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Review Article

Optimizing oxygen delivery in sepsis: A review

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ABSTRACT

Multiple organ failure syndrome (MOFS) is a hallmark of sepsis. The continued dysfunction of microvascular perfusion has been implicated as the inciting factor for this. Multiple etiopathological factors are involved in producing this disequilibrium in the demand, supply, and extraction of oxygen as a result of derecruitment of microcirculation. This is further complicated by mitochondrial dysfunction in the form of the inhibition of mitochondrial respiratory chain of enzymes, leading to difficulty in extraction of the oxygen at the cellular level. Eventually, although hemodynamic stability of systemic/macrovascular circulation may have been achieved, the process of deficient and defective delivery of oxygen to the tissues goes on relentlessly. The indicators and monitoring of this process of impairment of oxygen delivery (DO_2) have been discussed in this review. In addition, the review also encompasses various therapeutic modalities and their efficacy, based on the evidence. The latest guidelines regarding optimizing the DO_2 in sepsis are also included here.

Keywords: Sepsis, Microcirculatory and mitochondrial dysfunction, Defects in oxygen delivery, Etiopathogenesis, Therapeutic interventions

INTRODUCTION

Sepsis is a dynamic phenomenon which usually progresses rapidly causing global tissue hypoxia, cellular dysfunction, cellular death, shock, organ failure, and death. Essentially, this process may have started even before the patient has been brought to intensive care unit (ICU).[1] The shock-like condition in actuality is the imbalance between oxygen delivery (DO_2) and the extraction/consumption of oxygen at the cellular level (VO_2). Primarily, it is the disturbances in microcirculation compounded by the mitochondrial dysfunction, leading to the shock/sepsis, culminating into this imbalance between DO_2 and VO_2 in spite of correcting systemic DO_2. This process has been termed as microcirculatory and mitochondrial distress syndrome (MMDS).[2] It can be defined as persistent failure of microcirculatory perfusion and mitochondrial oxygen utilization in spite of the correction of systemic hemodynamic and oxygen-derived variables in the presence of sepsis. One of the postulated mechanisms for these is changes in mitochondrial function with inhibition of mitochondrial respiratory chain and decreased oxygen utilization. This can be supported by the fact that certain specific mediators such as peroxynitrite are produced due to the conflict between pathogenic agent and immune-mediated cytokine storm. In addition, these are associated with the systemic inflammatory response and can react with most of the electron transport chain. These factors can be considered as the main culprit for mitochondrial dysfunction.[3]

The same phenomenon is seen in sepsis causing increased oxygen consumption, decreased systemic vascular resistance, and thus altered distribution of blood flow in tissues, causing

ultimately the acute shutdown of microcirculation and multiple organ failure syndrome (MOFS).[4] This culminates into what is termed as "cytopathic hypoxia,"[5] leading to relentless, progressive and global tissue damage.

GLOBAL INDICATORS OF DO_2 AND THE ROLE OF MONITORING

To understand the concept of oxygen uptake, oxygen carriage, extraction, and utilization, one has to conceptualize the circulation into two structurally different divisions, namely;

1. Macrocirculation
2. Microcirculation
    1. The macrocirculation is physiologically obvious
        a. Myocardium with its chambers and valves
        b. Vascular tree
        - Arterial side up to small-sized arterial divisions just before the formation of arterioles
        - Venous side starting from end point of venules to form up to the great veins.

These units can be well correlated structurally and functionally as a single cohesive, organ system. The function being pumping oxygenated blood from central compartment to periphery and bringing it back in deoxygenated form. The controls, indicators, and therapeutic measures in this division of circulation are going to have an impact on the second division.

    2. Microcirculation: This is structurally and to certain extent functionally an entirely disparate entity. Although this is contiguous with the macrocirculation
        - The factors controlling it
        - The indicators of its function and
        - The therapeutic measures for its manipulation

vary to a certain extent from those in macrocirculation!

1. The microcirculation depends on four main determinants:[2]
    a. Driving pressure: Provided by the blood pressure
    b. Arteriolar tone: Distension of the vessels due to increased blood pressure is a fundamental stimulus for muscle contraction in arteriolar walls. As a consequence, microcirculation blood flow remains constant despite changes in systemic blood pressure
    c. The blood flow patterns
    d. Status of the capillaries, both systemically and in lungs: State of their intraluminal dimensions and permeability.
2. The regulatory mechanisms governing microcirculatory perfusion can be listed as follows:
    - Cellular (sensing stress and strain)
    - Metabolic (regulation controlled by oxygen, carbon dioxide, lactate, and hydrogen)
    - Neurohumoral (various neurotransmitters and mediators).

The endothelial cells which are situated in the inner walls of microcirculation seem to play a very useful role by regulating the flow sensing chemicals released due to either metabolic processes or by neurohumoral mechanisms, which ultimately govern the myogenic tone in arterioles due to smooth muscle cells, leading to more and more capillaries being rerecruited.[6] In addition, it has been proven that endothelial cell-to-cell signaling system transmits upstream information about hemodynamic conditions downstream.[7] As such endothelial cells play a major role in controlling coagulation and immune function, both of which directly affect the microcirculatory function.

1. The main characteristic of the microcirculatory dysfunction being heterogeneous abnormalities in blood flow, leading to some capillary units being underperfused while others having abnormally high blood flow, leading to disparity in DO_2 and oxygen extraction at tissue level.[8] These units then become progressively hypoxic which explains the deficit in oxygen extraction associated with sepsis. Thus, microcirculatory partial pressure of oxygen, which has been termed as μPO_2, becomes lesser than mixed venous oxygen pressure or tension (PvO_2).[2,9] In other words, arterial oxygen tension (PaO_2) may be adequate enough for providing required amount of oxygen to the tissues, but due to MMDS, the perfusion of oxygen across the membrane, extraction, utilization, and regulation of intracellular activity dependent on oxygen becomes totally imbalanced, leading to this disparity between μPO_2 and PvO_2. This disparity has been termed as "PO_2 gap," which can be used as a measurement of severity of functional shunting, which has been found to be highly significant indicator in conditions such as sepsis, hemorrhage, and trauma.[10] This seems to be the main reason why there remains a paradox when monitoring systemic hemodynamic-based and oxygen-derived variables in terms of predicting severity, leading to morbidity and mortality. This is termed as "masking of ongoing process."
2. As already mentioned, the microcirculatory endothelial cells get more and more derecruited and are unable to perform their regulatory function, due to disturbed signal transductional pathways, loss of electrophysiological communication, and smooth muscle control, leading to a condition, in which tissues cannot make full use of available oxygen, termed as severe tissue dysoxia and/or hypoxia.[2] The mechanism by which this happens is as follows:
   The nitric oxide (NO) system plays the central role in all regulatory control on microvascular circulatory tone, patency, the driving pressure of circulation, and ultimately DO_2. This NO system gets imbalanced by unequal expression of inducible NO synthase (iNOS) in

different microcirculatory beds, resulting in pathological shunting of flow.[11,12] As there is a variability in expression of iNOS in various tissues, areas which are lacking iNOS automatically have less NO-induced vasodilatation and remain underperfused, leading to hypoxia in these areas.

3. In addition, myogenic cells of the arteriolar walls, which are the keepers of tone and regulators of perfusion lose their sensitivity to adrenergic factors in sepsis.
4. The red blood cells (RBCs) are also supposed to play a major role in regulation of microcirculatory perfusion. In the presence of hypoxia, they have the capability of releasing NO and lead to vasodilation and thus increased perfusion.[13] This ability gets affected in sepsis.
5. The RBCs lose their elastic property, become less deformable, more rigid, and start aggregating more. This culminates into severe disturbances of coagulation, activation of coagulation cascade, fibrin deposition,[14] and formation of microthrombi. Ultimately, further impeding microcirculatory perfusion, function, and DO_2.
6. The leukocytes activated due to systemic inflammatory response start generating free radicals of reactive oxygen species, which directly start acting and destroying microcirculatory structure, cellular interactions and coagulatory function. Ultimately leading to altered permeability, structural defects and tissue edema, further deterioration of oxygen extraction deficit, parenchymal cellular respiratory distress, and resultant organ failure.[15,16]
7. MMDS[2] has already been mentioned earlier.

The entire process ultimately culminates into cellular dysoxia, regional disequilibrium in DO_2, and utilization, leading to cellular hypoxia and multiple organ failure and death.

The indicators which point to this are as follows:

A. Increased lactate levels: Lactate is an indicator of anaerobic metabolism, especially in the presence of tissue dysoxia. The factors which are responsible for production are as follows:
   a. Global: Sepsis, shock, and hypoxia
   b. Regional: Tissue ischemia
   c. Cellular: Mitochondrial dysfunction decreased clearance by liver and factors affecting hepatic function.

   It has been reported that, although lactate may serve as a useful indicator, its accuracy and usefulness as a predictor of outcome is questionable.[17]
B. Disturbed acid-base balance
C. High gastric or oral CO_2 levels
D. Clinical parameters such as color, capillary refill, and temperature of the peripheral parts of the body (fingers, toes, earlobes, nose, etc.)

   However, an objective and reliable method of monitoring microcirculatory organ perfusion and tissue oxygenation is still not available.
E. "Downstream" assessment of mixed oxygen saturation (SVO_2) in addition to the measurement of available oxygen (DO_2) and oxygen up to VO_2 is commonly used in day-to-day clinical critical care practice

   SVO_2 can be measured with pulmonary artery catheter (PAC) and is thought to reflect the average oxygen saturation of all the microvascular beds, especially on the "downstream."[1] It has been well documented that in sepsis, due to altered regional NO responsiveness, and resultant microcirculatory shunting, normal SVO_2 levels may be found in spite of severe local tissue dysoxia.[10]
F. Tonometric CO_2 assessment, which seems promising for the evaluation of tissue dysoxia, is a modification of previously used tool of regional intestinal capnography.[18]

   The method is based on the principle of CO_2 diffusion from the local anaerobic production site across tissue and cell membranes. Even more so the measurement of difference between gastric/intestinal PCO_2 and arterial PCO_2 has been found to be even better than that of pH alone: Logical reason for this being PCO_2 is dynamically variable in all the ventilated patients[19]

   However, in sepsis, there seems to be another problem, namely, as the areas of CO_2 offloading and reduced perfusion are in close proximity to hypoxic regions, clearer establishment of impaired perfusion becomes very difficult. Thus, interpretation of gastric/intestinal tonometry may be affected by microcirculatory shunting.[20]

   Recently, sublingual PCO_2 values have been used to correlate with those of gastric intramucosal PCO_2 and they seem to correlate well.[21] In fact, the baseline difference in sublingual PCO_2 and $PaCO_2$ values appears to be better and more suitable predictor of survival than changes in lactate levels or SVO_2 levels.[22]
G. All above-mentioned parameters are basically downstream from the pathological process in microcirculatory network and thus are indirect

   The direct method which has been described is called as intravital microscopy (IVM),[23] especially in animals. However, reservations against this in humans are as follows:
   a. The size of IVM equipment makes it useful only in eye, skin, or nail fold in humans
   b. Thus, observations limited only to the superficial layers of body and
   c. Potential toxicity of fluorescent dyes which have been used makes it difficult to use it in humans.
H. Spronk *et al*.,[1] have already described a method to study microcirculation called orthogonal polarization spectral imaging[24] with specific advantages quoted as
   a. No need of fluorescent dyes.
   b. The machine being handheld can be at bedside.

MONITORING, IN BRIEF

1. Routine hemodynamic
   - Mean arterial pressure (MAP), CVP, and PCOP.

2. Oxygen extraction/saturation parameters
   - SPO_2, $ScVO_2$, SVO_2, and falling venous oxyhemoglobin saturation.
3. Lactate levels >4 mmols/L , increasing and inversely correlating with $ScVO_2$ and SVO_2 "phase of global tissue hypoxia", indicate the transition of sepsis to severe disease

   Thus, all these serve as indicators of balance between systemic delivery and demand of oxygen and for quantifying global tissue hypoxia.
4. Anion gap, negative base excess and bicarbonate levels as indirect indicators. Lactate levels can be misleading as on an average of 22–25% of patients present with elevated lactate levels (4.0–6.9 mmol/L).
5. Other routine parameters suggestive of the intactness of systems/initiation of MOFS with, RFTs, LFTs, coagulation profile, PT, PTT, INR, and blood platelet levels
6. Sublingual, buccal, and subcutaneous CO_2 levels
7. Absorbance, refractoriness and near-infrared spectroscopy
8. SDF: Sidestream dark-field imaging.

Now let us discuss:

"The Principles of Therapy to improve micro-circulatory perfusion" as the goal.

Available evidence

1. Vasodilators: Bihari *et al.*[25] This was one of the earliest available studies, where it was found that vasodilatation might unmask a pre-existing tissue oxygen debt. After increasing DO_2 with the vasodilator prostacyclin, the survival of the patients was 100% as long as increase in DO_2 was not overshadowed by increased oxygen consumption. All the patients died who had increased oxygen consumption. Thus, it has been suggested that by vasodilatation, the microcirculatory networks, which had been derecruited, are rerecruited, thus making oxygen available to these previously hypoxic tissues
2. Vasoconstrictors: De Backer *et al.*,[26] reported that sublingual microcirculatory perfusion has been found to be compromised in non-survivors than surviving septic shock patients. This has been supported by Spronk *et al.*,[1] normal sublingual microcirculatory perfusion in a septic patient with hepatic failure on high doses noradrenaline and by Dubois *et al.*,[27] in a patient treated with vasopressin
3. NO: With conflicting evidence as the culprit or the savior of sepsis! What is now undebatable is "completely inhibiting vasodilatation" is not the proper answer to sepsis, but specifically inhibiting only the inducible form of NO synthase (iNOS) with the help of 1400 W (a synthetic blocker of iNOS) in a pig endotoxemia model improved gut wall perfusion by redistribution of blood and thus the survival of cells.[28] Hence, one can observe broadly that NO is an important vasodilator in microcirculation during sepsis and NO donors are effective in correcting microcirculatory oxygenation in animal studies and thus improving PO_2 and bringing intraluminal gastric PCO_2 levels to a baseline. In addition, after treatment with prostacyclin, there was increased glucose oxidation rate in septic patients.[29] What seems to be the best mid-ground strategy is.
   a. Improvement of oxygen supply to tissues by manipulating the microcirculatory and hemodynamic goals of
      - Optimized cardiac output
      - Adequate hemoglobin concentration and saturation
      - Physiological range of CVP/pulmonary arterial wedge pressure
      - Appropriate level of (<70%) $ScVO_2$.
   b. When no further improvement using volume resuscitation and/or dobutamine infusion can be achieved, the gastric pH can be improved after starting prostacyclin most probably due to improvement in splanchnic circulation/ microcirculation.[30]

THERAPEUTIC OPTIONS FOR IMPROVING OXYGENATION

After looking at available evidence, one needs to understand all the possible therapeutic options which can be used to improve the delivery of oxygen at tissue level.

1. Intravascular volume manipulation: Use of crystalloids/ non-homogenous colloids

The appropriate use of intravenous fluids has been the mainstay of critically ill patients, especially in other types of shock, namely, hypovolemic, anaphylactic, trauma, and acute hemorrhage. The volume restoration in the form of preload has been found to improve microcirculatory endothelial barrier function and promoting oxygen transport, leading to redistribution of DO_2 within the various organs.

However, the validity of this concept has not yet been established in patients with septic shock. Blood transfusion has been found to improve DO_2 to the microcirculation, logically blood being a better oxygen carrier than other fluids.[31]

2. Vasodilators or vasopressors or both?

After achieving normovolemia in macrocirculation, the recruitment of microcirculatory perfusion can be achieved by the use of vasodilators as this increases the driving pressure at the entrance of microcirculation.[32] The NO donors when used as adjuncts in combination with fluids have improved DO_2 and decreased gastric PCO_2. The resuscitative measures directed in considering adequate systemic blood pressure as end points could improve flows in larger vessels (macrocirculation) but not in microcirculation, confirming it

to be the site of distributive defect in the presence of sepsis.[2] In such situation, the administration of nitroglycerine with improved intravascular volume has been found to improve DO_2 at the tissue level.[33]

Vasopressors have a very conflicting and controversial role to play in microcirculatory scenario. A study[27] using vasopressin showed promising result in improving sublingual perfusion flows, while in another study, same vasopressor analog could effectively improve blood pressure, urine output but lead to complete constriction of regional circulation, derangement of DO_2, and death.[34] Animal studies also support these observations.

3. iNOS inhibitors and steroids

As already discussed previously, iNOS plays a very important role in producing total disequilibrium in regional microcirculatory perfusion patterns, pathological shunting of flows, and thus generalized hypoxia at various capillary circulations.

Hence, the newer promising area is iNOS inhibitors, can cause rerecruitment of various microcirculatory units, improved autoregulatory dysfunction, and protect barrier function of microcirculation. Steroids in relatively higher doses have been found very effective as iNOS inhibitors, especially if given early on, by preventing NO-induced inhibition of glucocorticoid receptors.[35]

MULTIMODAL APPROACH

1. Intravascular volume resuscitation with crystalloids/colloids, combined with vasoactive and inotropic support, can be effective in improving microcirculatory perfusion and DO_2

However, the patients not responding to this regimen have a very high mortality.[36]

2. NO donor can open microcirculation, improve perfusion and DO_2 while steroids or specific iNOS inhibitors decrease pathological shunting and cause recruitment of multiple microcirculatory units. The novel although experimental concept is combining these two modalities (1 and 2) together.
3. Early goal-directed therapy (EGDT).

In 2001, Rivers *et al.*,[37] gave impetus to EGDT using very basic and logical principle that hemodynamic optimization therapy initiated after ICU admission when sepsis may be in advanced stage, fails to reliably improve outcome. This may probably be due to irreversible organ damage due to early tissue hypoxia, whereby using central venous oxygen saturation ($ScVO_2$) and normal mixed venous oxygen tension (PVO_2) to adjust cardiac preload, afterload, and contractility during 6 h after presentation was shown to reduce mortality significantly in patients with sepsis and septic shock. It was postulated that by this method of balancing systemic DO_2 and consumption, can improve subsequent DO_2 to tissues, pH, lactate, negative base excess and sensitivity of illness scores. The criteria they used were the same as that used by Society of Critical Care Medicine and the American College of Chest Physicians except that they started them early and aggressively, as soon as patient was brought in the emergency department (ED). They randomized 263 patients with suspected sepsis into two groups: Either to get standard care or EGDT. Hence, in addition to hemodynamic support and appropriate antibiotic support in the ED itself, following protocol was followed at the presentation of severe sepsis symptoms: Optimizing-

i. Cardiac preload
ii. Cardiac afterload
iii. Myocardial contractility.

All the patients had central venous, arterial cannulation, and samples sent for microbiological assessment. The patients were randomized in two groups as standard and early therapy.

Early therapy group had monitoring of

1. Central venous oxygen saturation ($ScVO_2$) and pressure (CVP)
2. Ever half hourly 500 ml bolus of crystalloid to maintain CVP of 8–12 mmHg
3. Use of vasopressors (noradrenaline/vasopressin) and/or vasodilators (nitroglycerine) MAP was maintained between 65 and 90 mmHg
4. If $ScVO_2$ falls <70% RBC transfusion to achieve hematocrit of 30%
5. If $ScVO_2$ remained <70% in spite of these measures, dobutamine infusion (2.5–20 μg/kg/min) was administered to bring $ScVO_2$ to 70% or more. The results were striking in these patients. After 6 h,

    - Higher CVP and MAP, $ScVO_2$
    - Average arterial pH
    - Lower lactate levels, base deficit (lower than 4 mmol)
    - Better severity of illness (APACHE II score)
    - Significantly lower in-hospital mortality at 28 and 60 days
    - The survivors had lesser ICU and hospital stay (mean hospital stay was 14.6 days vs. 18.4 days)
    - Improving the cost analysis.

In 2006,[38] the original concept was reassessed with newer diagnostic and therapeutic interventions. Their findings and recommendations are as follows:

A. The monitoring of $ScVO_2$ and/or SVO_2 both is useful. If it is not suitable to pass PAC (Pulmonary Artery Catheter) then one may depend on SVO_2. SVO_2 up to 65% and $ScVO_2$ of 70% seem to be suitable end points
B. Crystalloids: It is imperative that improved intravascular preload is a basic prerequisite: Judicious timing of the fluid infusion is important. In initial 6 h aggressive fluid

management followed by 7–72 h of conservative fluid management seems to be optimum.

C. Vasopressor Therapy: The earlier infusion of fluids also makes the circulation more amenable to vasopressor use, lesser refractoriness and improved survival. At the same time, longer the need for vasopressor more the mortality
D. Vasodilator therapy (decreasing afterload): Nitroglycerin is the drug of choice due to its effects on preload, afterload, and coronary vasodilatation. The patients with pre-existing cardiac problem or already in CHF will need this.
E. Inotropic support: In spite of conflicting reports about dobutamine therapy and associated mortality, recommendation is dobutamine in small doses (2.5 μg/kg/min) in already adequate volume preloaded, but still hypotensive patients. Then, the rate increased by 2.5 μg/kg/min titrating it every 15–20 min to keep MAP >90 mmHg. Appearance of sinus tachycardia would be the indication for stopping dobutamine and switching over to alpha-agonists such as phenylephrine or noradrenaline.
F. RBC transfusion: In an adequate volume resuscitated patient, RBCs may be transfused so as to keep hematocrit of <30% which allows the $ScVO_2$ of >70% in nearly 79–80% of patients:
G. Appropriate system support
    - Antibiotic support
    - Monitoring
    - Physiologic scoring systems
        - APACHE II
        - MODS.
    - Mechanical ventilation.

Thus, they concluded that EGDT results in a significant reduction in mortality-morbidity, vasopressor use and health-care resource consumption.

All these modalities have been mired with controversies, with evidence for and against them.

SURVIVING SEPSIS CAMPAIGN[39,40]

In 2012, a consensus committee consisting of 55 experts from 25 international critical care organizations came out with a specific protocol, under the title of "surviving sepsis campaign." These guidelines compared available evidence, the credibility of it, weeded out the superfluous/ambiguous principles and practices, so as to optimize the evidence-based and relevant protocol for care of patients with sepsis. It would be beyond the scope as well as actual relevance of the current discussion to elaborate them. However, it would be prudent to highlight some of the relevant principles. All these are to be implemented as soon as the diagnosis of the sepsis or septic shock is made. Here, only the Grade IB or C evidence recommendations are mentioned. Interested reader may look up relevant references that are provided.

I. Sepsis and septic shock are medical emergencies and it is recommended that treatment and resuscitation begin immediately
II. Source control: The identification and control of source be made, as early as possible, as soon as the diagnosis of sepsis is made
III. Early drawing of samples for microbial cultures, preferably two sets of blood cultures, one in aerobic and another in the anaerobic sample collectors, to be drawn, from each of the vascular accesses, before starting the antimicrobial therapy
IV. A strong antibiotic may be started within 1 h or as early as possible. It is also recommended to start one or more antimicrobials to cover all the likely infective agents. Combination therapy is highly recommended when the neutropenia/bacteremia is suspected or evident
V. Initial resuscitation with a crystalloid in the aliquots of 30 ml/h may be initiated within first 3 h and then subsequently to be adjusted according to the continuous assessment of hemodynamic parameters
VI. The initial target MAP of 65 mmHg is to be achieved. If the initial fluid management does not produce the anticipated target pressures, the vasopressors need to be started. This was the recommendations of **Bundle six hour**[41]
VII. Noradrenaline is the first choice, as the vasopressor. Adrenaline may be added to or can be used as a potential substitute for noradrenaline, if and when an additional agent is needed to maintain adequate blood pressure
VIII. There is no role of low-dose dopamine as a renal protection. Dopamine as a supplement only in few selected patients with bradycardia and with low risk of tachyarrythmias
IX. Dobutamine up to the infusion of 20 μg/kg/min, to be added to the vasopressor, in confirmed cardiac dysfunction or ongoing tissue hypoperfusion
X. If no improvement is observed, shock progressing relentlessly, then to confirm the type of shock, the assessment of further hemodynamic parameters, such as cardiac function to be carried out
XI. The elevated lactate levels are to be taken as the markers of tissue hypoperfusion and need to be corrected
XII. As and when required, ventilation to be started. Neither higher nor lower but optimized positive end-expiratory pressure is to be initiated. Prone positioning during ventilation is preferred over supine
XIII. In sepsis-induced acute respiratory distress syndrome patients, neither high-frequency oscillatory ventilation nor beta-2 agonists in the absence of bronchoconstriction are recommended
XIV. The upper blood glucose levels to be controlled around 180 mg/dl, rather than tight glycemic control of 110 mg/dl. As and when required, insulin infusion may be started, to maintain these levels. The blood glucose

levels to be serially monitored every 1–2 hourly till stable. Then, every 4 hourly

XV. Use of total enteral nutrition (TEN) or combination of TEN with a combination of intravenous glucose rather than total parenteral nutrition

XVI. As a deep vein thrombosis prophylaxis, low-molecular-weight heparin (LMWH). Wherever, it is not suitable to use LMWH, the mechanical modalities to be initiated.

Since 2016, there has been introduction of the concept of **Hour -1 bundle**, which, basically reiterates the urgency of starting the therapeutic interventions as early as possible, preferably within the first hour, but not necessitating that need to be completed in the first hour. The latest guideline has been made effective after passing all approval points since October 1, 2019.[42]

In 1996, sepsis-related organ failure assessment (SOFA) had been introduced as a measure of severity, extent, and progression of organ dysfunction secondary to sepsis.[43] Since 2016, SOFA has been adapted as sequential SOFA score.[44]

Effectively the terminology, systemic inflammatory response syndrome was abandoned. There was also the suggestion of a newer bedside index termed as quick SOFA (qSOFA).[44-46] All the developments point out one thing glaringly, that, no matter how much efforts, thought process and research has been implemented in this, still "defining and controlling sepsis" remains an elusive goal, yet to be achieved.

CONCLUSION

The microcirculation plays the pivotal role in the tissue DO_2. In patients with sepsis, although apparently and clinically, the macrovasculature (cardiovascular/hemodynamic) parameters may appear to be near normal, in actuality at the cellular level, there is an emergent crisis due to imbalance between the DO_2 extraction and consumption. The terms which have been coined for these defects are MMDS, cytopathic hypoxia, dysoxia, and so on. To plan, precise modalities for "optimizing the DO_2" in such patients require one to have a thorough understanding of the various etiopathogenic factors and pathophysiologic processes involved and the monitoring which can help in identifying, detecting, and assessing the efficacy of therapeutic measures. Various "indicators of DO_2," "role of monitoring," as well as "method to improve oxygenation have been discussed on the basis of their merits and available evidence, even the recent developments".

It has been the earnest desire and eternal efforts of the authors to make this complicated topic as simplified as possible, to the nascent anesthesiologist intensivists and other interested clinicians!

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