VOLUME - 9, ISSUE - 11, November - 2020 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper | Medical Science

A NARRATIVE REVIEW ON NEUTROPENIC SEPSIS.

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ABSTRACT Neutropenic sepsis is a condition in which a patient has global bacterial blood infection, which causes the elevation of neutrophils, including the immature types. However, without the neutrophils, sepsis thrives, as is evident during immunosuppression in cancer treatment, leukemia, or a condition that compromises neutrophil response during bacterial infection. The normal neutrophil count in a healthy person is 1500-8000 neutrophil/mcL, with a differential range of 47/75% of total white blood cell count. However, the level increases beyond the normal range when a person has a bacterial infection. Contrariwise, neutropenia occur due to immunosuppression secondary to radiation, cytotoxicity, or infections that lyse white blood cells, which hinder cellular immunity from mounting an expected response during infection. The review below entails discussing the biomarkers of neutropenic sepsis in which their uses and scope of applicability emerge. Moreover, the study explains the need to manage sepsis in the early stages in which a pathway of progression of systemic damage reveals. Besides, the paper shows the complication that a patient with neutropenic sepsis would develop in which a pathophysiological explanation displays the events that lead to each complication.

KEYWORDS : Neutropenic Sepsis, Septic Shock, Sepsis Biomarkers, Sepsis Complications And Management.

Neutropenic Sepsis and Septic Shock

Neutropenic sepsis is evident when a patient has neutropenia and a quick sequential organ failure assessment (qSOFA) score greater than or equal to 2. However, neutropenia is a condition in which a patient has a neutrophil count of 500-1000 mc/L with a predictable decline to below 500 mc/L within 48 hours in the presence fever/fever of unknown origin symptomatic infection. qSOFA score enumeration is achievable by using the Glasgow coma scale (<15), systolic blood pressure (<100 mmHg), and respiratory rate (<20/min) as the parameters of which each feature has a score of one, and the total qSOFA score is 3 (Marik and Taeb, 2017, p.944). A qSOFA score =/> 2 is diagnostic with the presence of neutropenia is diagnostic of sepsis (Marik and Taeb, 2017, p.944). However, septic shock is diagnostic when a patient has hypovolemia that does not resolve with fluid resuscitation alone but requires vasopressor infusion to maintain the mean arterial pressure above 65mmgHg and serum lactate above 2mmol/L. Thus, the diagnosis of sepsis and septic shock relies on the qSOFA evaluation that deals with the symptoms of sepsis, hypovolemia, and Glasgow coma scale.

Neutropenic Sepsis Biomarkers

Neutropenic sepsis biomarkers are essential in the diagnosis and the evaluation of prognosis in a patient with sepsis. A suitable biomarker of neutropenic sepsis is definitive to a particular bacteria and reacts promptly in the presence of a specific antigen. Moreover, the amounts of the biomarker should remain at high levels for a long time, which allows measurement in a reasonable timeframe (Kuter et al., 2018, p.395). The method used in measuring the biomarkers should be rapid, easily accessible, reproducible, and compare different patient populations (Hamed et al., 2017, p.554; Wilson et al., 2018, p.133). While a single biomarker should hold all the mentioned properties, improved prediction of complication development in neutropenic sepsis is achievable by using multiple biomarkers of different test abilities (Wilson et al., 2018, p.133). For instance, the biomarkers should compose makers that reveal the excessiveness of host response, the progressing organ damage, and the microbes involved (Kuter et al., 2018, p.396). The biomarkers used in enumerating neutropenic sepsis include C-reactive protein, procalcitonin, and pentraxin 3 functions, as described below.

C-reactive protein (CRP) is an essential biomarker that reveals the bacteria involved in sepsis and the estimation of treatment response to the infection. CRP does not indicate the specific bacterial etiology, and it increases slowly with a peak time that goes up to two days (Wilson et al., 2018, p.134). Besides, patients with hematological conditions might have CRP elevation from malignancy or in response to the treatment they are receiving (Wilson et al., 2018, p.134). Hence, CRP indicates the bacteria involved in sepsis, projects the quality of treatment response, but it does not reveal the etiology of the microbes.

Procalcitonin is a sepsis biomarker used in diagnosing neutropenic sepsis and evaluating immune response to the condition using IL-6 and IL-10 levels. The method has advantages that include measuring the levels of pro-inflammatory interleukins (IL-6) and anti-inflammatory IL-10, which suggests the threat of the inflammatory process (Tujula et al., 2020, p.28). However, the disadvantage of using the

method is visible in the predictive values obtained in measuring pro-inflammatory and anti-inflammatory interleukins, which lacks a standard reference range due to lack of documentation (Tujula et al., 2020, p.29). Therefore, procalcitonin as sepsis biomarkers are essential in revealing the mediators and inhibitors of the inflammatory response by measuring the level of IL-6 and IL-10.

Pentrix 3 (PTX3) is a derivative molecule of CRP that helps in performing prognostic bio-marking. The biomarker has an advantage over the use of CRP due to its ability to reveal distinct etiology of microbe involved in sepsis and their kinetics (Hamed et al., 2017, p.555). Besides, the biomarkers have a single documented study in its uses in neutropenic sepsis, but the outcome in clinical trials and uses has promising results that make it a suitable CRP substitute (Hamed et al., 2017, p.555). Thus, the PTX3 is an upgrade of CRP, which helps identify the specific etiology of microbe involved in sepsis and gives the prognostic direction of the inflammatory process and sepsis.

Soluble urokinase-type plasminogen activator reception (suPAR) is a biomarker used in revealing the inflammatory course and blood clotting activities. The level of suPAR increase during chronic disease and is a predictor of mortality in patients with chronic conditions (Petersen et al.,). However, even with a lack of documentation of its usage in neutropenic hematological disorders, suPAR is a suitable sepsis biomarker in explaining the prognosis of the sepsis. Thus, suPAR is a biomarker under investigation that has passed all clinical trials but is ideal for projecting inflammatory course and prognosis in neutropenic sepsis.

Complication of Neutropenic Sepsis

Complications of neutropenic sepsis are widespread and systemic in nature, but septic shock commonly precedes other systemic derangements. Foremost, the hallmark of septic shock is hypotension that does not resolve with fluid resuscitation alone. The shock status in a patient with sepsis arises due to low peripheral resistance and impairment of the systolic phase of cardiac function. Moreover, sepsis causes limits of mitochondria function, activation of the complement system, depressed production of inflammatory regulators like interleukin-6, and under the myocardium regulation, which reduces activities that promote the pumping force of the myocardium (Rathkey et al., 2018, eaat2738). The events lead to systolic hypotension with systolic blood pressure lower than 90mmHg, with cold extremities. Hence, the hallmark of neutropenic sepsis complication is a septic shock from deranged myocardium, causing systolic hypotension.

Sepsis complicates acute kidney injury (AKI), resulting from the hypotensive status in septic shock. Hypotension secondary to septic shock occurs due to hypo-perfusion of kidney microtubules arise from poor microcirculation in the renal system (Harrois et al., 2018, p.161). Moreover, multifactorial processes mediate AKI in sepsis as oxidative stress, and immune response complex activities aggravate it in combination with macro- and micro-circulatory derangement (Wu et al., 2019, p.1731). Thus, AKI is a complication of sepsis that arise from multifactorial processes that include hypo-perfusion of kidney macro- and micro-circulation due to complex immunological events and oxygen stress.

Poor prognosis in neutropenic sepsis has a strong association with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). Lung injury occurs due to uncontrolled coagulation and attacks by leukocytes (Liu et al., 2019, p.177). Additionally, the production of complement components in the lung aggravates the injurious process brought by complement activation from activities of the neutrophil. Consequently, the massive amounts of complement components in the lungs overcome the protective mechanisms mounted by alpha-1 antitrypsin, IL-6, and IL-10, which leads to ALI and ARDS (Jiang et al., 2016, p.127). Furthermore, ARDS results from the accumulation of leukocyte and fluids and platelet aggregation in the alveoli, limiting gaseous exchange and resulting in pulmonary edema. Besides, the reduced pulmonary and cardiac functions form the basis of multi-organ damage (MOD) and multiple organ failure (MOF) alongside the widespread inflammatory events (Jiang et al., 2016, p.129). Therefore, poor prognosis in neutropenic sepsis occurs due to ALI and ARDS combined with a cardiac malfunction that leads to multiple organ damage and failure as a sequel.

In the cardiopulmonary system, acute lung injury, acute respiratory distress syndrome (ARDS), pulmonary edema, and cardiac output occur due to excessive sepsis without prompt treatment. Lung injury arises from inflammatory events in the lungs that alpha antitrypsin 3 and IL-10 cannot regulate (Liu et al., 2019, p.176). Consequently, fluids and platelets accumulate in the alveoli spaces and bronchioles, causing ARDS. Besides, cardiac output arises due to the derangement of the myocardium, which inhibits optimal contraction of the ventricular myocardium, resulting in peripheral hypo-perfusion, and hypovolemic shock (Jiang et al., 2016, p.127). However, the cardiopulmonary events in uncontrolled and excessive sepsis lead to hypo-perfusion of all organs and tissue, which causes organ damage from carbon dioxide toxicity. Therefore, without early management, the patient dies MOF and MOD secondary to cardiopulmonary limitation.

The inflammatory events during the widespread sepsis activate coagulation factors, leading to thrombosis and intravascular disseminated coagulopathy (DIC). Thrombosis and DIC lead to depletion of coagulation factors, which leaves the patient prone to prolonged bleeding that can lead to death. The inability of the liver to keep up with the production of coagulation factors lost during the DIC leads to the depletion of coagulation factors during sepsis. Besides, blood vessels lose coagulation factors as intravascular fluids escape into the surrounding tissues. Hence, sepsis causes loss of intravascular fluid into surrounding tissues and depletes coagulation factors, resulting in DIC, organ failure, and death.

Sepsis leads to hormonal imbalances in a patient. The inflammatory events in sepsis alter the normal secretion and response of the body to stress hormones, including cortisol and catecholamine and neuro-hormones such as vasopressin and adrenocorticotropic hormone. The impaired secretion and response to the hormones have systemic effects, including the acceleration of septic shock development. Besides, sepsis interferes with the relationship between inflammatory mediation and the autonomic nervous system, leading to an inadequate response to the autonomic nervous system. Furthermore, sepsis-induced encephalopathy, myopathy, and acute neuropathy result in disabling cognitive limitations. Nonetheless, sepsis disturbs hormonal and neurohormonal secretion and response by the body.

Neutropenic sepsis leads to disturbance of membranes of visceral organs. The disruption in the membrane of visceral organs leads to gut permeability, which enhances organ failure. For instance, altering the conductivity and composition of the gut membranes leads to extravasation of pathogenic material from the gut lumen into circulation of the host, which further increases immunological response by inflammation. However, the extravasation fluids in the gut and the circulation include vital circulatory proteins such as albumin, which maintain the oncotic pressure in the blood and prevents hemolysis of red blood cells. Nevertheless, sepsis

interferes with the membranes of visceral organs, which leads to extravasation of gut content into the circulation and peritoneum, which aggravates inflammation and loss of vital blood proteins.

Sepsis increases the level of protective cytokines such as IL-10, which results in the reduced or unregulated immune response to the condition. In essence, the secretion of IL-10, an anti-inflammatory cytokine, prevents an excessive inflammatory response, resulting in increased sepsis complications. For instance, autopsy and biopsy results from patients with widespread systemic sepsis show a high level of immunosuppression from the high levels of circulating IL-10 that gives lethal inflammatory outcomes. The condition of compensatory anti-inflammatory response syndrome (CAR) has a characteristic of reduced levels of different leukocyte numbers, which cause immunosuppression, catabolism syndrome, and persistent inflammation. Thus, sepsis interferes with the immune response by activating protective cytokines, which results in increased and persistent inflammation and catabolism syndrome.

Reasons for Early Management of Sepsis

Early intervention is essential in evaluating the stage of sepsis in a patient and according them specific treatment that prevents organ damage and failure. The early evaluation using the biomarkers that evaluate the level of inflammation and predict organ damage is essential in ensuring the treatment course is delivering the desired results. Besides the biomarkers are essential in predicting the prognosis of the condition in relation to the intervention undertaken on the patient. Therefore, early intervention helps in evaluating the patient in relation to the level of inflammation, prediction of organ damage, and prognosis of the treatment course.

Sepsis causes multiple organ damage and multiple organ failure that leads to death if not managed early enough. The global presence of bacteria in the circulation of a patient leads to an immune response composed of cellular immune, antibody, cytokine, and complement system interventions that result in widespread inflammation (Kochanek et al., 2019 p. 1051). The inflammation leads to interference in different body systems as follows.

Early intervention prevents the occurrence of the massive inflammatory events that aggravate tissue injury in many organs and results in organ failure. The immune system produces pro-inflammatory cytokines such as IL-6, which aggravates inflammation in all the organs. In contrast, the immune mediators such as interleukin-10 remain suppressed, which allows the elevated and persistent systematic inflammation to thrive with a sequel (Kochanek et al., 2019 p. 1052; Iba and Levy, 2018, p.232). The high inflammation levels in all the body systems lead to system oxygen deprivation that hinders normal function (Levy, 2018, p.232). The series of cellular response trigger the production of antibodies by the B-lymphocytes and activation of the complement system that increases inflammatory events. However, intervention with antibiotics such as third generation cephalosporin, nitroimidazoles, or coamoxiclavulonic acid that covers for gram negative, gram positive, aerobes, and anaerobes helps in clearing the bacteria and reducing the stimulation of immune response that has ravaging effect on body systems. Besides, the introduction of corticosteroid therapy reduces the inflammatory process that gives the body a protective mechanism against the inflammatory response (Iba and Levy, 2018, p.233). However, lack of such an intervention leads to a series of sepsis-associated events that cause MOF and death. Therefore, an early intervention helps in preventing the widespread inflammatory reaction, which prevents the patient from developing complications such as organ damage or multiple organ failure.

Early treatment of sepsis prevents the sepsis from complicating into acute kidney injury (AKI) that arise from the hypotensive status in septic shock. Hypotension secondary to septic shock occurs due to hypo-perfusion of kidney microtubules and closure of the microcirculation of the renal system (Harrois et al., 2018, p.161). Moreover, multifactorial processes mediate AKI in sepsis. For instance, oxidative stress and immune response complex activities aggravate AKI in combination with macro- and micro-circulatory derangement (Harrois et al., 2018, p.161). Failure to counter the sepsis and treat shock leads to peddle and abdominal ascites, encephalopathy, and peripheral neuropathy due to accumulation of metabolic waste and electrolyte imbalance in the body. Thus, the early treatment of sepsis prevents the patient from developing AKI as a complication from multifactorial processes that include hypo-perfusion of kidney macro- and micro-circulation due to complex immunological events and oxygen stress.

Early intervention in sepsis prevents renal failure from cardiopulmonary derangement squeal. Low cardiac output and reduced mean arterial pressure lead to poor perfusion of the micro-vascular compartment of the kidney, which inhibits metabolic waste excretion. Consequently, kidney injury occurs from acidosis and mineral accumulation in the blood and vessels (Harrois et al., 2018, p.162). Consequently, reduced glomerular filtrate level occurs, resulting in kidney failure that affects many organ systems. Hence, early intervention protects the kidney from dysfunction and death of the patient.

If not treated early, poor prognosis ensue in neutropenic sepsis and this has a strong association with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). Lung injury occurs due to uncontrolled coagulation and attacks of the parenchyma by leukocytes (Liu et al., 2019, p.176). Additionally, the production of complement components in the lung aggravates the injurious process brought by complement activation in response to neutrophil activities. Consequently, the massive amounts of complement components in the lungs overcome the protective mechanisms mounted by alpha-1 antitrypsin, IL-8, and IL-10, which leads to ALI and ARDS (Liu et al., 2019, p.177). Furthermore, ARDS results from the accumulation of leukocyte and fluids and platelet aggregation in the alveoli, limiting gaseous exchange and resulting in pulmonary edema. The stage is preventable by reducing inflammation using corticosteroid and antibiotic therapy (Jiang et al., 2016, p.127). Corticosteroids such as dexamethasone helps in reducing the inflammatory reaction while antibiotics clear bacteria that initiates the process (Jiang et al., 2016, p.129). However, lack of prompt treatment leads to reduced pulmonary and cardiac functions that form the basis of multi-organ damage (MOD) and multiple organ failure (MOF) alongside the widespread inflammatory events. Thus, lack of early intervention leads to poor prognosis in neutropenic sepsis occurs due to ALI and ARDS combined with a cardiac malfunction that leads to multiple organ damage and failure as a sequel.

Overall, neutropenic sepsis occur when bacteria invades the circulation when a person is immunocompromised. In the immunocompromised state, neutrophil production is low, which means that bacteria thrives despite the response mounted by leukocyte. The system goes into a widespread inflammatory process that protective mechanisms cannot sustain, which results in organ damage and failure. However, the evaluation of neutropenic sepsis is achievable using biomarkers. The biomarkers of sepsis predicts inflammatory levels and shows elements of organ damage or failure, which makes them a tool for predicting treatment outcome and prognosis. Besides, neutropenic sepsis has complication that involves many systems in the body and if not treated early,

leads to organ damage and failure. The inflammatory events in sepsis causes acute kidney injury and failure, acute lung injury, and failure, ascites, pulmonary edema, cor-pulmonale, encephalopathy, and viscera damages. Early intervention with antibiotics prevents septic shock, organ damage, organ failure, and death of the patient. The interventions relevant to a patient in sepsis include fluid therapy, antibiotic intervention, and corticosteroid therapy that caters for fluids prevents inflammation, and clears the bacteria. Therefore, biomarkers of sepsis predicts inflammation, indicate organ damage, helps in determining prognosis, while early intervention in neutropenic sepsis prevents multiple organ damage and failure.

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