Chapter

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Tight Control of Diabetes in the ICU Setting

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Diabetes mellitus (DM) is a state of chronic hyperglycemia with a variety of well established micro and macrovascular complications. As any other human being, patients with DM can suffer from acute illness which can make them critically sick requiring care in intensive care units (ICU). Further, a diabetic is much more prone to develop acute infectious complications due to various inherent abnormalities of self defence mechanisms discussed below. Hyperglycemia is potentially harmful because it acts as (i) a procoagulant (ii) impairs neutrophilic function, (iii) increases the risk of infection, (iv) induces apoptosis, (v) impairs wound healing and (vi) associated with increased risk of death[1].

Critical care is initially centered around resuscitation of patients at extremes of physiological deterioration. This requires thorough understanding of pathophysiology of a critically sick patient[2]. The common etiological factors are given in Table 1.

Table 1: Common etiological factors in critically ill patients

Infectious causes
Falciparum malaria
Sepsis – GI, Skin, UTI, Puerperal
Pneumonia -ARDS
Viral encephalitis
Filarial septicemia
Infectious hepatitis
Severe pancreatitis
Meningitis
CNS tuberculosis – compromised host
Invasive procedures and devices
Non-infectious causes
Cardiogenic – Ac. M ., Myocarditis, Arrhythmias, etc.
Cerebral hemorrhage, infarction
Subdural, Subarachnoid hemorrhage
Cirrhosis of liver
Acute abdominal condition
Head injury
Fracture of major bones , femur, pelvis etc.
Chest injury
Pulmonary embolism

PATHOPHYSIOLOGICAL ABNORMALITIES[2]

The pathophysiological abnormalities in a diabetic subject who is critically ill can be:

1. Shock
2. Respiratory failure
3. Systemic inflammatory response syndrome (SIRS)
4. Multisystem organ failure (MSOF).

Shock

Currently, shock is defined as multisystem end-organ hypoperfusion consequent to reduced mean arterial pressure (MAP). The patient is likely to have tachycardia, tachypnea, acute altered mental status with cool skin and extremities and oliguria. There is a fall is systemic vascular resistance (SVR) with hypotension.

Respiratory Failure

Respiratory failure can be of four types, viz., Type 1. There is acute hypoxic failure with alveolar flooding leading to adult respiratory distress syndrome (ARDS). This is a near drowning like situation which can occur due to sepsis, falciparum malaria, gastric aspiration syndrome, pneumonia, multiple blood transfusions, etc. Type 2: This is consequent to alveolar hypoventilation

with ineffective CO_2 elimination. This is seen in situation like CNS catastrophe (cerebral hemorrhage, massive cerebral infarction), neuromuscular failure, severe bronchospasm and conditions with reduced lung compliance. Type 3: It is due to peri-operative respiratoy failure because of atelectesis of the lungs seen as a complication of anesthesia. Type 4: It is a due to hypo-perfusion of respiratory muscles in conditions of shock.

Systemic Inflammatory Response Syndrome

SIRS is a response to a wide variety of severe clinical insults, manifested by two or more of the following (i) temperature > 38°C or < 36°C (ii) Heart rate > 90 beats / min (iii) RR > 20 breaths / min or $PaCO_2$ < 32 mmHg (iv) TLC > 12000 / cmm or < 4000 / cmm or presence 10% of premature neutrophils (band forms) in the peripheral smear. While SIRS can be due to a variety of causes, sepsis is defined as "SIRS due to documented infection". Septic shock is a severe form of sepsis with hypotension despite adequate fluid resuscitation along with perfusion abnormalities[3].

Multi-System Organ Failure

MSOF occurs in the presence of physiological dysfunction and / or failure of two or more organs simultaneously. Any severe inflammatory condition whether infective, immunologic or otherwise; shock due to any cause, trauma whether surgical, accidental or due to other causes produce MSOF. The important facts regarding MSOF are, mortality increases as patients accrues additional organ failure and prognosis worsens with increased duration of organ failure.

IMMUNOLOGICAL RESPONSE[4]

In health, cytokines released are beneficial to the individual. During stressful conditions like infections and non-infectious challenges there is up-regulation of production of cytokines as a host defence mechanism against such injurious agents. Cytokines, in majority, are pro-inflammatory in nature, viz, TNF family especially TNF-α is the major mediator of inflammation while IL-6 is a marker of SIRS, IL-8 decreases leukocyte activity and IL-1 correlates more with mortality. IL-10 is the only established anti-inflammatory cytokine. In patients who are critically sick there is excessive production of pro-inflammatory cytokines which leads to organ injury and death. However, suppression of cytokines released without appropriate treatment of the primary condition will be more harmful to the patient.

METABOLIC DERANGEMENTS[5]

The metabolic derangements seen in any patient who is critically sick can be discussed under the following headings.

1. Increased glucose production
2. Insulin resistance
3. Enhanced peripheral glucose uptake
4. Hyperlactatemia
5. Abnormalities in lipid metabolism.

Increased Glucose Production

This is one of the main mechanism of persistent hyperglycemia in the fasted state in patients with diabetes mellitus. The situation worsens when a diabetic becomes critically sick. Due to persistently raised levels of counter regulatory hormones and cytokines (TNF-α, IL-1, IL-6) there is progressive decreased in the ability of circulating glucose to suppress gluconeogenesis. The recycling of lactate to glucose (CORI'S CYCLE) is increased by two to three folds. Alanine which comes from breakdown of muscles is utilized for gluconeo-genesis causing loss of lean body mass. Glycerol, released from triglycerides due to excessive lipolysis, is also utilized as a substrate for gluconeogenesis. Thus excessive gluconeogenesis occurs at the cost of muscle and fat pool of the body.

Insulin Resistance[6,7]

Sepsis is a condition of insulin resistance. TNF-α inhibits tyrosine kinase activity of the insulin receptor and so impairs the action of insulin on target cell. This action of TNF-α is accentuated by the excessive β-adrenergic drive present in patients who are critically ill. Therefore, there is suppression of insulin mediated glucose uptake by skeletal muscle, adipose tissue and myocardium vis-a-vis impaired glycogen synthesis in skeletal muscle. The degree of insulin resistance is directly proportional to stress.

Enhanced Peripheral Glucose Uptake

Although there is insulin resistance in the body-building bulkier tissue, of the body, glucose utilization is enhanced in tissues rich in macrophages like liver, lung and spleen. This glucose uptake is non-insulin mediated involving glucose-transporter 1 (GLUT-1) and is enhanced by cytokine like TNF-α. Unfortunately GLUT-1 mediated enhanced glucose uptake persists during hypoglycemia which can worsen the already

Table 2: Stratification of severity of stress by metabolic parameters

Stress level	*Plasma lactate (mM/L)*	*Plasma Glucose (mg/dl)*	*Insulin resistance*	*Oxygen consumption (ml/min/M2)*
Low	<1.5	<150	No	<140
Middle	1.5-3.0	150-250	Some	140-180
High	> 3.0	>250	Yes	>180

deranged metabolic condition of the critically sick patient.

Hyperlactatemia

Tissue hypoperfusion and cellular hypoxemia stimulates glycolytic flux with increased production of lactate. Lung tissue produces lactate during sepsis. Similarly other tissues rich is macrophage also produce lactate in conditions of sepsis and stress which leads to hyperlactatemia. Blood lactate levels may be 2-5 mmol/L in the presence of normal blood PH or alkalemia.

Lipid Metabolism

Cytokines like TNF-α and IL-1 enhance lipolysis in the peripheral circulation leading to increased plasma levels of FFA. Raised FFA levels stimulates hepatic TG synthesis leading to hypertriglyceridemia. Persistent increasing TG synthesis with poor secretion from hepatocytes can lead to hepatic steatosis. Interestingly TNF-α and IL-1 suppress ketogenesis due to increase in hepatic melonyl CoA levels and so plasma ketone bodies are lower than in simple starvation.

Stratification of severity of stress in a critically sick patient using metabolic parameters is given in Table 2.

INCREASED SUSCEPTIBILITY TO INFECTIONS

Patients with diabetes mellitus are objectively different from nondiabetic with regards to susceptibility to infection because hyperglycemia renders circulating polymorphs defective in chemotaxis, adherence and phagocytosis. Hyperglycemia interferes with the crucial activity of phagocytic cells and impairs "respiratory burst". This respiratory burst is required to kill the phagocytosed bacteria[1,8]. Glucose gets diverted into polyol pathway consuming NADPH and imparing generation of free radicals which are required for intracellular phagocytosed microorganisms. Hyperglycemia suppresses lymphocytic activation, cytokine release and cell-mediated immunity. Thus diabetics are more prone for bacterial infection as well as fungal infections.

Table 3: Parameters to be evaluated in critically ill patients

Clinical

Age of the patients, temperature, Mean arterial BP (MAP), Heart rate, Respiratory rate, eye opening, verbal command

Hematological

Hematocrit, Total leukocyte count, Total platelet count

Biochemical

Arterial pH, Sr. Na, Sr K, Sr. Creatinine, Sr. Bicarbonate, Sr. Lactate, Oxygenation i.e. FiO_2

Table 4: Score systems used in critically ill patients

Apache	:	Acute physiologic and chronic health evaluation
MPM	:	Mortality probability model
SAPS	:	Simplified acute physiology score
GCS	:	Glasgow coma score
ODDS	:	Organ dysfunction description score

Critically sick diabetics whether due to sepsis, trauma, surgery or other stress, are more prone to develop ketoacidosis consequent to increased counter-regulatory hormones, increased gluconeogenesis, decreased insulin release from β-cells due to excess catecholamine action and cytokine induced insulin resistant state.

APPROACH TO THE CRITICALLY ILL PATIENT

Assessment

The severity of illness as well as progress in a critically ill patient needs to assess objectively. The parameters evaluated are clinical, hematological and biochemical as given in Table 3. The following score systems need to be adopted to evaluate such patients (Table 4).

Stabilization

Initial stabilization should be aimed at "A", maintenance of airways "B" maintenance of breath and respiration, if required by ventilatory support "C" maintenance of circulation. Assessment of hypovolemia is required and is graded as mild, moderate and severe. The parameters of assessment are given in Table 5. When the patient is in shock, volume replacement should be done by crystalloids like sodium chloride and ringers solution. Blood, fresh frozen plasma, packed cell and albumin infusion should be given as and when required. Vasopressor therapy is to be instituted when hypotension persists despite adequate volume replacement so as to maintain the MAP > 60 or Systolic

Table 5: Assessment of hypovolemic shock

- Mild (<20% of blood volume)
  - — Cold extremities
  - — Increased capillary refill time
  - — Diaphoresis
  - — Collapsed veins
  - — Anxiety
- Moderate (<20-40% of blood volume)
  - — All as above
  - — Tachycardia, Tachypnea
  - — Oliguria, Postural hypotension and changes
- Severe (>% of blood volume)
  - — All as above
  - — Hemodynamic instability, hypotension
  - — Marked tachycardia
  - — Deterioration of mental status

blood pressure (SBP) > 90 mmHg. Dopamine is the usual choice and norepinephrine is preferred when hypotension persists despite dopamine infusion. Some patients with myocardial dysfunction and cardiac dysfunction may require infusion of dobutamine and phosphodiesterase inhibitors (Amrinone and Milrinone).

Insulin Therapy[9]

Tight glycemic control, where blood glucose has to be maintained between 80 and 110 mg/dl, has been shown to reduce mortality significantly. This is very much required in patients with sepsis and MSOF. Even in patients with no previous history of DM, but having hyperglycemia intensive insulin therapy has been recommended to control blood glucose and reduce mortality[10]. Intensive insulin therapy has been shown to decrease the requirement of prolonged ventilatory support, renal replacement therapy, improve peripheral neuromuscular dysfunction and reduce bacteremia. Insulin is anti-inflammatory in nature[11]. It decreases production of TNF, inhibits free radical generation and macrophage migration inhibitory factor (MMIF) as well as reduces the plasma levels of ICAM-1, MCP-1 and PIA-1 and so has antiplatelet induced adhesion effect. Insulin induces vasodilatation and prevents axonal degeneration. Intensive insulin therapy in critically ill patients protects endothelial and mitochondrial function[12,13].

Other Measure

Besides tight glycemic control, measure should be taken to maintain pH of blood, so as to avoid low levels of ionized calcium. Bicarbonate therapy is recommend when the pH is less than 7.2 or serum $HCO_3 < 9$ mmol/L.

In the presence of high levels of leuketriens TNF-α and lower levels of substrate/nutrient, there can be accelerated lipolysis with enhanced FFA production. Therefore, modest administration of carbohydrate is required to overcome the potential state of ketogenesis from excess circulating FFA.

Control of Infection

In the presence of trivial infection, there can be induction of insulin resistance and worsening of metabolic stress in a patient with diabetes mellitus. As it not always possible either to localize the focus of infection or isolate the pathogen in a critically sick patient, empiric antibiotic therapy is desirable as per the suspected source of infection[14]. The recommended antibiotic to be used are given Table 6.

Nutritional Support

Enteral feeding is always preferred to total parenteral nutrition (TPN) in a critically sick patient unless otherwise prohibited[15]. Enteral feeding should consist of structural lipid emulsions containing fish oil (omega 3 fatty acid) and medium chain triglycerides both for supplying calories aswell as to modify the cytokine response through omega 3 fatty acid in patients with stress.

Table 6: Empiric antibiotic selection as per suspected source

	Lung	*Abdomen*	*Skin and soft tissue*	*Urinary tract*	*CNS*
Community acquired	Ceftriaxone, macrolide, levofloxacin, tricarcillin + clavulanate	Piperacillin + Tazobactam ± Aminoglycoside, Meropenem	Amoxiclav, Piperacillin + Tazobactam, Vancomycin ± Imipenem–cilastatin	Ciprofloxacin + Aminoglycoside	Ceftriaxone ± Vancomycin
Nosocomial	Cefepime, Imipenem–cilastatin + Aminoglycoside	As above, ± amphotericin B	Vancomycin + Cefipime	Aztreonam, Vancomycin + Cefepime	Cefepime, Meropenem + Vancomycin

CONCLUSION

Tight control of DM in the ICU setting should aim at controlling the primary mechanisms involved for stress response as well as to manipulate through pharmacological interventions so as to maintain a near normal milieu with regards to blood glucose, lipids and cytokines. Tight glycemic control, overcoming insulin resistance, and controlling sepsis and shock are vital to survival of such critically ill patients.

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