Critical illness and its association with sepsis

Pallavi Rain[1], Jyoti Batra[1], Satish Kumar[2], Manjari Rain [3]

[1]Department of Biochemistry, Santosh Medical College, Santosh University, Ghaziabad, Uttar Pradesh, India

[2]Department of Anaesthesia and Critical care, B.R.D. Medical College, Gorakhpur, Uttar Pradesh, India

[3]CSIR-Institute of Genomics and Integrated Biology, Delhi, India

Corresponding Author:

Pallavi Rain

Department of Biochemistry

Santosh Medical College, Santosh University

No.1 Santosh Nagar, Ghaziabad, Uttar Pradesh, India, 201009

E-mail: pallavirain18@gmail.com

Contact no. +91 7518178601

Abstract

Critical illness is a life-threatening condition in which if medical intervention is lacking it can result in mortality. Critical illness can be acute or chronic and it's generally seen after an initial insult to the body which can be trauma, surgery, cancer, or sepsis. To support critically ill patients, intensive care unit has been established in hospitals. In most of the critically ill patients, ventilatory support is essential for survival besides this trained clinician plays an important role by cataloguing the vital signs accurately and recognizing the abnormal values and deciding appropriate treatment accordingly. Sepsis is a common outcome in critically ill patients and it is also the most common cause of the increase in mortality in these patients. In sepsis, dysfunction of the organ develops which is because of the imperfectly regulated host response to infection, and due to that overdrive of the immune system response, this is a life-threatening condition. Sepsis can lead to severe sepsis which leads to septic shock if proper and timely treatment is not provided. Septic shock is a very severe form of sepsis in which body blood pressure drops to alarmingly low levels after an infection which is a potentially fatal condition. Therefore, it is essential to recognize sepsis in the early stages by interpreting appropriate biomarkers, which guides to easy management and proper treatment protocol can be set for critically ill patients in the intensive care unit. This review paper gives a brief account of critical illness and its association with sepsis and its management.

Keywords: Critical illness, sepsis, septicaemia.

Introduction

Critical illness is a health condition often occurs following primary insult like trauma, surgery, stroke, cancer and many more and require management in intensive care unit (ICU) where patients are managed with close monitoring, frequent necessary investigations with treatment protocol accordingly and organ support. Approximately 5-10% of critical ill patients who require mechanical ventilation in early illness will go on to develop chronic critical illness (Nelson et al. 2010). The overall prevalence of chronic critical illness is estimated to be 34.4 per 1,00,000 of the population (Kahn et al. 2015). The characteristic clinical feature associated with critical illness is prolonged requirement for mechanical ventilation due to respiratory failure (Nelson et al. 2010). It is undeceive whether a patient will recover or die (Girard et al. 1985). Most of the adult patients do not survive chronic critical illness in ICU and even many discharged patients often die soon after release due to recurrence cardiopulmonary insufficiency (Nelson et al. 2004).

Chronic critically ill patients experience profound weakness, polyneuropathy and myopathy. Patients are at increased risk of infection and also disposed to metabolic changes and hormonal changes. Patients are distressed with pain, dyspnoea, thirst, anxiety, depression, and from inability to speak due to endotracheal intubation (Nelson et al. 2004). Patients who are discharged after treating critical illness have impairments of physical function or a protracted or permanent delirium, or other cognitive impairment may materialize among critically ill patients (Cox et al. 2007; Engoren et al. 2004; Nelson et al. 2006). The psychological and physical symptoms of critical illness are very severe, including a tendency to develop post-traumatic stress syndrome (Nelson et al. 2004).

Critical illness after surgery

Surgery is performed on an individual to treat a pathological condition such as disease and injury. Although surgery is essential for a patient and is done in controlled way following necessary protocols, it is also a substantial traumatic experience for the body (Efron et al. 2018). This primary insult to body might incline the physiology towards early multiple organ failure. If patients do not succumb to early multiple organ failure, then patient may rapidly restored to immunologic homeostasis or immunologic dysfunction persists and leads to chronic critical illness, characterized by persistent organ dysfunction requiring ICU resources for more than 14 days (Loftus et al. 2017; Mira et al. 2017; Stortz et al. 2018). Development of critical illness after surgery has

become regular. The post-surgical critically ill patients show biomarker profiles consistent with persistent immunosuppression and catabolism, and increased inflammatory cytokines (Stortz et al. 2018). A detailed review on critical illness after surgery is compiled by Efron et al. 2018.

Critical illness and cancer

One of the main causes of morbidity and mortality worldwide is cancer (Heron 2018). About 15% of patients admitted to ICU have cancer and approximately 5% of these can develop critical illness (Azoulay et al. 2017b; Puxty et al. 2015). These numbers could vary according to geographical and demographical distributions. A higher proportion of cancer patients survive at ICU (Puxty et al. 2015; Shimabukuro-Vornhagen et al. 2016]. Early ICU admission is associated with high survival rate, thus admitting cancer patients to ICU should not be avoided and timely identification of patients with ICU requirement is critical (Azoulay et al. 2017b; Hanzelka et al. 2013; Mokart et al. 2013; Song et al. 2012). Sometimes critically ill cancer patients need chemotherapy inside the ICU. Organ support therapies accompanied by chemotherapy may be beneficial in critically ill cancer patients (Barth et al. 2018).

The main reasons for admitting cancer patients to ICU are postoperative care, acute respiratory failure (ARF), and sepsis. Cardiac complications, acute kidney injury, neurological disorders, bleeding, and oncological emergencies are the other clinical reasons for admission to ICU (Soubani 2017). Ventilatory support is used in 35%-50% of critically ill patients with cancer (Almeida et al. 2014; Torres et al. 2016; Yoo et al. 2013). ARF is the leading cause ICU admission among cancer patients (Azoulay et al. 2017a). Cancer patients with compromised immune system are prone to bacterial infection, which is the main cause of ARF (Yoo et al. 2013). Non-infectious causes such as lung and leukemic infiltrates, diffuse alveolar hemorrhage, and non-infectious lung diseases are difficult to identify and need more invasive diagnostic method (Bergeron et al. 2018; Maschmeyer et al. 2015).

Neutropenia is another reason for ICU requirement by cancer patient. Neutropenia was independently associated with unfavourable outcomes among critically ill cancer patients (Georges et al. 2018). Neutropenia is related to septic shock, severe invasive infections, multiple organ dysfunction, and increased mortality (Mokart et al. 2015). Severe (100-499 cells/mm3) neutropenia is risk for infection and sepsis. We will discuss sepsis in detail further in the article.

Anticancer therapies are generally cardiotoxic and lead to cardiovascular collapse, sepsis/septic shock, chemotherapy-associated cardiotoxic disease (CACD), pulmonary embolism, and cardiac tamponade (Cappetta et al. 2017). Cardiomyopathy or myocarditis is a serious and common consequence of CACD (Curigliano et al. 2016). Incidence of cardiovascular diseases in cancer patients after therapy need ICU care and up to 33% of cancer survivors may die due to heart disease (Nebigil et al. 2018).

When a cancer patients undergo surgery such as removal of tumour, they need ICU support because of the complexity of surgical procedure and other complications, which arise mainly due to side effects of chemotherapy. Neurological symptoms and signs are commonly seen in cancer patients mostly in patients with brain cancer. Neurological disorders in cancer patient are produced due to direct or indirect effects of cancer and treatment effects (Baldwin et al. 2012). Neurological disorders need early diagnosis and treatment to avoid or reduce functional loss and often require surgical treatment (Todd et al. 2016).

Sepsis

Critically ill patients are prone to sepsis. Sepsis or septicaemia is a life-threatening condition in which inflammation is triggered throughout the body in response to infection. This causes a cascade of molecular events leading to release of various biomolecules, which may cause multiple organ failure and death. Sepsis is identical to Systemic inflammatory response syndrome (SIRS) with an exception that sepsis is defence response against infection while SIRS is defence response against infection, trauma, surgery, pancreatitis, malignancy, burns. ischemia and more (American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference. 1992).

Symptoms of sepsis include fever, low blood pressure, fast heart rate, difficulty in breathing, and mental confusion (Levy et al. 2003). Clinicians take into account presence of two out of four conditions to confirm sepsis. These conditions are body temperature >38ºC or <36ºC, heart rate >90 beats/min, white blood cells count of >12,000 or <4,000 cells/mm^2 and, respiratory rate of >20 breaths/min or PaCO2<32 mmHg.

Sepsis definition and criteria was latest revised in 2016 (Singer et al. 2016), stating that “Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection.” Organ dysfunction is represented by an increase in the sepsis-related Sequential Organ Failure Assessment (SOFA) score of 2 points or more. It was concluded that the term severe sepsis is redundant and septic shock should be considered as a

subset of sepsis. In septic shock cellular, circulatory, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of ≥65 mm Hg and serum lactate level >2 mmol/L (>18 mg/dL) in the absence of hypovolemia. This arrangement is associated with hospital mortality rates >40% (Singer et al. 2016).

In recent times, number of elderly patients admitted in ICU has increased due to fall in mortality rate and increase in life expectancy (Marik 2006). The prevalence and incidence of sepsis is directly proportional to age (Martin et al. 2006). Clinicians have to take extra care and modify treatment of sepsis in ICU due to presence of co-morbidities in the elderly. Co-morbidity is a risk factor for acquiring sepsis in addition to malnutrition, endocrine deficiency and aging itself (Nasa et al. 2012). The elderly are also at increased risk for colonization by gram-negative bacteria, which predispose the elderly to sepsis and they may be multi-drug resistant, compromising the treatment in elderly (Valenti et al. 1978). Furthermore, the immune system is also compromised in both cell-mediated immunity and humoral immune responses in the elderly (Opal et al. 2005). Thus, sepsis is important cause of mortality in elderly admitted to ICU.

Sepsis at cellular level

Manifestations of sepsis includes septic shock, multiple organ dysfunction, adult respiratory distress syndrome (ARDS), and systemic inflammatory response syndrome (SIRS) (Christaki et al. 2011; Giamarellos-Bourboulis and Raftogiannis 2011). A varied interplay between immunological stimulation, systemic inflammation, and coagulopathy is the cause of heterogeneity in sepsis manifestations (van der Poll and Opal 2008). Uncontrolled inflammatory response or SIRS initiates by activation of pattern recognition receptors, which lead to production of pro-inflammatory molecules such as TNF-α, IL-1β, IL-2, IL-6, IL-8, and IFN-γ and anti-inflammatory cytokines. This further initiate downstream responses including enhanced phagocytic activity, vascular endothelial injury with capillary leak, chemotaxis of leukocytes to sites of infection/inflammation, activation of the coagulation system, and synthesis of acute phase proteins by the liver (Casey 2000; Christaki et al. 2011; Cinel and Opal 2009; Giamarellos-Bourboulis and Raftogiannis 2011).

The initial release of cytokines or chemokines is the hyper-inflammatory, cytokine storm phase of sepsis. If a patient survives this phase, then he or she develops a delayed and potentially prolonged anti-inflammatory state,

which was initially referred to as a compensatory anti-inflammatory response syndrome (CARS) or immune-paralysis (Bone 1996; Frazier and Hall 2008; Hotchkiss and Karl 2003; Munford and Pugin 2001).

In hyper-inflammatory response, NFκB and caspase cleavage is activated leading to production of pro-inflammatory cytokines and IL-1β, respectively. NFκB and caspases simultaneously induce apoptosis in adaptive immune cells (Cinel and Opal 2009; Senftleben and Karin 2002; Weighardt and Holzmann 2007). Peroxisome proliferator activated receptor (PPARγ) is activated in polymicrobial sepsis, resulting in to decreased IL-2 that induces expression of Bcl-2, an anti-apoptotic protein (Schmidt et al. 2011). Further, TNF-α is also increased, which cause release of pro-inflammatory cytokines and chemokines and T-cell apoptosis (He and Ting 2002). Reduction in T-cells, B-cells and dendritic cells is reported in sepsis mouse model and in patients with severe sepsis (Boomer et al. 2011; Boomer et al. 2012; Hotchkiss et al. 1999; Hotchkiss et al. 2001). Individuals who succumbed to sepsis have significantly lower CD4 and CD8 T-cells in spleens and lymph nodes (Boomer et al. 2011).

Immune dysfunction decreases the anti-inflammatory response leading to increased host susceptibility to secondary bacterial infections and opportunistic organisms, and increased risk of multiple organ dysfunction (Kollef et al. 2008; Monneret et al. 2011; Osuchowski et al. 2007; Ziemann et al. 2008). CARS is mediated by a prevalence of Th2 response, apoptosis of lymphocytes, increased Tregs, and decreased MHC class II (HLA-DR) on monocytes/macrophages (Frazier and Hall 2008; Opal 2011). IL-10, an anti-inflammatory cytokine, is detected in serum of septic patients. It has been reported that increased ratio of IL-10 to TNF-α associates with mortality in septic patients with community-acquired infection (Gogos et al. 2000; van Dissel et al. 1998). Pro-inflammatory cytokines TNF-α, IL-1β, and IL-6 are decreased in CARS (Ertel et al. 1995 Munoz et al. 1991; Rigato and Salomao 2003).

Sepsis also initiates endoplasmic reticulum (ER) stress because of accumulation of unfolded or misfold protein in the cytoplasm (Kim et al. 2008; Ron and Walter 2007). To restore the cellular homeostasis, unfolded protein response (UPR) is activated (Hetz 2012; Pluquet et al. 2015; Zhu and Lee 2015). However, under uncontrolled ER stress apoptosis is initiated (Bernales et al. 2006; Sano and Reed 2013; Senftand Ronai 2015).

Prediction of Sepsis

One of the most frequent causes of death in ICU among critically ill patients is sepsis. The risk profile for sepsis among the patients is not clearly defined. Thus, it is crucial to identify various symptoms and biomarkers to predict sepsis at early stage. This will aid in timely and efficient treatment of critically ill patients.

Release of cytokines, due to inflammation, leads to secretion of C-reactive protein (CRP) and procalcitonin (PCT) from the liver. These two acute phase proteins are most commonly estimated for sepsis (Levy et al. 2001; Lichtenstern et al. 2012, Rey et al. 2007). CRP is commonly used to predict sepsis in neonates (Hofer et al. 2012). PCT is used as biomarker for sepsis prediction for bacterial infection (Simon et al. 2004). However, the increase in CRP and PCT is non-specific as it can also increases after surgery and trauma (Clyne et al. 1999; Fritz et al. 2003; Meisner et al. 1998; Limper et al. 2010; Rau et al. 2007; Schneider et al. 2009). Although high PCT levels associate with sepsis with poor outcome, the prognostic value is low for PCT (Lichtenstern et al. 2012; Oberhoffer et al. 1999; Viallon et al. 2008). CRP is appropriate for diagnosis of sepsis complications rather than predicting early sepsis (Kojic et al. 2015; Lobo et al. 2003; Póvoa et al. 2005; Schmit et al. 2008). Production of CRP is triggered by interleukin-6 (IL-6), which is another biomarker for sepsis (Bloos et al. 2014; Henriquez-Camacho et al. 2014; Uusitalo-Seppälä et al. 2011). IL-6 rapidly increases after initiation of the inflammatory cascade. IL-6 expression correlates with sepsis severity (Lichtenstern et al. 2012) and can predict survival on 28th day of sepsis onset (Panacek et al. 2004). However, increase in IL-6 is also non-specific as it also increases after trauma, surgery or in autoimmune diseases (Barbić et al. 2013; Iking-Konert et al. 2013; Schlüter et al. 1991).

Another known biomarker is pentraxin 3, which is released in initial phase of inflammatory response (Bottazzi et al. 1997; Bottazzi et al. 2009, Diniz et al. 2004; Nauta et al. 2003). Patients with severe sepsis have increased level of pentraxin 3 and the levels associate with disease severity 53, 54. Thus, pentraxin 3 is also considered as a potential biomarker of disease severity (Kojic et al. 2015).

Cell surface receptors and their soluble form are also biomarker for sepsis as they increase in activated immune cells. Some of these receptors are truncated form of soluble receptor of advanced glycation end products (sRAGE) (Bopp et al. 2008; Nakamura et al. 2011), soluble triggering receptor expresses on myeloid cells-1 (sTREM-1) (Knapp et al. 2004; Wu et al. 2012), soluble urokinase-type plasminogen activator receptor

(suPAR) (Donadello et al. 2014; Huttunen et al. 2011; Koch et al. 2011), and human leukocyte antigen-DR on circulating monocytes (mHLA-DR) (Cheron et al. 2010; Venet et al. 2007), which need further investigation to establish them as a potent biomarker for sepsis. Soluble CD14 subtype (sCD14-ST) or presepsin is the most promising receptor to be used as a biomarker of prognosis and for diagnosing sepsis and septic shock (Behnes et al. 2014; Chenevier-Gobeaux et al. 2014; Shozushima et al. 2011; Ulla et al. 2013).

Biomarkers like Cytokeratin 18 (Hofer et al. 2009; Roth et. 2004), Angiopoetin-1, Angiopoetin -2 (Giuliano et al. 2014; Ricciuto et al. 2011), troponin (Brivet et al. 2006; Kalla et al. 2008) and other markers of organ failure and tissue dysfunction has also been investigated as biomarker of sepsis prediction. However, one cannot rely on the outcome of a single biomarker and should consider a combination of biomarkers (Kojic et al. 2015) as well as other non-laboratory biomarkers such as body temperature (Drewry et al. 2013), heart rate variability (Barnaby et al. 2002; Chen et al. 2007; Godin et al. 1996), clot-Lysis-Index (Adamzik et al. 2010; Brenner et al. 2012) and microcirculatory blood flow (Spanos et al. 2010; Trzeciak et al. 2007). It is still unclear that among all biomarkers which is the most consistent biomarker or biomarkers to predict sepsis at an early stage.

Management of critically ill patients

Advancement of ICU care techniques has reduced ICU mortality and increased survival in acute critical illness. However, this advancement has also led to rise in number of chronic critical illness with prolonged dependence on mechanical ventilation and requirement of strategic ICU care (Nelson et al. 2010). Fluid resuscitation remains the first line treatment in the management of severe sepsis and septic shock. Fluid is administered intravenously to support intravascular volume (Rivers et al. 2001). Fluid used for treatment could be natural or artificial and colloids or crystalloid solutions (Dellinger et al. 2004). Some of the administered fluids are saline, albumin, hydroxyethylstarch and glucose.

Normal saline is most commonly used crystalloid solution. However, mortality rate is lower when albumin is administered as compared to saline and other solutions (Delaney et al. 2011; Finfer et al. 2004). Balance salt solution is better than normal saline as it contains other anions such as acetate, lactate, gluconate, and malate to reduce the concentration of chloride and avoid dilutional hyperchloremic metabolic acidosis (Guidet et al. 2010; Morgan et al. 2004).

Hydroxyethyl starch is used in the category of colloids. It is particularly used in Europe and is manufactured from a highly branched starch called amylopectin, which is obtained from maize or potatoes (Finfer et al. 2010). Hydroxyethyl starch is available is different formulations. The higher molecular weight and higher molar hydroxyethyl starch decreases hydrolysis leading to increased intravascular persistence and prolonged plasma volume expansion, while the lower molecular weight and lower molar hydroxyethyl starch is safer (Dart et al. 2010). However, hydroxyethyl starch is harmful and is a risk factor for acute kidney injury and death (Dart et al. 2010; Perner et al. 2012).

Controlling blood glucose level, by insulin therapy, is beneficial in improving ICU patient outcome and decreases the mortality rate (Malmberg et al. 1995; van den Berghe et al. 2001). It has been reported that with controlled glucose patients' dependency on antibiotics is also reduced (van den Berghe et al. 2001). Insulin therapy should be started in critically ill patient when blood glucose is >180 mg/dL (10 mmol/L) and should be maintained between 144 and 180 mg/dL (8–10 mmol/L) (American Diabetes Association 2012; Dellinger et al. 2012). Further, norepinephrine is used to minimize arrhythmia in critically ill patient with septic shock, but it does not improve mortality rate (Choudhury et al. 2017; Gordon et al. 2016; Liu et al. 2018; Myburgh et al. 2008).

Ventilatory support for critically ill patients in the ICU is very common, in US alone, annually more than a million persons require mechanical ventilation in ICUs (Kersten A et al. 2004), especially in patients who develops chronic critical illness (CCI). In CCI patients acute respiratory distress syndrome is a very common complication which requires protective lung ventilation which is associated with improved morbidity (Roy G Brower et al. 2000). Prolonged mechanical support (PMV) is also a requirement in CCI patients, A fraction of critically ill patients i.e., 10% and 34% of patients who are already on ventilation for two days require long periods of ventilatory support (PMV). More than or equal to 21 days of mechanical ventilation is considered as PMV which is generally lead to other complications and associated with poor outcome especially in elderly patients (Christopher E. Cox et al. 2007; Jennifer M. Maguire et al. 2013; Cox CE et al. 2007; Nelson JE et al. 2004; Carson SS et al. 2002; Cox CE et al. 2007; Seneff MG et al. 1996) Non invasive mechanical ventilation (NIMV) is preferred in critically ill hematology patients with respiratory failure as intubation has its own complications and it is observed that it improves the outcome but failure in NIMV increases risk of organ failure and death (Rosario Molina et al. 2012). After extubation conventional oxygen therapy is commonly used

in critically ill patients. Failure in extubation means reintubation within 2-7 days after extubation with leads to PMV, longer ICU stay, ventilator associated pneumonia and high mortality (Salvatore Maurizio et al. 2018).

Cardiovascular failure is one of the most important risk factors for death in ICU. Cardiac support in critically ill patients is required to manage pulmonary or/and cardiac failure which is a life threatening stage. Over recent years mechanical circulatory support is evolved markedly, extra corporeal membrane oxygenation (ECMO) is used as temporary support in cardiac transplant or in place of a more permanent device, to provide time in recovery of organs or treatment of cardiogenic shock, ARDS, lung transplantation graft failure, pneumonia and trauma. ECMO can be deployed in a veno arterial or veno venous configuration which depends upon the distress. (Viktoria D Mayr et al. 2006; Silvana et al. 2008) In critically ill patents ionized hypocalcemia is frequently seen due to numerous pathophysiological disturbances which is a cause of poor prognosis. To maintain vascular tone and myocardial function calcium is essential. In critically ill patients calcium supplementation is beneficial and it may be helpful in decrease in mortality but may cause cellular damage. (S Jankowski et al. 1995; Zhongheng Zhang et al. 2015). To optimise oxygen and to stabilize circulation, inotropic support is often required in intensive care patients. Medicine like dobutamine which is used to treat cardiac decompensation symptoms and catecholamines (epinephrine, norepinephrine, dopamine) is mainly used for this purpose, these agents improve diastolic relaxation, reduce left ventricular afterload and enhance contractility which ultimately improve cardiac performance. (P J Kulka et al. 1993)

Organ support-

Thyroid dysfunction known as euthyroid sick syndrome, is also a common phenomenon in critically ill patients which are septic. The change in hormone levels are quite significant but they are transient in nature. Low levels of thyroid hormone is observed in septic patients mostly FT3 sometimes FT4 and in severe cases TSH can also be low and this is associated with poor outcome. (Iglesias P et al. 2009; Simons RJ et al. 1990; Angellousi A et al. 2011). Survival of critically ill patient is affected by endocrine dysfunction because it plays important role in developing multiple organ dysfunction by a state of stress created in the body due to hypermetabolism, hyperglycaemia, increase energy expenditure and muscle loss (Farwell AP 2003; DeGroot LJ 2003; Adler SM et al. 2007). Thyroid hormone therapy is recommended because of low level of thyroid hormone but its effect can be beneficial or harmful it is a debate going on So, it is difficult to recommend thyroid hormone therapy in critically ill patients. (Nikolaos Stathatos et al. 2001) Management of critically ill patients can be different for

every patient as it depends upon the type of disease or distress that patient possessed and also it has to cover numerous factors involving in survival of these patients which may change each day for a particular patient according to their condition.

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