequate MAP. **(6) Sodium Bicarbonate** - Sodium bicarbonate may be given to patients with severe bicarbonate levels < 5 mEq/L and/or pH < 7.1 or AKI stage 2 or 3. **(7) Acetaminophen** - Acetaminophen should be administered as a symptomatic drug.

Note: AKI: acute kidney injury; FR: fluid responsiveness; FT: fluid tolerance; HFNC: high-flow nasal cannula; LMWH: low-molecular-weight heparin; MAP: mean arterial pressure; NE: norepinephrine; PCT: procalcitonin; PPI: proton pump inhibitor; RRT: renal replacement therapy; SSC: surviving sepsis campaign; UFH: unfractionated heparin; VP: vasopressin; VTE: venous thromboembolism

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CHAPTER 6

DIAGNOSTIC & PROGNOSTIC MARKERS IN SEPSIS

6.1 Diagnostic Markers in Sepsis

Early and accurate diagnosis of sepsis is crucial for timely intervention and improved patient outcomes. However, the nonspecific clinical presentation of sepsis often poses significant diagnostic challenges.(Bauer et al., 2015) To address this, researchers have focused on identifying biomarkers that can aid in the early detection and risk stratification of sepsis. This essay will delve into the details of various diagnostic markers employed in sepsis, highlighting their significance and limitations.

6.1.1 Conventional Markers

a. Systemic Inflammatory Response Syndrome Criteria

Traditionally, sepsis diagnosis relied on the presence of systemic inflammatory response syndrome criteria, which include abnormalities in temperature, heart rate, respiratory rate, and white blood cell count.(Bauer et al., 2015) However, SIRS criteria lack specificity, as they can be triggered by various non-infectious conditions, leading to overdiagnosis and unnecessary antibiotic use.

b. C-reactive Protein and Procalcitonin

CRP, an acute-phase reactant, and PCT, a prohormone of calcitonin, are commonly used biomarkers for sepsis.(Simonsen et al., 2014) Elevated levels of both markers indicate an inflammatory response, but they lack specificity for infection. CRP levels can rise in response to various inflammatory stimuli, while PCT levels can be elevated in non-infectious conditions like trauma and surgery.

6.1.2 Novel Biomarkers

a. Presepsin

Presepsin, a soluble CD14 subtype, has emerged as a promising biomarker for sepsis.(Aulin et al., 2022) It is rapidly released into the bloodstream during bacterial infections and exhibits a shorter half-life compared to CRP and PCT, potentially allowing for earlier detection of sepsis.(Aulin et al., 2022)

b.Cytokines

Cytokines, signaling molecules involved in immune responses, have been investigated as potential sepsis biomarkers.(Simonsen et al., 2014) Interleukin-6, interleukin-8, tumor necrosis

factor-alpha, and interferon-gamma have shown promise in differentiating sepsis from non-infectious inflammation.(Simonsen et al., 2014) However, their clinical utility is limited by their short half-lives and complex interactions.

c.Cell Surface Antigens

Soluble intercellular adhesion molecule (sICAM) and CD64, cell surface antigens involved in leukocyte adhesion and activation, have also been explored as sepsis biomarkers.(Simonsen et al., 2014) Elevated levels of these markers reflect endothelial activation and inflammation associated with sepsis.

Limitations and Future Directions

While numerous biomarkers have been investigated for sepsis diagnosis, several limitations persist. Most markers lack specificity for infection and can be elevated in various non-infectious conditions. Additionally, biomarker kinetics can vary significantly between individuals, making interpretation challenging.

Future research should focus on identifying highly specific and sensitive biomarkers or panels of biomarkers that can accurately diagnose sepsis, predict disease severity, and guide treatment decisions. Additionally, developing point-of-care diagnostic tools that can rapidly measure these biomarkers at the bedside would significantly improve sepsis management.

d.Conclusion

Early and accurate diagnosis of sepsis is paramount for improving patient outcomes. While conventional markers like CRP and PCT provide valuable information, they lack specificity. Novel biomarkers like presepsin, cytokines, and cell surface antigens hold promise for earlier and more accurate sepsis diagnosis. However, further research is needed to validate their clinical utility and develop reliable diagnostic algorithms.

Diagnostic markers	Description	Significance	Limitations
Systemic Inflammatory Response Syndrome Criteria	Criteria include abnormalities in temperature, heart rate, respiratory rate, and WBC count	Traditional approach to identifying systemic inflammation.	Lack specificity; can be triggered by non-infectious conditions
C-reactive Protein (CRP)	Acute-phase reactant indicating general inflammation	Elevated levels suggest inflammatory response but not specific to infection.	Increases with any inflammatory stimulus, limiting specificity for sepsis.
Procalcitonin (PCT)	Prohormone elevated in bacterial infections.	Useful for indicating bacterial origin of infection.	Elevated in non-infectious conditions like trauma, limiting specificity.
Presepsin	**Soluble CD14 subtype released during bacterial infections.**	Rapid release allows for early detection; shorter half-life than CRP/PCT.	Limited data compared to CRP/PCT; specificity needs further validation.
Cytokines (e.g., IL-6, IL-8)	Signaling molecules indicating immune response activation.	Differentiate sepsis from non-infectious inflammation.	Short half-lives make timing of sample collection critical; complex interactions.
Cell Surface Antigens (e.g., sICAM, CD64)	Reflect endothelial activation and leukocyte involvement in sepsis.	Provide insights into inflammation associated with sepsis.	Interpretation may be influenced by other inflammatory conditions; clinical utility evolving.

6.1.3 Inflammatory bio-markers in prognostication of sepsis at cellular level-

1. **C-reactive Protein (CRP)** - CRP is produced by the liver in response to inflammation, especially interleukin-6 (IL-6) release. Elevated CRP levels are nonspecific but indicate the presence and intensity of inflammation. [(1)]
2. **Pro-Calcitonin (PCT)** - PCT is a precursor peptide for calcitonin that is released in response to bacterial infections, particularly systemic infections. PCT levels are more specific for bacterial infections, and guide antibiotic therapy. [(2)]
3. **Interleukin-6 (IL-6) -** IL-6 is a pro-inflammatory cytokine released by immune cells in response to infection and tissue injury. Elevated IL-6 levels are associated with systemic inflammatory response syndrome (SIRS) and can predict the development of severe sepsis and septic shock. [(3)]
4. **Tumor Necrosis Factor-alpha (TNF-alpha)** - TNF-alpha is a cytokine produced mainly by macrophages and plays a key role in initiating and amplifying the inflammatory response. Elevated levels contribute to the cytokine storm in sepsis, leading to endothelial dysfunction, organ injury, and shock.
5. **Interleukin-1 beta (IL-1β)** - IL-1β is another pro-inflammatory cytokine involved in the early stages of the inflammatory response. IL-1β levels are elevated in sepsis and contribute to fever, leukocytosis, and activation of other inflammatory mediators. IL-1β levels provide the intensity of the inflammatory response. [(5,6)]

OTHERS-

6. Erythrocyte Sedimentation Rate (ESR)
7. Soluble Triggering Receptor Expressed on Myeloid Cells-1 (sTREM-1)
8. Pentraxin-3 (PTX3)
9. Lipopolysaccharide-Binding Protein (LBP)
10. Neutrophil Gelatinase-Associated Lipocalin (NGAL)
11. Neutrophil Elastase
12. Toll-like receptors (TLR)

Prognostic Markers in Sepsis

Bio-markers in prognostication of sepsis at organ level :-

1. Cardiovascular System:

Cardiac biomarkers	**Cardiac Troponin T**
	Cardiac Troponin I
Vascular biomarkers	Angiopoietin-1
	Pigment Epithelium-Derived Factor (PEDF)
	Syndecan-1
	Hyaluronic Acid

2. Renal system:

Serum biomarkers of kidney injury	**Creatinine**
	Cystatin C
Urinary biomarkers of kidney injury	Neutrophil Gelatinase-Associated Lipocalin (NGAL)
	Kidney Injury Molecule-1 (KIM-1)
	Interleukin-18 (IL-18)

3. Central Nervous system:

Biomarkers of Brain Injury	**S100B**
	Neuron-Specific Enolase (NSE)
	Glial Fibrillary Acidic Protein (GFAP)
	Tau Protein
	MicroRNA (miRNA) - miR-21, miR-223
Biomarkers of Cerebral Inflammation	Interleukin-6 (IL-6)
	Tumor Necrosis Factor-alpha (TNF-alpha)
Biomarkers of Blood Brain Barrier Dysfunction	Matrix Metallo proteinases (MMPs)

4. Respiratory System:

Biomarkers of Lung Injury	**Angiopoietin-2**
	Surfactant Protein D (SP-D)

5. Gastro Intestinal System-

Biomarkers of Intestinal Injury	**Intestinal Fatty Acid-Binding Protein (I-FABP)**
	D-Lactate
	Fecal Calprotectin
	Tight Junction Proteins (e.g., Zonulin)
Biomarkers of Liver Injury	Aspartate Aminotransferase (AST)
	Alanine Aminotransferase (ALT)
	Alkaline Phosphatase (ALP)
	Gamma-Glutamyl Transferase (GGT)
	Cytokeratin-18 (CK-18)

6. Coagulation:

Biomarkers of Disseminated Intravascular Coagulation	**D-dimer**
	Fibrin Degraded Product (FDP)
	Thrombo-modulin

7. Metabolic:

Biomarkers of metabolic disorders	**Ph**
	Base Deficit
	Lactate Clearance

Factors effecting the outcome in sepsis -

1. Age: Elderly and very young children has weak immune response
2. Presence of Pre-existing Comorbidities
3. Microbiological Factors: antibiotic resistant pathogen being the source of infection
4. Delay in Initiation of Treatment
5. Poor Response to Treatment
6. Presence of Organ Dysfunction at presentation
7. Presence of Shock
8. Elevated levels of Biomarker
9. Quality of healthcare delivery
10. Presence of infection lead Complications like ARDS, DIC.
11. Immune Status & Nutritional Status of the patient.
12. Genetic Factors
13. Hospital Acquired Infections

6.1.4 Prognostication of sepsis based on scoring system-

a. Sequential Organ Failure Assessment (SOFA) Score:

SOFA Score evaluates organ dysfunction based on respiratory, cardiovascular, hepatic, renal, coagulation, and neurological parameters. Higher SOFA scores indicate more severe organ dysfunction and are associated with increased mortality in sepsis. The total SOFA score is the sum of points from all systems, ranging from 0 to 24. Higher scores indicate more severe organ dysfunction and higher mortality risk. [7]

Organ System	0 points	1 point	2 points	3 points	4 points
(Respiratory) **PaO2/FiO2**	> 400	≤ 400-300	≤ 300-200	≤ 200-100	≤ 100 (or need for mechanical ventilation)
(Coagulation) **Platelets in $\times 10^3/\mu l$**	> 150	≤ 150	≤ 100	≤ 50	≤ 20
(Liver) **Bilirubin (mg/dL)**	≤ 1.2	> 1.2-1.9	2.0-5.9	6.0-11.9	> 12.0
(Cardiovascular)	MAP (mmHg) ≥ 70	MAP (mmHg) < 70	Dopamine-1 to 5 (µg/kg/min) (or) Dobutamine - any dose	Dopamine-5.0 to 15 (µg/kg/min) (or) epinephrine/ norepinephrine < 0.1	Dopamine > 15.0(µg/kg/min) (or) epinephrine/ norepinephrine > 0.1
(CNS) **Glasgow Coma Scale**	15	13-14	10-12	6-9	≤ 5
(Renal) **Creatinine (mg/dl) Urine Output (mL/day)**	<1.2	1.2-1.9	2.0-3.4	3.4-4.9 > 500	>5 < 200

b. Quick Sequential Organ Failure Assessment (qSOFA):

qSOFA includes respiratory rate, altered mental status, and systolic blood pressure. it helps identify patients at risk of poor outcomes in sepsis outside of the intensive care unit (ICU) setting. [8]

Criteria	Score
Altered Mental Status	1
Systolic Blood Pressure ≤ 100 mmHg	1
Respiratory Rate ≥ 22 breaths/min	1

c. Acute Physiology and Chronic Health Evaluation (APACHE) Score:

APACHE II score includes physiological variables (e.g., temperature, heart rate, and blood pressure), age, and chronic health conditions. APACHE III & IV incorporates additional parameters and is more comprehensive. Higher APACHE scores correlate with increased severity of illness and mortality risk in critically ill patients, including those with sepsis. [9]

d. Predisposition, Infection, Response, and Organ Dysfunction (PIRO) Score:

PIRO score Includes factors related to predisposition, infection, response and organ dysfunction. It helps to stratify sepsis patients based on risk factors and predict outcomes related to infection and organ dysfunction. [10]

Factors	Components	Score
Predisposition	Age	0-2
	Comorbidities (e.g., chronic diseases)	0-2
	Immunosuppression	0-2
Infection	Source of infection	0-4
	Severity of infection (e.g., sepsis, severe sepsis)	0-4
Response	Vital signs (e.g., temperature, heart rate, blood pressure)	0-4

	Laboratory parameters (e.g., WBC count, lactate level)	0-4
Organ Dysfunction	Respiratory dysfunction (e.g., PaO2/FiO2 ratio)	0-4
	Cardiovascular dysfunction (e.g., hypotension)	0-4
	Renal dysfunction (e.g., creatinine level)	0-4
	Neurological dysfunction (e.g., Glasgow Coma Scale)	0-4
TotalPIRO Score		**0-26**

e.Mortality in Emergency Department Sepsis (MEDS) Score:

MEDS score includes demographic factors (age), comorbidities (e.g., cirrhosis, cancer), vital signs (e.g., heart rate, respiratory rate), and laboratory values (e.g., lactate, serum albumin). Predicts 28-day mortality risk in patients with sepsis presenting to the emergency department. [(11)]

f.Sepsis Severity Score (SSS):

Sepsis Severity Score includes clinical parameters (e.g., temperature, heart rate), laboratory values (e.g., white blood cell count, platelet count), and comorbidities. This score correlates with sepsis severity and helps predict patient outcomes. [(12)]

g.Modified Early Warning Score (MEWS):

Modified Early Warning Score includes vital signs (e.g., heart rate, respiratory rate, temperature, systolic blood pressure), altered mental status, and oxygen saturation. MEWS is used for early detection of clinical deterioration in hospitalized patients, including those with sepsis. [(13)]

Variables	Points
Terminal illness	6
Tachypnea or hypoxemia	3
Septic shock	3
platelet count, <150,00 cells/mm^3	3
Bands > 5%	3
Age, >65 years	3

Lower respiratory infection	2
Nursing home resident	2
Altered mental status	2
Total	**27**

Interpretation

MEDS score	Expected mortality; %
0-4	**0.9**
5-7	**2.0**
8-11	**7.8**
12-14	**20.2**
>15	**50.0**

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CHAPTER 7

7.1 Prospects for the Future to Lower the Global Sepsis Burden

Sepsis is a burdensome condition worldwide in terms of morbidity, mortality and financial cost to health systems.[1]

Although different organisms have varying virulence, overall sepsis is associated with substantial hospital mortality of 25%–30%[2] globally, which increases to 40%–50% in patients with complications and in lower-income countries.[3]

The collection of data on diagnosis, management and outcomes specifically related to sepsis needs to be improved in line with its global burden. Furthermore, better sharing of data and experiences across health systems is required to make headway on reducing rates.

Sepsis may result from, and is the final common pathway for death and disability from, various infections including malaria, respiratory tract infections, urinary tract infections and gastrointestinal infections. Consequently, various traditional studies focus on morbidity and mortality outcomes for single disease processes, and then link to preventive measures and treatment strategies for specific diseases. For example, the Global Burden of Disease study recently characterized the leading causes of global morbidity and mortality,[4] describing sepsis from the lens of neonatal and maternal health

When health care providers encounter a critically ill patient, identifying the cause of sepsis is less important than the screening and initial management of the common deranged physiology that characterizes sepsis regardless of its cause. This approach is even more relevant for health care workers in low- and middle-income countries, who have limited resources with which to manage patient care. For this reason, the new definition of sepsis requires the presence of just two simple clinical features — increased respiratory rate, altered mental status or reduced blood pressure — to screen for the presence of sepsis.[5]

The Surviving Sepsis Campaign[6]has outlined intervention bundles that should be given within three to six hours of a patient presenting with sepsis. Notably, adequate sepsis management can begin without identifying the underlying cause or microorganism. Despite the various causes, patients with sepsis and septic shock exhibit profound cardiovascular dysfunction, and the approach to their initial care is similar.

A research agenda that identifies sepsis as a major contributor to mortality in its own right would help to shift focus away from determining cause and toward rapid resuscitation with interventions that could save lives.

As protocols for sepsis become well defined, categorizing sepsis as a disease may unify and organize health facility frameworks required to manage sepsis. The need for structural facilities (properly equipped emergency departments and critical care units), adequately trained health care providers, intravenous fluids and necessary antibiotics, and the financial resources to

support these, becomes clear. A focus on clearly identifying a patient as having sepsis will help to ensure that health care providers recognize that the patient is critically ill so as to begin rapid mobilization of lifesaving therapies. In addition, developing a framework around sepsis allows hospitals to develop care plans and to monitor, evaluate and improve their timely delivery.

In an effort to advocate for greater awareness of sepsis and the importance of its individual categorization as a condition of global burden, the Global Sepsis Alliance[7] (GSA) is raising awareness through its World Sepsis Day campaign and World Sepsis Declaration.

Despite the fact that sepsis is acknowledged as a critical global health issue, the present global burden of this illness may be underestimated since there is a dearth of data from lower- and middle-income nations, where the majority of sepsis cases are likely to occur.[8,9]
Therefore, in order to rectify this discrepancy in representation, robust public health initiatives that enhance awareness of sepsis globally must support advancements in both acute and personalized treatment of the condition. Both the African Sepsis Alliance and the Latin-American Institute of Sepsis signed the Kampala Declaration in 2017 and the São Paulo Declaration in 2018, respectively, emphasising the need for immediate national and international action to enhance sepsis prevention, diagnosis, and treatment, as well as the allocation of human and financial resources towards these objectives.[10,11]

7.2 Conclusion

Sepsis is an extremely deadly and complicated illness that involves various organ dysfunction along a tortuous path from infection to death.
The danger of death increases with each organ lesion, and there is complex interplay across the entire system.
The great underlying heterogeneity of sepsis may account for the inability of therapies beyond supportive measures, such as infection management, to improve outcomes, despite its high prevalence and extensive research.
More individualized treatment is required, and new developments employing innovative research techniques have yielded encouraging outcomes in this area.
Strong global public health measures will be necessary to support this study and the interventions that follow.
All of these initiatives will support sepsis patients in shifting their course from death to recovery.

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Thank You