Adegboro et al. *Afr. J. Clin. Exper. Microbiol.* 2021; 22 (2): 133 - 145 https://www.afrjcem.org

African Journal of Clinical and Experimental Microbiology. ISSN 1595-689X Apr 2021; Vol.22 No.2
AJCEM/2071. https://www.ajol.info/index.php/ajcem

Review Article **Open Access**

Recent advances in the pathophysiology and management of sepsis: a review

*[1]Adegboro, B. A., [1]Imran, J., [2]Abayomi, S. A., [3]Sanni, E. O., and [4]Biliaminu, S. A.

Departments of [1]Medical Microbiology and Immunology, [3]Haematology, and [4]Chemical Pathology,
Nile University of Nigeria, Abuja, Nigeria
[2]Department of Medical Microbiology, LAUTECH Teaching Hospital, Ogbomoso, Nigeria
*Correspondence to: boazadegboro@gmail.com

Abstract:

Sepsis is a syndrome consisting of physiological, pathological and biochemical anomalies caused by infectious agents. It causes clinical organ dysfunction, which is identified by an acute increase in the Sequential (sepsis-related) Organ Failure Assessment (SOFA) score of two or more points. SOFA score is a score of three components that can be easily used at the bedside to track the clinical status of a patient while on admission, and these are altered respiratory rate of ≥ 22 breaths/minute, altered mental status, and systolic blood pressure of ≤ 100 mmHg. A patient with SOFA score of ≥ 2 has an attributable 2 - 25-fold increased risk of mortality compared to a patient with SOFA score of < 2. This present review provides information on the new definition of sepsis and septic shock, aetiology, pathophysiology, biochemical, pathological and haematological changes, morbidity and mortality parameters, management, and prognostic factors in patients with sepsis.

Key words: Sepsis, septic shock, SOFA score, pathophysiology, management bundles

Received Aug 21, 2020; Revised Nov 2, 2020; Accepted Nov 21, 2020

Progrès récents dans la physiopathologie et la gestion de la septicémie: une revue

*[1]Adegboro, B. A., [1]Imran, J., [2]Abayomi, S. A., [3]Sanni, E. O., et [4]Biliaminu, S. A.

Départements de [1]Microbiologie médicale et d'immunologie, [3]Hématologie et [4]Pathologie chimique,
Université du Nil du Nigéria, Abuja, Nigéria
[2]Département de microbiologie médicale, Hôpital universitaire LAUTECH, Ogbomoso, Nigéria
*Correspondance à: boazadegboro@gmail.com

Abstrait:

La septicémie est un syndrome constitué d'anomalies physiologiques, pathologiques et biochimiques causées par des agents infectieux. Il provoque un dysfonctionnement des organes cliniques, qui est identifié par une augmentation aiguë du score d'évaluation séquentielle (liée à la septicémie) de la défaillance d'organe (SOFA) d'au moins deux points. Le score SOFA est un score de trois composants qui peuvent être facilement utilisés au chevet du patient pour suivre l'état clinique d'un patient lors de son admission, et il s'agit d'une fréquence respiratoire altérée ≥ 22 respirations / minute, d'un état mental altéré et d'une pression artérielle systolique de ≤ 100 mmHg. Un patient avec un score SOFA ≥ 2 a un risque de mortalité attribuable 2 à 25 fois plus élevé qu'un patient avec un score SOFA de < 2. Cette revue fournit des informations sur la nouvelle définition de la septicémie et du choc septique, l'étiologie, la physiopathologie, changements biochimiques, pathologiques et hématologiques, paramètres de morbidité et de mortalité, prise en charge et facteurs pronostiques chez les patients atteints de septicémie.

Mots clés: septicémie, choc septique, score SOFA, physiopathologie, faisceaux de prise en charge

Introduction:

Sepsis is a major public health concern at individual, health system and societal levels both in the developed and developing nations of the world (1). It is characterized by syndrome of physiological, pathological and biochemical anomalies caused by infectious agents (2). The incidence of sepsis over the years is on the increase. About 49 million cases of sepsis and 11 million sepsis-related deaths were reported globally in the year 2017 (3), which constitute about 20% of all deaths globally.

On annual basis, estimated 3 million and 1.2 million cases of sepsis are reported globally among newborns and children respectively. About 30% of neonatal sepsis-related deaths are due to multidrug resistant organisms (4). The total cost of managing sepsis in the US hospitals in 2011 amounted to 20 billion US dollars, constituting 5% of US total hospital bill (3,5).

This present review provides information on the new definition of sepsis and septic shock; aetiology, biochemical, pathological and haematological changes in patients with sepsis, morbidity and mortality parameters, and management and prognostic factors of sepsis.

Methodology:

Two electronic databases (PubMed and Google Scholar) were examined for list of publications written in English Language relating to pathophysiology and management of sepsis. Additional publications were obtained from textbooks and other hardcopy journals. After removing duplicate and non-relevant publications, a total of 87 publications were included for the review. Fig 1 depicts the process by which publications used for the review were selected.

Pathophysiology of sepsis:

Sepsis is a condition of dysregulated host response that was *ab-initio* initiated to exterminate the invading pathogens into the body (6). The host response is mediated by the innate and adaptive immune systems. The various cell types including monocytes, macro phages, neutrophils, dendritic and epithelial cells involved in innate immune system possess pattern-recognition receptors (PRRs). The PRRs are essential for recognizing invading bacteria and subsequent initiation of immune response. They recognize both pathogen-associated molecular patterns (PAMPs) which are conserved motif expressed by pathogens and damage-associated molecular patterns (DAMPs) also called alarmins, which are host cell molecules released during inflammatory stress (7).

Following the invasion by the pathogen and its interaction with the host innate immune cells, there is a coordinated host response characterized by both proinflammatory and anti-inflammatory/immunosuppressive reactions that are directed to eliminate the pathogens and restore normal homeostasis. When the pathogen

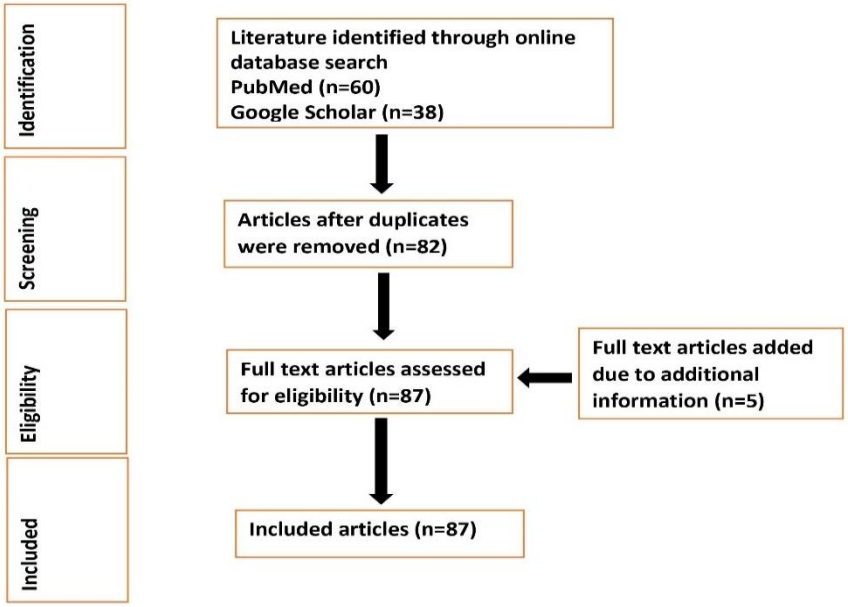

Fig 1: Process for selection of articles for the review

succeeds in circumventing the protective host immunity, there is continuous stimulation of host cells resulting in excessive and injurious immune response, and inability to restore homeostasis. This is exactly what transpired in a host with sepsis (4).

Hyperinflammation

Initiation of inflammation

The first line of defense against invading pathogens include the anatomical barriers such as the skin and mucosal lining of the respiratory, gastrointestinal and urogenital tracts. This is followed by interaction with the innate immune system that comprise of complement system, sentinel phagocytic cells, and natural killer cells, which serve to activate the adaptive immune system. The innate immune system broadly recognizes various antigens by sensing the carbohydrate and fatty acid molecules present on the surface of most pathogens, collectively known as pathogen associated molecular patterns (PAMPs) or host cell molecules expressed during inflammatory stress called damage associated molecular patterns (DAMPs). PAMPs or DAMPs bind to pattern-recognition receptors (PRRs) on the cells of these innate immune system resulting in signaling cascade that leads to sustained immune activation and dysfunction from hyperproduction of cytokines. The PRRs are grouped into various families such as Toll-like receptor (TLRs), C-lectin receptors (CLRs), retinoic acid-inducible gene-like (RAG) receptors, and nucleotide-binding oligomerization domain-like (NOD) receptors (4). The most widely studied of the PRRs is the TLR.

In pathogenesis of sepsis, implicated proinflammatory cytokines include IL-1β, IL-12, IL-18, and TNF. Also involved are high mobility group box 1 (HMGB1), a nuclear protein actively secreted following inflammatory stimuli, and S100A8/9 (calprotectin), a heterodimer protein expressed in neutrophil. Both HMGB1 and S100A8/9 levels are elevated in sepsis. HMGB1 can act as cytokine or chemotactic factor via TLR4 signaling while S100A8/9 stimulates systemic inflammation also via TLR signaling. If these processes are not curtailed promptly, and local response spread systemically, the TLR-signaling activation of the immune system will result in harmful hyperinflammatory response initiated by proinflammatory cytokines which is called the "cytokine-chemokine storm". This is believed to be responsible for all the various consequences seen in early phase of sepsis, which has therefore been the target of many clinical trials with the use of antibodies or inhibitors of cytokines such as TNF-α and β, IL-1β and other anti-inflammatory strategy (4,8). The primary aim of the innate immune system is complete extermination of the pathogen through this primary inflammatory reaction which is then followed by resolution of the immunological process by the adaptive immune system.

Activation of complement system

Complement system is the second most important contributor to the inflammatory reaction that occurs in the pathogenesis of sepsis. Complement system is made up of small proteins that are primarily synthesized by the liver and are triggered by the presence of PAMPs and DAMPs in the host body via interaction with complement components C1q, mannose-binding lectin (MBL), and ficolins. Complement system can be activated through classical, alternate or lectin pathways. However, various intracellular (elastase, neutral proteases) and extracellular (thrombin, activated clotting factors) proteases are known to also generate complement proteins such as C3a and C5a, which are small protein fragments called anaphylatoxins that exert strong proinflammatory effect on leukocytes, endothelial cells and platelets. C5b protein mediates formation of membrane attack complex (MAC) that results in lysis of bacteria. In addition, complement proteins once activated multiply the effects of local immune reactions by putting yet more cytokines into play (9).

Activation of coagulation system and vascular endothelium

Activation of the coagulation system during host-pathogen interaction elicits immune defense mechanisms such as induction of immune response via protease-activated receptors (PARs) activation, release of antimicrobial peptides, and recruitment and activation of phagocytic cells (10). In recent time, the term "immunothrombosis" has been hypothesized to demonstrate the independence of the innate immune and coagulation systems (11). The high-level activation of coagulation seen in sepsis occurs through the tissue factor-extrinsic pathway, resulting in net procoagulant state with high risk of microvascular thrombosis. Disseminated intravascular coagulopathy (DIC) characterized by microvascular thrombosis and haemorrhage is one of the most important complications of sepsis. Vascular injury in sepsis exposes tissue factors to coagulation factors in blood, leading to clotting. Endothelial cells and macrophages are triggered to express large amount of tissue factors by both PAMPs and proinflammatory cytokines. Coagulation can also be activated in sepsis via the intrinsic

pathway and stimulate inflammation through the kallikrein-kinin system. This is enhanced by the reduced activity of the main anticoagulant pathways such as the tissue factor pathway inhibitor (TFPI), antithrombin, and the protein C system (4).

Interactions of the complement and coagulation systems

There is an increasing evidence from clinical and experimental studies which showed that coagulation proteases can activate the complement system and vice vasa. In sepsis, the functions of coagulation and complement systems are closely intertwined. Some components of coagulation and fibrinolytic system such as factors IXa, Xa, XIa and thrombin, and the central fibrinolytic protease plasmin can convert C3 and C5 proteins into C3a and C5a respectively. Conversely, C5a and membrane attack complex can stimulate exposure of tissue factors in endothelial cells due to the structural alteration caused by the complement products (4,12).

Vascular endothelial and multiorgan dysfunction

Following entry of pathogens into the host body, platelets and leukocytes migrate to the sites of proliferating microbes through the vascular endothelium. There is a significant nexus between sepsis and disruption of the integrity of endothelial barrier. This results in exposure of the underlying collagen fibres and tissue factors to blood cells in circulation, triggering activation of platelets and the complement system. Thrombin, cathepsin G, matrix metalloproteinase (MMP), trypsin and plasmin are known activators of protease-activated receptors (PARs). Activated PARs cause dysfunction of endothelial lining via derangement of cytoskeletal system, contraction and rounding of endothelial cells resulting in disruption of cell-to-cell contact and vascular hyperpermeability. There is usually high level of circulating MMP in sepsis (13).

The primary cause of death in septic shock are either refractory hypotension or multi-organ failure. The vascular hyperpermeability results in severe hypotension refractory to intravenous fluid resuscitation and vasopressor therapy. In addition, there is inability to sustain high cardiac output. These are the major causes of refractory hypotension (14). Local and systemic inflammatory responses cause microvascular injury that result in organ failure. The number of failed organ systems determine the outcome of sepsis. About 70% mortality seen in sepsis is due to multiorgan (≥3 organ systems) failure, and about 18% of patients develop respiratory failure. Renal failure resulting from renal hypoperfusion, intra-renal shunting, and use of nephrotoxic agents (such as antibiotics, and radiologic imaging dye) is seen in about 15% of septic patients (14).

Platelets activation

Recent evidence showed that platelets, which are small circulating anucleate cells, play a vital role in inflammation and immunity. Activated platelets secrete various molecules including thromboxane A2 and adenosine diphosphate which have positive feedback effects on platelets activation (15). In sepsis, activated platelets trigger formation of platelet-leukocyte complex, platelet-platelet aggregation as well as release of granular cellular components such as chemokines, adhesive proteins, coagulation factors, mitogenic factors and regulators of angiogenesis. Sepsis therefore results in platelets consumption (thrombocytopenia) with high risk of mortality. Also, there is decline in the levels of ADAMTS 13 (disintegrin and metalloproteinase with thrombospondin type1 motif 13) which is a cleaver of large von Willebrand factor. This results in enhanced platelet-endothelium (injured) complex, promoting the development of vaso-occlusive thrombi in the microvasculature that contribute to most organ failure seen in sepsis (15). Platelet activation in sepsis occurs through many mechanisms; thrombin, a coagulation activation product, is a great activator of platelets through the PARs. In the same vein, platelets can also be activated by von Willebrand factor via binding platelet glycoprotein Ibα (4).

Anti-inflammatory induction and host immunosuppression

Induction of anti-inflammatory reaction in sepsis is meant to counteract/limit excessive and harmful inflammatory process as well as stimulate tissue repair. However, immunosuppression results from persistence of anti-inflammatory reactions seen among septic patients who required intensive care, a condition referred to as "persistent inflammatory, immunosuppression and catabolism syndrome" (6,16). Secondary infections with less virulence organisms such as *Acinetobacter* spp., *Enterococcus* spp., *Stenotrophomonas*, *Candida* spp., cytomegalovirus and herpes simplex virus reactivation can occur as a sequel of persistent immunosuppression (17).

Suppression of innate immune cell functions

Neutrophil extracellular traps (NETs), a product of neutrophil made up of DNA, histones, and neutrophil-derived protease, play an important role in protective immunity through captu-

ring and killing of microbes. In sepsis however, there is defect in neutrophil chemotaxis and recruitment to the sites of infection, and depressed capacity of neutrophils to produce essential effector molecules such as reactive oxygen species (ROS) and cytokines. Moreover, there is impaired expression of HLA-DR and reduced ability to release pro-inflammatory cytokines by antigen presenting cells (APCs) such as monocytes, macrophages, and dendritic cells. This condition is referred to as "immuno-paralysis" but their ability to express anti-inflammatory mediators such as IL-10, is however retained (4).

Suppression of adaptive immune cell functions

Significant decline in $CD4^+$ and $CD8^+$ T-lymphocytes, B lymphocytes and dendritic cells due to programmed cell death (apoptosis) is a common finding in sepsis (17,18). In many studies with experimental models, administration of inhibitors of lymphocyte apoptosis results in profound improvement in treatment outcome. The interaction of programme cell death 1 (PD-1), which are immune checkpoint (IC) molecules on the surface of T-cells, with its corresponding ligands (PD-L1) on the surface of antigen presenting cells (APCs) results in high degree of immunosuppression of the adaptive immune system. The functions of monocytes and neutrophils are also inhibited by regulatory T cells (Tregs) (17).

Biochemical, hormonal and organelle dysfunctions

Some Gram-positive bacteria are capable of producing and releasing exotoxins, which are often products of plasmids and episomes, that act as superantigens (19). The cell wall of Gram-negative bacteria are endotoxins, the glycoprotein components of which act as toxins, that cause pyrexia, vasodilatation, sepsis, and endotoxic shock. Bacterial toxins are known to play a pivotal role in pathophysiology of sepsis (20).

Oxidation of plasma components

Oxidation of the components of the blood is one of causes that provide distant tissues injury and dysregulation in sepsis. Oxidation of plasma components is caused by oxygen release to plasma, and it destroys humoral regulation of different cells, tissues and organs (21). The stimulation of surface receptors of erythrocytes by bacteria causes the oxygen release. The higher the concentration of oxygen released from erythrocytes to the arterial blood, the more severe the sepsis. There are many complications which arise as a result of the release of a large amount of oxygen. Erythrocytes are unable to transport oxygen. This results into general multi-organ hypoxia. Secondly, the released oxygen is highly reactive, and tends to destroy and transform plasma proteins, peptides, immune complexes, hormones, amino acids, fatty acids, vitamins and many other substances necessary for cell nutrition, proliferation, protection, and energy production and functioning (21).

Reduction of enzymatic activities and intravascular coagulation

Oxidative changes to proteins can lead to diverse functional consequences such as inhibition of enzymatic and binding activities, increased susceptibility to aggregation (intravascular coagulation) and proteolysis, increased or decreased uptake by cells, and altered immunogenicity (22). The most important aspect of this oxidation is inactivation of regulatory substances, in particular, hormones including the pituitary gland hormones (23).

Impairment of growth hormonal function

The growth hormone and insulin-like growth factor-1 (IGF-1) axis plays a pivotal role in critical illnesses. Derangement in the functions of these hormones leads to profound changes in metabolism such as protein wasting, with loss of skeletal muscle, delay in wound healing, and impairment in recovery of organ systems (23,24).

Insulin resistance

Inactivation of other proteins such as insulin impairs the ability of cells to uptake glucose, amino acids, and other essential substances. Formation of dityrosine decreases and abolishes insulin biological activity (25). Insulin is necessary for glucose to enter many cell types therefore inactivation of insulin causes hyperglycemia, which is one of the metabolic derangements that influence sepsis outcome (26,27).

Adrenal and thyroid hormonal insufficiency

The oxidation of blood components by reactive oxygen species (ROS) released from erythrocytes may affect the hypothalamic-pituitary-adrenal axis (28) resulting in primary and secondary adrenal insufficiency in patients with sepsis, and is associated with a poor outcome (29,30,31). The oxidation of the blood components can also affect the hypothalamo-pituitary-thyroidal axis, leading to inactivation of thyrotropin, the thyroid gland hormones (triiodothyronine TT3 and thyroxine TT4), and their binding proteins. The thyroid hormones

regulate metabolism and they have impacts on sepsis prognosis. The level of TT4 is lower in patients with septic shock than in patients without septic shock (32,33).

Generalized vasodilatation and shock

Vasopressin (an antidiuretic hormone) is also oxidized by the reactive oxygen species released from erythrocytes. Vasopressin plays a role in circulatory homeostasis and serum osmolality. Oxytocin and vasopressin are oxidized, with the formation of dityrosine (34). Vasopressin oxidation and depletion cause vasodilatory shock, a situation associated with high mortality (35). Low expression of angiotensin II and angiotensin converting enzyme (ACE) are valuable in predicting the mortality of patients with severe sepsis (36). Systemic vasodilatation and arterial hypotension are landmarks of septic shock.

Development of oedema

Oxidation of albumin causes hypoalbuminemia in sepsis (37,38). Albumin is the main determinant of plasma oncotic pressure. It plays an important role in modulating the distribution of fluids between compartments, transport of endogenous and exogenous compounds, modulation of capillary permeability, neutrophil adhesion and activation, haemostasis and free radical scavenging (39). Hypoalbuminaemia is a poor prognostic factor in sepsis (40).

Immunoglobinopathies

Reactive oxygen species released from erythrocytes also destroys other proteins, including immune complexes and immunoglobulins, particularly IgG and IgM. The initial steps of oxidation may change the specificity and avidity of immunoglobulins due to chemical alteration of the hypervariable region. Oxidation of IgG significantly changes the immunoreactivity and specificity of IgG fractions (41). Oxidized immunoglobulins have autoimmune and proinflammatory activity (42,43). Low levels of immunoglobulins are frequent in severe sepsis and septic shock (44). However, intravenous immunoglobulins (IVIG) as adjunctive therapy have not shown benefits in treatment of sepsis (45).

Anaemia

When oxygen is released from erythrocytes into the plasma in arterial blood, they cause failure of oxygen delivery to cells resulting in tissue hypoxia, which can lead to anaemia (46). Many factors contribute to the development of anaemia in sepsis and these include blood sampling, decreased erythrocyte synthesis, bone-marrow suppression, reduced production of erythropoietin, and increased erythrocyte uptake (47). The main factor of anaemia in sepsis is increased destruction of erythrocytes caused by; (i) erythrocyte membrane injury caused by bacteria on the surface of erythrocytes; (ii) erythrocyte membrane pores with haemoglobin pouring out as a result of bacterial penetration into the inner space of erythrocyte; and (iii) increased destruction of injured erythrocytes and bacteria containing erythrocytes in plasma and reticulo-endothelial system (RES) particularly spleen (46,48,49).

Mitochondrial dysfunction

Tissue-related hypoxic injury results from hypoxaemia, hypoperfusion and cytokine-mediated mitochondrial dysfunctions, termed cytopathic hypoxia (50,51,52). The lack of oxygen transforms cell metabolism from aerobic to anaerobic. As a result, the Krebs cycle is suppressed and with anaerobic metabolism, lactic acid accumulation occurs. Lack of oxygen delivery to the tissues results in decreased cellular metabolism and increase in cellular lactate production (42). Elevated lactic acid is a marker of suboptimal supply of oxygen to the tissues. High levels of lactic acid are associated with increased mortality in sepsis (53), and its non-clearance in sepsis is a significant independent predictor of death (53,54).

Clinical manifestations of sepsis

The clinical features of sepsis and septic shock are non-specific, and include fever or hypothermia, tachypnoea, tachycardia, and organ dysfunctions which manifest as altered mental status, decrease capillary refill, and cyanosis (2,55). These presentations are largely dependent on the presence or absence of co-morbidities.

Haematological manifestations in sepsis

Frequent haematological findings seen in patient with sepsis include anaemia, leukocytosis, low platelets, as well as haemostatic system activation (56). Patients with sepsis often develop anaemia. Factors responsible for anaemia in sepsis includes inhibition of erythropoiesis secondary to repressive consequence of inflammatory cytokines, impaired iron homeostasis, reduced life span of the red blood cells and haemolysis. Other causes of anaemia in patients with sepsis include nutritional deficiencies due to reduced intake, bleeding secondary to disseminated intravascular coagulopathy and frequent phlebotomy (57). The haematologic manifestations are varied and include anaemia, leukopaenia, leukocytosis and DIC.

Anaemia

The effect of pro-inflammatory cytokines on erythropoietin production has been reported. Such cytokines include TNF-α, IL-1 and IL-6. Apoptosis of the colony forming unit erythroid and the burst forming erythroid by interferon gamma (IF-γ) and IL-1 contributes significantly to anaemia seen in patients with sepsis. Bleeding in this category of patients secondary to DIC and gastrointestinal bleeding from stress ulcers (57) could cause anaemia.

Iron metabolism is impaired in patient with sepsis. The altered iron metabolism is secondary to increased levels of hepcidin (58), which is produced mainly in the liver, and its level is elevated secondary to increased expression of IL-6 in patients with sepsis (20). There is also inhibition of iron release from the RES, inhibition of iron absorption from the intestinal mucosa as well as inhibition of iron incorporation into maturing erythrocyte, with increased levels of hepcidin, leading to iron deficit erythropoiesis (59). Sepsis reduces erythrocyte lifespan by causing alteration in erythrocyte metabolism, and by reducing 2,3-bisphosphoglycerate, it can cause significant increase in production of deformed red cells. The cumulative effects of these alterations affect the membrane of the red blood cells, and reduce its survival (60).

Neutrophilia

The major haematologic findings in patients with sepsis are leukocytosis and neutrophilia. These are usually accompanied with peripheral blood film features of toxic granulation of neutrophils and vacuolations. Left shift are often seen, in which maturing myeloid cells, including myelocytes, metamyelocytes and band forms, appear in the peripheral blood. Sometimes few promyelocytes and blasts are observed (61). High leucocyte count (up to $50x10^9$/L) referred to as leukaemoid reaction, may be seen in some bacteria sepsis and may need to be differentiated from chronic myeloid leukaemia (CML). One of the criteria for diagnosis of sepsis includes left shift, with immature myeloid cells greater than 10. Neutropaenia has also been noted in some patients with sepsis, usually in the elderly and young children (62).

Lymphopaenia

Lymphopaenia has been documented in patients with sepsis, usually due to apoptosis of the lymphocytes and lymphocyte redistribution from the compartment of blood to tissues of lymphoid origin (62).

Thrombocytopaenia

Thrombocytopaenia (low platelet count) occurs commonly in patients with sepsis. The cause and contributing factors to thrombocytopaenia in patients with sepsis include reduced platelets production, consumption of platelets in DIC, platelet destruction via immune mediated mechanism, and haemodilution (63). Aggregation of platelets as well as its attachment to the endothelium and leukocytes may contribute to thrombocytopaenia that is observed in patients with sepsis. Immunoglobulin of the IgG class has been associated with immune mediated thrombocytopaenia and reported in up to 30%-40% of the patients with sepsis (64).

Reported findings of coagulopathy in patients with sepsis are common. The spectrum may range from subtle initiation of coagulation cascade to DIC. Patients with sepsis may present with venous forms of thromboembolism or DIC. Contributory factors to coagulopathy in patients with sepsis include increased tissue factor expression, endothelial cell dysfunction with inhibition of the natural anticoagulant process, and inhibition of the fibrinolytic pathways (65,66).

Disseminated Intravascular Coagulation (DIC)

The maintenance of steady blood flow is enhanced by balance between the procoagulant and anticoagulant systems. Coagulopathy in patients with sepsis is associated with increased levels of procoagulant proteins and reduced levels of naturally occurring anticoagulants. There is increased tissue factor expression in patients with sepsis, which is responsible for initiation of the coagulation cascade (67). The natural anticoagulant system is impaired in sepsis, with reduced levels of anti-thrombin III and protein C. Thrombin production is increased with subsequent generation of fibrin, and with consumption of the coagulation factors, DIC may occur (68).

Biochemical changes in sepsis

Inflammatory cytokines (IL-6, IL-8 and TNF-α) are elevated in patients with sepsis and septic shock, so are the levels of nitrous oxide and lactic acid (69). Only elevated levels of IL-6 and IL-18 are associated with increased mortality in patients with sepsis and septic shock, while elevated levels of TNF-α, lactate and nitrous oxide (though observed in patients with sepsis) are not associated with increased mortality (58). Creatinine levels are only elevated when there is an associated liver damage.

Biomarkers, which are genes, molecules or other host factors help in the identification of health and disease processes. Biomarkers of importance in patients with sepsis can be grouped into diagnostic and prognostic markers. Diagnostic biomarkers provide sensitive and specific information that can be used to differentiate sepsis from all other forms of non-infectious critical illnesses. This enhances antibiotic stewardship program as it helps reduce unnecessary use of antibiotics where they are not required (55). However, prognostic biomarkers are used to monitor patients with sepsis on treatment and also in predicting prognosis including complications.

Monocyte anergy which presents with decreased expression of monocyte HLA-DR, is has been reported to be an independent predictor of poor prognosis in patient with sepsis. Recently, the term theranostics was introduced and entails biomarker tests that help in the selection and monitoring of treatment response, a step towards personalized medicine. According to the Surviving Sepsis Campaign (SSC) guidelines, procalcitonin is the only biomarker with potential usefulness in the choice of antibiotics in critically ill patients. Other biomarkers with lower sensitivity and specificity include C-reactive protein (CRP), IL–6, LPS binding proteins (LBPs) and lactate (5,55).

Complications of sepsis

The main complication of sepsis is septic shock. However, there are other sets of possible complications, which include kidney failure, multiple organ failure, and heart dysfunction. Dialysis may be needed temporarily or permanently if the kidneys fail, and death can occur from multiple organ systems dysfunctions and failure. Stroke due to low blood pressure on the brain and cognitive decline have been reported in some patients with septic shock (70).

Management of sepsis

The major principles of management of sepsis include; timely identification of sepsis features, titrated fluid resuscitation, adequate source control, obtaining blood culture samples prior to commencement of antimicrobials (this is the gold standard for diagnosis of sepsis), and organ support (77).

Clinical assessment and management

In the management of sepsis, clinical assessment is carried out initially to detect the risk factors for infection. These include age, chronic disease, immunosuppressive therapy, AIDS, pre-existing co-morbidities such as diabetes mellitus (DM), renal failure, and bleeding disorders. The aim of physical examination is to identify the possible foci of infection. The vital signs are used to evaluate clinical improvement during hospital admission (77,78).

Serious cellular, circulatory, and metabolic abnormalities occur in patients with septic shock. Clinically, patients with septic shock require a vasopressor to maintain mean arterial blood pressure of ≥ 65 mmHg and serum lactate level >2 mmol/L (>18 mg/dl) in the absence of hypovolemia. A patient with suspected infection can be rapidly identified as being more likely to have poorer outcomes typical of sepsis if they have at least 2 of the following clinical criteria which together constitute a new bedside clinical score termed quick SOFA (qSOFA); respiratory rate ≥22/min; altered consciousness (Glasgow coma score < 13) and systolic blood pressure (SBP) ≤ 100 mm/Hg (78).

The particular site of infection in the body should be identified as soon as possible, at least within 6 hours of presentation. This is referred to as source control (79), and helps define early goals of management e. g. presence of invasive devices suspected to be source of infection can be promptly removed. Distinction should be made between sepsis and septic shock in order to guide management of patient. During the first 6 hours of presentation, initial resuscitation involves achieving the following goals; central venous pressure of 8-12 mmHg, mean arterial pressure of 65 mmHg, urine output of 0.5 ml/kg/Hr, and central venous/ mixed venous oxygen saturation of 70%/65% respectively.

The fluid of choice for initial resuscitation of patients with sepsis/septic shock is crystalloids with the aim of achieving a minimum of 30 ml/kg of crystalloids (4). Blood culture samples and urine culture or sputum samples should, as much as possible, be obtained before administration of antibiotics. However, treatment should not be delayed if this is not possible. Intravenous antibiotics should be administered within the first hour of recognition of sepsis/septic shock (3). A broad-spectrum antibiotic that can penetrate the tissues in adequate concentration should be used. If the cause of sepsis/septic shock is suspected to be of viral origin, appropriate antiviral therapy (if available for the virus) should be initiated (70).

Laboratory assessment

Blood culture

This is the "gold standard" for diagnosis

of sepsis. A minimum of two sets of blood cultures (aerobic and anerobic) should be collected as much as possible before initiating antimicrobial therapy. Urine, pus, ascitic fluid, pleural fluid, cerebrospinal fluid, and other body fluids may be collected as well.

Ancillary laboratory studies

Other laboratory studies essential for diagnosis and monitoring of progress of patients with sepsis (58,80) include; complete blood count (total and differentials), electrolytes, urea and creatinine (E, U, Cr), prothrombin time, liver function tests, arterial blood gas analysis, urinalysis, chest X-ray (to identify source of pulmonary infection and respiratory distress), computerized tomography (CT) scan, positron emission tomography (PET-CT) and magnetic resonance imaging (MRI) techniques to identify source of primary infections

Estimation of biomarkers of sepsis

In recent years, biomarkers that allow early diagnosis of sepsis have been sought for in order to allow early diagnosis of sepsis, since culture-based diagnosis is slow. These biomarkers include C-reactive protein, lactate and procalcitonin. C-reactive protein (CRP) is an acute phase protein produced by the liver and alveolar macrophages. Its level increases after trauma and inflammation. Bacterial infections are powerful stimuli which produce rapid rise in CRP levels in few hours. Its production is stimulated by IL-1, IL-6 and TNF-α. Changes in plasma levels of CRP are useful in diagnosis/ prognosis of infection, a fall in plasma levels indicates infection resolution and its assay is less expensive (71).

Procalcitonin (PCT) has been popularly referred to as the most useful marker of severe systemic inflammation (72). It is normally found in blood at very low level but its production can be stimulated by inflammatory cytokines and bacterial endotoxins, causing its release in higher concentration in response to infection and to systemic infections in patients with viral disease (73). It provides an indicator of risk of sepsis, the higher the level of PCT, the greater the likelihood of systemic infection and sepsis. It is regarded as the most sensitive biomarker to help diagnose bacterial sepsis. This can help allow earlier diagnosis of sepsis and better monitoring of its progression.

Lactate is another biomarker of sepsis. An increase in its level implies poor tissue perfusion and progression to organ dysfunction and are related to or associated with increases mortality rate from 35% to 70%. The use of lactate as a marker for diagnosis, prognosis and treatment of tissue hypoxia in septic shock has been established to be important. Therefore, a patient with sepsis and significant lactic acidosis should receive early antibiotics, haemodynamic monitoring, and adequate resuscitation (73). Absence of lactate clearance in the blood predicts death of sepsis patient. A high level of lactate may be a manifestation of organ dysfunction because its clearance is dependent on the liver and kidney functions. Lactate has been reported to be very useful as a prognostic indicator of state of septic shock (74,75,76).

Venous-arterial pressure difference (dPCO2) is another important biomarker of septic shock. The measurement of dPCO2 is a good prognostic indicator in septic shock, as it provides an index of tissue oxygenation (76).

Sepsis treatment care bundles

The mortality rate in septic shock is high. Over the years, due to the high incidence and mortality rate of sepsis and septic shock, the Surviving Sepsis Campaign (SSC) was set up by a group of international critical care and infectious disease experts. The SSC third revised guidelines, published in 2017, aims to improve the outcome of sepsis and septic shock (55).

In the revised guideline, the previous 6-hour and 3-hour bundles have been compressed into a one-hour bundle with 5 steps initiated at time zero of patient presentation. The one-hour Surviving Sepsis Campaign Bundle of Care (81,82) includes; (i) measure lactate level with repeat measurement if baseline lactate is > 2 mmol/L; (ii) obtain blood culture samples prior to initiation of antibiotics; (iii) use of broad-spectrum antibiotics; (iv) commence rapid administration of crystalloid at 30 ml/kg for hypotension or lactate level of ≥ 4 mmol/L; and (v) administer vasopressors if patient remains hypotensive during or after resuscitation to ensure mean arterial pressure (MAP) at ≥65mmHg. The "time-zero" or "time of presentation" is defined as the time of triage at the emergency department or if presenting from another care facility, from the earliest chart annotation consistent with all elements of sepsis or septic shock ascertained through chart review (82).

Discussion:

About 49 million cases of sepsis, and 11 million sepsis-related deaths were reported globally in the year 2017 (3). These sepsis-related deaths constitute about 20% of all deaths globally. Sepsis is often seen in patients with background of previous medical conditions,

and are caused by opportunistic organisms from patient's own microbiota (55,83). The SOFA score, consisting of altered respiratory rate of 22 breaths/minute or more, altered mental status, and systolic blood pressure of 100mmHg or less, is designed to measure the severity and prognosis from sepsis and septic shock (55).

Sepsis is a life-threatening organ dysfunction caused by dysregulated host response to infection. Clinically, organ dysfunction is identified by an acute increase in the SOFA score of two or more points. A patient with SOFA score of ≥2 has an attributable 2 - 25-fold increased risk of mortality compared to a patient with < 2 SOFA score (61). The most commonly isolated Gram-positive bacteria are *Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae,* and *Enterococcus* spp., while the most commonly implicated Gram-negative bacteria causes are *Escherichia coli, Klebsiella* spp*., Pseudomonas* spp*.,* and *Acinetobacter* spp. Among patients with background co-morbidity or hospital-acquired sepsis, the isolated pathogens are mostly multidrug resistant staphylococci*, Pseudomonas, Acinetobacter* and *Candida* spp (84). Other organisms such as *Burkholderia pseudomallei* and *Salmonella enterica* have been reported (85,86).

The pathophysiology of sepsis is a complex event involving hyperinflammatory syndrome that results in 'cytokine-chemokine storm', anti-inflammatory response and host immunosuppression that can lead to secondary infection, and a variety of host biochemical, hormonal and organelle dysfunctions (4,8,16, 17,18,19,20). The clinical symptoms and signs of sepsis and septic shock are tachypnoea, fever or hypothermia, tachycardia, and organ dysfunctions manifested as altered mental status, decrease capillary refill, and cyanosis (2,4). Frequent haematological findings seen in patient with sepsis include anaemia, leukocytosis, thrombocytopaenia and activation of haemostatic system (56). Anaemia in sepsis is mainly due to increased levels of pro-inflammatory cytokines such as TNF-α, IL-1 and IL-6, apoptosis of the colony forming unit erythroid and burst forming erythroid by IF-γ IL-1, and impairment of iron metabolism secondary to increased levels of hepcidin (57,58).

Leukocytosis and neutrophilia are also major findings in patients with sepsis, along with peripheral blood film features of toxic granulation of neutrophils and vacuolations. Left shift with maturing myeloid cells, myelocytes, metamyelocytes and band forms, appear in the peripheral blood. Sometimes few promyelocytes and blasts are visible (61). High leucocyte count (up to $50x10^9$/L) referred to as 'leukaemoid reaction', may be seen in some bacteria sepsis and should to be differentiated from chronic myeloid leukaemia (63).

Thrombocytopaenia that is observed in patients with sepsis is due to the aggregation of platelets, as well as its attachment to the endothelium and leukocytes. Immunoglobulin of the IgG class has also been associated with immune mediated thrombocytopaenia, and was recorded in up to 30%-40% of the patients with sepsis (64). Inflammatory cytokines (IL-6, IL-8, IL-10 and TNF-α) are elevated in patients with sepsis and septic shock, so are levels of nitrous oxide and lactic acid (69). Elevated IL-6, IL-8 and IL-18 levels are associated with increased mortality in patients with sepsis and septic shock but elevated levels of TNF-α, lactate and nitrous oxide (though observed in patients with sepsis) are not associated with increased mortality, and creatinine levels are only elevated when there is an associated liver damage (58). The main complications of sepsis are septic shock, multiple organ failures, DIC and cardiac dysfunction. Death occur when multiple organ systems become dysfunctional and shutdown. Stroke due to low blood pressure on the brain and cognitive decline can also complicate septic shock (72).

Clinical assessment is based on the risk factors for infection which include age, underlying chronic disease, immunosuppressive therapy, HIV/AIDS, pre-existing co-morbidities such as diabetes mellitus (DM), renal failure, and bleeding disorders. There is an urgent need to identify the possible foci of infection, and vital signs are measured and used to evaluate clinical improvement during admission (77,78). A patient with suspected infection can be rapidly identified as being more likely to have poorer outcomes from sepsis if they have at least 2 SOFA score (qSOFA); respiratory rate ≥22/min, altered consciousness with GCS score of < 13, and systolic blood pressure (SBP) of 100mm/Hg (78,79,81).

Treatment of sepsis is based on intravenous fluid administration and correction of acidosis, identification of primary site and agent of infection, administration of antimicrobial agents based on the local susceptibility pattern of the causative agents, and implementing the 1-hour 'Sepsis-3 Bundles' or 'The SSC 2018 Update' as described by the Surviving Sepsis Campaign, depending on the clinical assessment of the patient (80,81,82,88).

Conclusion:

Sepsis is a medical emergency resulting from infection by bacteria, fungi and viruses

including severe acute respiratory syndrome coronavirus-2 (SARS-COV-2), the aetiology of the ongoing COVID-19 pandemic. The SOFA score is used for the initial assessment and monitoring of such patients, and management is based on identification of primary site and agent of infection, intravenous fluid administration and correction of acidosis, administration of anti-microbial agents determined by the local susceptibility pattern of the causative agents, and implementation of the 1-hour 'Sepsis-3 Bundles' or 'The SSC 2018 Update' described by the Surviving Sepsis Campaign, depending on the clinical assessment of the patient.

References:

1. Baudouin, S. V. Sepsis: Introduction and Epidemiology. In: Baudouin S. V. (ed). Sepsis. 1st edition. London: Springer; 2008.
2. Bethany Lehman, P. D. Sepsis: Disease Management.2020. http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/infectious-disease/sepsis/
3. Opal, S. M., Rubenfeld, G. D., Poll, T., Van Der, V. J., and Angus, D. C. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016; 315 (8): 801–810.
4. Tom Van der P, W. J. Sepsis and Septic shock. In: Bennett, J. E., Dolin, R. B. M. (ed). Mandell, Douglas, and Bennett's Principle and Practice of Infectious Diseases. 9th edition. Saunders Elsevier; 2020: 990–1008.
5. Martin, G. S., Mannino, D. M., and Eaton, S. M. M. The Epidemiology of Sepsis in the United States from 1979 through 2000. N Engl J Med. 2003; 348: 1546–1554.
6. van der Poll, T., van de Veerdonk, F. I., Scicluna, B. P., at al. The immunopathology of sepsis and potential therapeutic targets. Nat Rev Immunol. 2017; 17: 407-420.
7. Takeuchi, O., and Akira, S. Pattern recognition receptors and inflammation. Cell. 2010; 140: 805-820.
8. Wiersinger, W. J., Leopold, S. J., Cranendonk, D. R., at al. Host innate immune responses to sepsis, Virulence. 2014; 5: 36-44
9. Merle, N. S., Noe, R., Harlbwachs-Micerelli, I., et al. Compliment system part II: role in immunity. Front Immunol. 2015; 6: 257
10. van der Poll, T., and Herwald, H. The coagulation system and its function in early immune defense. Thromb Haemost. 2014; 112: 640-648
11. Engelmann, B., and Massberg, S. Thrombosis as an intravascular effector of innate immunity. Nat Rev Immunol. 2013; 13: 34-45
12. Oikonomopoulou, K., Ricklin, D., Ward, P. D., et al. Interaction between coagulation and compliment – their role in inflammation. Semin Immunopathol. 2012; 34: 151-165
13. Opal, S. M., and van der Poll, T. Endothelial barrier dysfunction in septic shock. J Intern Med. 2015; 277: 277-293
14. Bloch, K. C. Infectious disease. In: Hammer, G. D., McPhee, Stephen J. (ed) Pathophysiology of Disease: An Introduction to Clinical Medicine. 7th edition. McGraw Hill; 2014:61-88
15. de Stoppelaar, S. F., van't Veer, C., and van der Poll, T. The role of platelets in sepsis. Thromb Haemost. 2014;112.
16. Gentile, L. F., Cuenca, A. G., Efron, P. A., et al. Persistent inflammation and immunosuppression: a common syndrome and new horizon for surgical intensive care. J Trauma Acute Care Surg. 2012; 172: 1491-1501.
17. Hotchkiss, R. S., Monneret, G., and Payen, D. Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy. Nat Rev Immunol. 2013; 113: 862-074.
18. Boomer J. S., To, K., Chang, K. C., et al. Immunosuppression in patients who die of sepsis and multiple organ failure. JAMA. 2011; 306: 2594-2605
19. Balk, R. A. Severe sepsis and septic shock: definitions, epidemiology, and clinical manifestations. Crit Care Clin. 2000, 16:179-192
20. Horn, K. D. Evolving strategies in the treatment of sepsis and systemic inflammatory response syndrome (SIRS). Qt J Med. 1998; 91:265-277
21. Berlett, B. S., and Stadtman, E. R. Protein oxidation in aging, disease and oxidative stress. J Biol Chem. 1997; 272: 20313–20316
22. Shacter, E. Quantification and significance of protein oxidation in biological samples. Drug Metabolism Rev. 2000; 32 (3&4):307–326
23. Hovorka, S. W., Hong, J., Cleland, J. L., and Schöneich, C. H. Metal-catalyzed oxidation of human growth hormone: Modulation by solvent-induced changes of protein conformation. J Pharm Sci. 2001; 90(1): 58–69.
24. Elijah, I. E., Branski, L. K., Finnerty, C. C., and Herndon, D. N. The GH/IGF-1 system in critical illness. Best Pract Res Clin Endocrinol Metab. 2011; 25 (5):759-567
25. Voerman, H. J., van Schijndel, R. J., Groeneveld, A. B., de Boer, H., Nauta, J. P., van der Veen, E. A., and Thijs, L. G. Effects of recombinant human growth hormone in patients with severe sepsis. Ann Surg. 1992; 216(6):648-655
26. Leonidou, L., Michalaki, M., Leonardou, A., et al. Stress-induced hyperglycemia in patients with severe sepsis: a compromising factor for survival. Am J Med Sci Dec. 2008; 336(6): 467-471.
27. Inzucchi, S. E. Management of hyperglycemia in the hospital setting. N Eng J Med. 2006; 355 (18): 1903–1911
28. Zaloga, G. P., and Marik, P. Hypothalamic-pituitary-adrenal insufficiency. Crit Care Clin. 2001; 17:25-41
29. Annane, D., Sébille, V., Troché, G., Raphaël, J. C., Gajdos, P., and Bellissant, E. A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. JAMA. 2000; 283:1038-1045
30. Koo, D. J., Jackman, D., Chaudry, I. H., and Wang, P. Adrenal insufficiency during the late stage of polymicrobial sepsis. Crit Care Med. 2001; 29:618-622
31. Schroeder, S., Wichers, M., Klingmüller. D., et al. The hypothalamic-pituitary-adrenal axis of patients with severe sepsis: altered response to corticotropin-releasing hormone. Crit Care Med. 2001; 29:310-316
32. Lodha, R., Vivekanandhan, S., Sarthi, M., Arun. S., and Kabra, S. K. Thyroid function in children with sepsis and septic shock. Acta Paediatr. 2007; 96 (3): 406-409
33. Burman, K. D., and Wartofsky, L. Thyroid function in the intensive care unit setting. Crit Care Clin. 2001; 17: 43- 57.
34. Rosei, M. A., Coccia, R., Blarzino, C., Foppoli, C., and Mosca, L. The oxidation of oxytocin and vasopressin by peroxidase/H2O2 system. Amino Acids. 1995; 8: 385-391.
35. Singh, R. G. Antidiuretic hormone replacement therapy to prevent or ameliorate vasodilatory shock. Med Hypotheses. 2002; 59 (3): 337 - 340

36. Zhang, W., Chen, X., Huang, L., Lu, N., Zhou, L., Wu, G., and Chen, Y. Severe sepsis: Low expression of the renin-angiotensin system is associated with poor prognosis. Experimental and Therapeutic Medicine. 2014; 7 (5): 1342-1348
37. Delaney, A. P., Dan, A., McCaffrey, J., and Finfer, S. The role of albumin as a resuscitation fluid for patients with sepsis: a systematic review and meta-analysis. Crit Care Med. 2011; 39:386-391
38. Tamion, F. Albumin in sepsis. Ann Fr Anesth Reanim. 2010; 29(9):629-634
39. Evans, T. W. Review article: albumin as a drug—biological effects of albumin unrelated to oncotic pressure. Aliment Pharmacol Ther. 2002; 16 (Suppl 5): 6–11.
40. Lee, S. H., Jo, Y. H., Kim, K., Lee, J. H., Park, H. M., Rhee, J. E., and Kim, D. H. Prognostic Importance of Hypoalbuminemia in Patients with Severe Sepsis and Septic Shock. J Korean Soc Emerg Med. 2013; 24 (5):599-606
41. Bozic, B., Cucnik, S., Kveder, T., and Rozman, B. Changes in avidity and specificity of IgG during electro-oxidation. Relevance of binding of antibodies to beta2-GPI. Autoimmun Rev. 2006; 6 (1): 28-32
42. Dimitrov, J. D., Vassilev, T. L., Andre, S., Kaveri, S. V., and Lacroix-Desmazes, S. Functional variability of antibodies upon oxidative processes Autoimmun Rev. 2008; 7(7):574-8
43. Omersel, J., Jurgec, I., Cucnik, S., Kveder, T., Rozman, B., Sodin-Semrl, S., and Bozic, B. Autoimmune and proinflammatory activity of oxidized immunoglobulins. Autoimmun Rev. 2008; 7 (7): 523-529.
44. Päsler, M., Dietz, S., and Werdan, K. Hypogamma-globulinemia in Sepsis. In: Vincent P. J. L. (ed). Annual Update in Intensive Care and Emergency Medicine. Berlin Heidelberg: Springer; 2012: 98–108
45. Shankar-Hari, M., Spencer, J., Sewell, W. A., Rowan, K. M., and Singer, M. Bench-to bedside review: immunoglobulin therapy for sepsis - biological plausibility from a critical care perspective. Crit Care. 2012;16: 206).
46. Minasyan, H. Mechanisms and pathways for the clearance of bacteria from blood circulation in health and disease. Pathophysiology. 2016; 23:61-66
47. Piagnerelli, M., Boudjeltia, K. Z., Gulbis, B., Vanhaeverbeek, M., and Vincent, J. S. Anemia in sepsis: the importance of red blood cell membrane changes. Alternatives Transfusion Med. 2007; 9(3): 143–149
48. Minasyan, H. Erythrocyte: Bacteria Killer and Bacteria Prey. Antibacterial Cellular and Humoral Immunity. Int J Immunol (Special Issue). 2014; 2 (5-1): 1-7
49. Minasyan, H. Erythrocyte and Leukocyte: Two Partners in Bacteria Killing. Int Rev Immunol. 2014; 33 (6):490–497
50. Galley, H. F. Oxidative stress and mitochondrial dysfunction in sepsis. Br J Anaesth. 2011; 107 (1): 57–64
51. Brealey, D., and Singer, M. Mitochondrial dysfunction in sepsis. Curr Infect Dis Rep. 2003; 5 (5):365–371
52. Bar-Or, D., Bar-Or, R., Rael, L. T., and Brody, E. N. Oxidative stress in severe acute illness. Redox Biol. 2015; 4C: 340–345
53. Arnold, R. C., Shapiro, N. I., Jones, A. E., et al. Emergency Medicine Shock Research Network (EMShockNet) Investigators. Multicenter study of early lactate clearance as a determinant of survival in patients with presumed sepsis. Shock. 2009; 32 (1): 35–39
54. Nguyen, H. B., Rivers, E. P., Knoblich, B. P., et al. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. Crit Care Med. 2004; 32 (8): 1637– 1642.
55. Vincent, J., Rello, J., Marshal, J., et al. International study of the prevalence and outcomes of infection in intensive care units. JAMA. 2009; 30 (21): 2323–2329.
56. World Health Organization. Sepsis WHO, Geneva. 2018. https://www.who.int/news-room/fact-sheets/detail/sepsis
57. Goyette, R. E., Key, N. S., and Ely, E. W. Haematologic changes in sepsis and their therapeutic implications. Semin Respir Crit Care Med. 2004; 25 (6): 645-59. doi: 10.1055/s-2004-860979.
58. Faquin, W. C., Schneider, T. J., and Goldberg, M. A. Effect of inflammatory cytokines on hypoxia induced erythropoietin production. Blood. 1992; 79 (8): 1887–1894.
59. Eidt Fernanda, M. V., Nunes, B., Pedrazz, L., et al. Biochemical and inflammatory aspects in patients with severe sepsis and septic shock: The predictive role of IL-18 in mortality. Clinica Chimica Acta. 2016; 453: 100-106
60. Drakesmith, H., and Prentice, A. M. Hepcidin and the iron-infection axis. Science. 2012; 338 (6108): 768–772.
61. Wrighting, D. M., and Andrews, N. C. Interleukin-6 induces hepcidin expression through STAT3. Blood. 2006; 108 (9): 3204–3209.
62. Bateman, R. M., Sharpe, M. D., Singer, M., and Ellis, C. G. The Effect of Sepsis on the Erythrocyte. Int J Mol Sci. 2017; 18 (9): 1932. doi: 10.3390/ijms18091932.
63. Bone, R. C., Balk, R. A., Cerra, F. B., et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest. 1992; 101: 1644–1655
64. Joshi, V. D., Kalvakolanu, D. V., and Cross, A. S. Simultaneous activation of apoptosis and inflammation in pathogenesis of septic shock: a hypothesis. FEBS Lett. 2003; 555 (2): 180–184.
65. Vardon-Bounes, F., Ruiz, S., Gratacap, M. P., Garcia, C., Payrastre, B., and Minville, V. Platelets Are Critical Key Players in Sepsis. Int J Mol Sci. 2019; 20: 3494. doi:10.3390/ijms20143494.
66. Kelton, J. G., Neame, P. B., Gauldie, J., and Hirsh, J. Elevated platelet-associated IgG in the thrombocytopenia of septicemia. N Eng J Med. 1979; 300: 760–764.
67. Semeraro, N., Ammollo, C., Semeraro, F., and Colucci, M. Coagulopathy of Acute Sepsis. Semin Thromb Hemost. 2015; 41 (6): 650 - 658. doi: 10.1055/s-0035-1556730.
68. Pernerstorfer, T., Stohlawetz, P., Hollenstein, U., et al. Endotoxin induced activation of the coagulation cascade in humans: effect of acetylsalicylic acid and acetaminophen. Arterioscler Thromb Vasc Biol. 1999; 19: 2517-2523.
69. Suffredini, A. F., Harpel, P. C., and Parrillo, J. E. Promotion and subsequent inhibition of plasminogen activation after administration of intravenous endotoxin to normal subjects. N Eng J Med. 1989; 320: 1165-1172.
70. Higuera, V. what is septic shock? Everything to know about the complication of sepsis. 2018. Everyday health .com.
71. Pavoa, P., Coelho, L., Almeida, E., et al. CRP as a marker of infection in critically ill patient. Clinical microbiology Infect. 2005; 11: 101-108
72. Riedel, S., Melendez, J. H., An, A. T., et al. Procalcitonin as a marker for the detection of bacteriaemia and sepsis in emergency department.

Am J Clin Pathol. 2011; 135 (2): 182-189
73. Ahn, S., Kim, W. Y., Kim, S., H. et al. Role of procalcitonin and C-reactive protein in differentiation of mixed bacterial infection from 2009 H1N1 viral pneumonia Influenza. Viruses. 2011; 5 (6): 398-403.
74. Rhee, C., Murphy, M. V., Li, L., Platt, R., and Klompas, M. Center for disease and control and prevention. Prevention epicenters program. Lactate testing in suspected sepsis: trends and predictors of failure to measure levels. Crit Care Med. 2015; 43 (8): 1669-1676
75. Vincent, J. L., Quintairos, E., Silvia, A., Couto, L., and Taccone, F. S. the value of blood lactate kinetics in critically ill patients: a systemic review. Crit Care. 2016; 20 (1); 257
76. Bhat, S. R., Swenson, K. E., Francis, M. W., and Wira, C. R. Lactate clearance predict survival among patients in emergency department with severe sepsis. West J Emerg Med. 2015; 16 (7): 118-126
77. Bolvardi, E., Malmir, J., Reihani, H., et al. The role of lactate clearance as a predictor of organ dysfunction and mortality in patients with severe sepsis. Mater Sociomed. 2016; 28 (1): 57-60.
78. Patwary, M. I., Bari, M. Z. J., and Isha, I. T. Management of sepsis: Recent advancement. Journal of Bangladesh College of Physicians and Surgeons. 2016; 34 (4): 206-212
79. Singer, M., Deutshman, C. S., Seymour, C. W., et al. The third international consensus definition for sepsis and septic shock. 2016. JAMA. 315 (8): 801-810
80. Levy, M. M., Evans L. E., and Rhodes, A. The Surviving Sepsis Campaign Bundle: 2018 Update. Crit Care Med. 2018; 46 (6): 997-1000
81. Dellinger, R. P., Carlet, J. M., Masur, H., et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock, 2008. Crit Care Med. 2008; 36 (1): 296-327
82. Dellinger, R. P., Levy, M. M., Rhodes, A., et al. Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock. Crit Care Med. 2013; 41: 580-637
83. Kanoksil, M., Jatapai, A., Sharon, J, and Peacock, D. L. Epidemiology, Microbiology and Mortality Associated with Community-Acquired Bacteremia in Northeast Thailand: A Multicentre Surveillance Study. PLoS One. 2013; 8 (1): e54714.
84. Reddy, E. A., Andrea, V., and Shaw, J. A. C. Community-acquired bloodstream infections in Africa: a systematic review and meta-analysis. Lancet Infect Dis. 2010; 10 (6): 417–432.
85. Martin, G. S., David, M., and Mannino, M. M. The effect of age on the development and outcome of adult sepsis. Crit Care Med. 2006; 34 (1): 15–21.
86. Rudd, K. E., Johnson, S. C., Agesa, K. M., et al. Global, regional, and national sepsis incidence and mortality, 1990 – 2017: analysis for the Global Burden of Disease Study. Lancet 2020; 395 (10219):200–211. http://dx.doi.org/10.1016/S0140-6736(19)32989-7
87. Blanco, J., Muriel-Bombin, A., Sagredo, V., et al. Incidence, organ dysfunction and mortality in severe sepsis: a Spanish multicenter study. Crit Care. 2008; 12: R158