Refractory Shock. Casuistics

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Abstract

Introduction

Shock Syndrome is an acute progressive circulatory insufficiency where the Heart is unable to circulate the blood in time unit, for supplying with O2 to the cells and to take out from them CO2 and other final and intermediate toxic metabolites. Shock is acute inadequate organ perfusion to meet the tissue's oxygenation demand. Shock means: an Acute suffering of cells and organ`s tissues of organism. The term refractory shock is applied when, in spite of apparently adequate therapy, the shock state continues. There are three types of refractory shock: Refractory (or Irreversible) shock, Refractory (Septic) shock, Refractory (Cardiogenic) shock (RCS).

Diagnosis

Evaluation should focus on the identification of the primary cause and reversible secondary contributors, such as hypovolemia, pump failure, or obstruction that is causing shock. Differential diagnosis must be done with: septic shock, vasodilatory shock and cardiogenic shock.

Treatment

Coronary PP > 50 mm Hg, Improve myocardial function, C.I. < 3.5 is a risk factor, 2.5 may be sufficient. Fluids first, then cautious pressors. Remember aortic DIASTOLIC pressures drives coronary perfusion (DBP-PAOP = Coronary Perfusion Pressure) .If inotropes and vasopressors fail, intra-aortic balloon pump Temporary circulatory support with extracorporeal membrane oxygenation (ECMO). Sol. natrium bicarbonat 8.4% (PH ≤7.2).

Recomandation

Refractory shock which is mainly caused by cardiogenic shock and Septic shock are severe conditions which cause increased mortality in patients with such conditions. Advances in the treatment of these serious conditions have enabled the healing of these patients and the relative reduction of Mortality.

Key Words. *IS-Inflammatory Shock; HS – Hemorrhagic Shock; CS-Cardiogenic Shock, CVP-Central Venous Pressure; UO – Urine Output; BP – Blood Pressure; HR – Heart Rhythm; MAP-Mean Arterial Pressure; CO/CI-Cardiac Output/Cardiac Index; SVR-Systemic Vascular Resistance; PAP-Pulmonary artery Pressure; SvO2- Mixed Venous Saturation ; (a-v)DO2- arterial-venous difference of Oxygen Deliv*ery; OE/R-Oxygen Extraction Ratio.

Definition and Terminology of Shock Syndrome

Is an acute progressive circulatory insufficiency where the Heart is unable to circulate the blood in time unit, for supplying with O2 to the cells and to take out from them CO2 and other final and intermediate toxic metabolites. Shock is acute inadequate organ perfusion to meet the tissue's oxygenation demand. Shock means: an Acute suffering of cells and organ`s tissues of organism.

Pathologic Physiology. There are four important factor that influence in Shock Syndrome:

-Acute Hypoxia; -Hypotension -Metabolic Acidosis -Paralytic Capillary Vasodilatation (during Septic and/or refractory Shock).

Classification of Shock Syndrome.

Shock Syndrome have four main categories:

1- Hypovolemic –non-hemorrhagic Shock and Combustion Shock, and Hemorrhagic Shock
2- Cardiogenic –acute cardiac pathologic problems and cardiac trauma prob lems
3- Distributive- including: Septic, Anaphylactic, Toxic, Pharmacological, Neurogenic, Endocrine,
4- Obstructive Extra-cardiac Shock – Thoracic Trauma, Cardiac Tamponade, Tension Pneumothorax, Massive Pulmonary Embolus

Definition of Refractory Shock

The terms refractory shock and irreversible shock are widely used by physicians and other medical workers to refer to types of shock that present particularly difficult problems. The term refractory shock is applied when, in spite of apparently adequate therapy, the shock state continues. Commonly, the treatment later proves to have been inadequate, in which case the shock was not true refractory shock. This often occurs following a major injury in which there is internal bleeding, leading to underestimation of true blood loss and therefore to inadequate transfusion. In certain cases, however, even if the therapy actually is appropriate, the shock state persists; if patients in such cases respond to further special treatment, then this is true physiological refractory shock.

Shock is a syndrome characterized by signs and symptoms, which are the result of the different organs response to a situation of low perfusion for their basic metabolic needs. The temporal sequence of the manifestations follows a pattern of inverse priority in the economy of human body physiology. Cryptic shock and two-hit clinical model of physiological deterioration are nowadays established concepts that need to be kept in focus if we want to prevent shock from reaching a NRP ('no-return point').

The term "cryptic shock" is often used for patients with deceptively normal hemodynamic parameters, yet presenting high risk for morbidity and mortality because of global ischemia with increased lactate blood level. If blood pressure is normal, but lactate blood level is high secondary to global tissue ischemia, some call this condition Normotensive shock instead of "cryptic shock".

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If blood pressure is normal, but lactate blood level is high secondary to global tissue ischemia, some call this condition Normotensive shock instead of "cryptic shock" (Sylvain Beurtheret et al., 2013).

Cryptic shock and two-hit clinical model of physiological deterioration are nowadays established concepts that need to be kept in focus if we want to prevent shock from reaching a NRP ('no-return point').

In fact, Cryptic Shock is an unifying concept – Circulation from normal physiology to cessation of life.

Actually, some patients can even be in Hypertensive shock! ....For example:

(a) in cardiogenic or hypovolemic shock with marked sympathetic system activation,
(b) during a hypertensive crisis due to pheochromocytoma, or
(c) during eclampsia

In those cases, shock is easily diagnosed by finding out that organs are dysfunctional or failing while lactate blood level is high! And this, despite normotension or even hypertension!

Refractory (or Irreversible) Shock ensues as consequence of direct hit or as result of inadequate or delayed treatment and is characterized by drug-resistant hypotension.

Refractory (Septic) shock is a persistently low mean arterial blood pressure despite vasopressor therapy and adequate fluid resuscitation.

Refractory (Cardiogenic) shock (RCS) is defined as cardiac and circulatory failure resulting in organ hypoperfusion unresponsive to conventional medical therapies (W.G. Prout)

It is important to note that many physicians do not believe that patients with normal blood pressure can be in shock

For those non-believers, they should at least admit that a previously chronically hypertensive patient with blood pressures running chronically in the 180/100 mmHg range, and presenting to the emergency room department with a blood pressure of 100/70 ("normal BP"), can be in full blown shock!

In these cases, compensatory mechanisms are at play (vasoconstrictive autonomic system) and maintain blood pressure through severe increase in systemic vascular resistance. This severe vasoconstriction induces tissue ischemia/hypoxia and, as a consequence, lactic acidosis.

Note that, without betablockade, these patients tell you that they are sick: they are tachycardic! and in severe cases, sweating profusely!

In severe or prolonged shock states, the myocardial blood supply is sufficiently diminished to damage the heart's pumping action temporarily or permanently. Also, noxious products of inadequately perfused tissues may circulate and affect the heart muscle.

While the flow of blood through major vessels is under the control of the nerves, circulation through the capillary beds is of a more primitive type and is under the influence of local metabolic products. In shock, arteriolar constriction causes inadequate flow through the tissues, and local waste products increase. These cause dilation of the capillary sphincters and opening of the whole capillary bed, which thus contains an increased proportion of the blood volume. The capillaries become further engorged with slowly flowing blood, and fluid leaks through the vessel walls into the tissues. Thus, the body is further deprived of circulating blood volume.

Widespread clotting of the blood can occur during capillary stagnation. This leads to severe damage to the cells unsupplied by flowing blood. Later, when enzymes dissolve the fibrin of the clots, the flow through these areas carries toxic metabolic products to vital organs—such as the heart, kidneys, or liver—and the ensuing damage leads to irreversibility of shock.

Some characteristics of Refractory Septic Shock

Refractory septic shock is a persistently low mean arterial blood pressure despite vasopressor therapy and adequate fluid resuscitation.

Refractory septic shock is due to a dysregulated immune response that is caused by a bacterial or a fungal infection in the blood. Endotoxins like lipopolysaccharide (LPS) from bacteria stimulate the release of pro-inflammatory mediators including tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1). These cytokines activate leukocytes resulting in the release of additional inflammatory mediators promoting widespread inflammation. This leads to refractory septic shock, which adversely affects the cardiovascular, respiratory and renal systems. In this review, current therapies to manage septic shock are examined and novel treatments are proposed to make sepsis more manageable in the clinical setting. ICU patients diagnosed at an early stage have the highest rate of survival as they can be effectively treated to prevent the onset of septic shock. However, patients that have progressed into later stages of sepsis have complications due to septic shock. We suggest treating these patients with cytokine inhibitors and anti-LPS molecules (cationic lipids and poly-L-histidines) in addition to therapeutics for organ-localized complications. This two-pronged approach treats the adverse effect due to inflammation that has already occurred and prevents further inflammation, resulting in an improved clinical outcome.

Some characteristics of Refractory Cardiac Shock

Refractory cardiogenic shock (RCS) is defined as cardiac and circulatory failure resulting in organ hypoperfusion unresponsive to conventional medical therapies. Despite recent advances, therapeutic options are limited, and RCS is almost uniformly fatal when emergency circulatory support cannot be initiated in a timely manner. If such patients can be stabilized by extracorporeal membrane oxygenation (ECMO), possible outcomes include ECMO weaning to recovery (bridge to recovery), heart transplantation (bridge to transplantation), or implantation of a long-term assist device (bridge to bridge). When this strategy based on temporary circulatory support is available in specialized and experienced centers, up to 40% of the patients with RCS can survive to hospital discharge in various pathophysiological situations, including acute myocarditis and acute myocardial infarction (Combes et al., 2008).

Nonetheless, this strategy is currently restricted to a very limited number of tertiary-care centers with specialist capabilities for instituting and supporting ECMO. In remote hospitals, however, without ECMO capability, management

of RCS patients is considerably more difficult, as transfer to tertiary centers is often essential to save the patient but is often not feasible in such medically unstable patients. We hypothesized that instituting ECMO in remote institutions followed by stabilization and transfer might be logistically feasible, allowing an improved rate of survival.

To test the feasibility of offering ECMO (Extra-corporeal membrane oxygenation) support to RCS patients in remote hospitals, we set up a specific program based on coordinating staff and a Mobile Unit of Cardiac Assistance (MUCA), able to initiate and manage circulatory support in institutions that do not host local circulatory support teams.

Causes of Refractory Shock

Refractory shock with vasodilatation is caused by sepsis, hemorrhagic shock, after cardiopulmonary bypass, milrinone intoxication, organ donors receptors, burned patients and after placement of ventricular assistance dispositive. Inappropriately low levels of vasopressin (VP) which plays an important role in the maintenance of systemic vascular resistance index (SVRI) and mean arterial pressure (MAP) are present (Asaumi 2005; Bonanno 2011).

- Infectious Disorders (Specific Agent)
- Meningococcemia/meningococcus
- Infected organ, Abscesses
- Peritonitis, acute
- Granulomatous, Inflammatory Disorders
- Pancreatitis, acute
- Hemorrhagic pancreatitis, necrotizing
- Allergic, Collagen, Auto-Immune Disorders
- Anaphylaxis, generalized
- Idiopathic Anaphylactoid Reactions/Recurrent
- Anatomic, Foreign Body, Structural Disorders
- Internal bleeding/trauma
- Arteriosclerotic, Vascular, Venous Disorders
- Mesenteric artery embolism
- Reference to Organ System
- Disseminated intravascular coagulopathy
- Pathophysiologic
- Capillary leak syndrome
- Drugs

- Iron intoxication, acute
- Poisoning (Specific Agent)
- Mercury salts/bichloride acute toxicity

Pathology-physiology of refractory shock

Irreversible shock ensues as consequence of direct hit or as result of inadequate or delayed treatment and is characterized by drug-resistant hypotension.

The clinical aspects of shock syndromes are described from their inception as compensated physiology to a stage of decompensation. The clinical significance of hypotension, fluid-responsive and non fluid-responsive hypotension, is discussed. Untimely or inadequate treatment leads to persistent subclinical shock despite adjustments of the macrohemodynamic variables, which evolves in a second hit of physiological deterioration if not aggressively managed. Effects of inadequate perfusion on cell function.

There are four stages of shock. As it is a complex and continuous condition there is no sudden transition from one stage to the next. At a cellular level shock is the process of oxygen demand becoming greater than oxygen supply.

Initial

During this stage, the state of hypoperfusion causes hypoxia. Due to the lack of oxygen, the cells perform lactic acid fermentation. Since oxygen, the terminal electron acceptor in the electron transport chain is not abundant, this slows down entry of pyruvate into the Krebs cycle, resulting in its accumulation. Accumulating pyruvate is converted to lactate by lactate dehydrogenase and hence lactate accumulates (causing lactic acidosis).

Compensatory

This stage is characterised by the body employing physiological mechanisms, including neural, hormonal and bio-chemical mechanisms in an attempt to reverse the condition.

As a result of the acidosis, the person will begin to hyperventilate in order to rid the body of carbon dioxide (CO_2). CO_2 indirectly acts to acidify the blood and by removing it the body is attempting to raise the pH of the blood. The baroreceptors in the arteries detect the resulting hypotension, and cause the release of epinephrine and norepinephrine. Norepinephrine causes predominately vasoconstriction with a mild increase in heart rate, whereas

epinephrine predominately causes an increase in heart rate with a small effect on the vascular tone; the combined effect results in an increase in blood pressure. Renin-angiotensin axis is activated and arginine vasopressin (Anti-diuretic hormone; ADH) is released to conserve fluid via the kidneys. These hormones cause the vasoconstriction of the kidneys, gastrointestinal tract, and other organs to divert blood to the heart, lungs and brain. The lack of blood to the renal system causes the characteristic low urine production. However the effects of the Renin-angiotensin axis take time and are of little importance to the immediate homeostatic mediation of shock.

Compensatory Shock have three main elements of Path-Physiology:
-Hypoxia - (low PaO2, low SvO2,)
-Metabolic Acidosis -(low Ph, high PaCO2 and high lactates in blood),
-Hypotension (low BP, low MAP, low PAP, high/low SVR).

Compensatory significances:

1. Maintain normal arterial pressure
(a) returned blood volume↑
Auto blood transfusion
Auto fluid Transfusion
Aldosterone and Antidiuretic Hormone (ADH) y ↑
(b) cardiac output ↑
(c) peripheral resistances↑

2. Maintain blood supplying to heart and brain
(a) blood vessel of brain
(b) coronary artery
(c) normal arterial pressure

Progressive

Should the cause of the crisis not be successfully treated, the shock will proceed to the progressive stage and the compensatory mechanisms begin to fail. Due to the decreased perfusion of the cells, sodium ions build up within while potassium ions leak out. As anaerobic metabolism continues, increasing the body's metabolic acidosis, the arteriolar smooth muscle and precapillary sphincters relax such that blood remains in the capillaries. Due to this, the hydrostatic pressure will increase and, combined with histamine release, this will lead to leakage of fluid and protein into the surrounding tissues. As this

fluid is lost, the blood concentration and viscosity increase, causing sludging of the micro-circulation. The prolonged vasoconstriction will also cause the vital organs to be compromised due to reduced perfusion. If the bowel becomes sufficiently ischemic, bacteria may enter the blood stream, resulting in the increased complication of endotoxic shock (Fine et al., 1959).

Cellular and tissue suffering of Organs and Systems that result to the inadequate perfusion on cell functions.

First: Kidneys, Skin (to save main Systems SNC, Heart &CVS, and Respiratory System);

Second: all other organs: Gastro-intestinal System, Endocrine System, and finally: SNC damage, with C-V and Respiratory Failure.

Refractory

At this stage, the vital organs have failed and the shock can no longer be reversed. Brain damage and cell death are occurring, and death will occur imminently. One of the primary reasons that shock is irreversible at this point is that much cellular ATP has been degraded into adenosine in the absence of oxygen as an electron receptor in the mitochondrial matrix. Adenosine easily perfuses out of cellular membranes into extracellular fluid, furthering capillary vasodilation, and then is transformed into uric acid. Because cells can only produce adenosine at a rate of about 2% of the cell's total need per hour, even restoring oxygen is futile at this point because there is no adenosine to phosphorylate into ATP.

Changes in Micro circulation

The microcirculation undergoes massive alterations during sepsis/septic shock (Ravin and Fine, 1962). There are numerous changes, including slowing of capillary blood flow due to depressed perfusion pressure as a result of systemic pressure reduction and local arteriolar constriction. Observations suggest that the microcirculation is shut off early capabilities in severe sepsis, allowing the effects of hypoperfusion and attacks by microorganisms to prevail in their destructive widespread capillary dilation may ultimately occur.

However, with blood flow diverted through some arteriovenous channels, important areas of capillary exchange are bypassed. Decreased capillary blood flow during shock results from failure to allow normal passage of cellular elements, including erythrocytes and neutrophils. This defect occurs, in part, because of decreased perfusion pressure, decreased deformability of red and white cells, constricted arterioles, circulating obstructive fragments (including

hemoglobin), and plugging of microvessels with "sludge." Other factors are adherence of cells to capillary and venular epithelial membranes creating increased resistance to flow, loss of fluid through abnormal transcapillary exchange, differential vascular resistance changes between various beds (e.g., intestinal vs. muscle), and the relative absence of regulatory neurohumoral control of small vessel segments of the circulation. During sepsis/septic shock, endothelial cells are reported to modulate vascular tone, control local blood flow, influence the rate of leakage of fluids and plasma proteins into tissues, modulate the accumulation and extravasation of white cells into tissues, and influence white cell activation. As a result of the predominance of many destructive factors, a subsequent round of tissue damage may occur. Because of prolonged capillary vascular stasis, deficient flow, and factors released from injured cells, the microcirculation becomes a trap for uncontrolled bacterial growth enhanced by sustained hypoxemia, acidosis and toxemia. These events may combine to contribute to the loss of normal cell integrity and death of the host.

Microcirculatory alterations improve rapidly in septic shock survivors but not in patients dying with multiple organ failure, regardless of whether shock has resolved.

The initial responses to endotoxemia are detectable in the microcirculation as a microvascular inflammatory response characterized by activation of the endothelium stimulating these cells from their normal anticoagulant state to a procoagulant state with increased adhesiveness for leukocytes and platelets. Concomitantly, arteriolar tone is lost and reactivity to a variety of agonists is modified. Tissue damage subsequently results not only from reduced perfusion of the exchange vessels, but also from injurious substances released from activated, sequestered leukocytes as well as activated endothelial cells, macrophages, and platelets. This is the result of endotoxins inducing activation and interaction of a number of effector cells, cascades, and acute-phase responses, such as the complement, coagulation, bradykinin/kinin, and hematopoietic systems accompanied by the release of a myriad of mediators. These include eicosanoids, cytokines, chemokines, adhesion molecules, reactive free radicals, platelet-activating factor, and nitric oxide. This paper briefly reviews the microvascular responses to endotoxemia and discusses some of the mechanisms involved.

Refractory Shock with Irreversible conditions of all organs functions cause:
- irreversible vasodilatation and diminishing of systemic vascular resistance,
- pooling of blood (sludge) to the system (capillary sphincter relax)
- Release of Microbial and Fungal toxins (Baumgarten et al., 2006).
- Primary and Secondary Inflammatory Mediators
- Metabolic Acidosis

-Vasodilatation -is fourth element at Path-Physiology during the Refractory (Irreversible) Shock.

a. In Case of Hemodynamic Refractory Shock (HS, CS)
Vasodilatation is caused by:
- Hypoxia (in lack of O2), and because of much cellular
 ATP- adenosine cause – an capillary vasodilation,
- Metabolic Acidosis -from stagnant waste products of cells, especially Lactic Acidosis
 -production of NO (nitric oxide)
- pooling of blood (sludge) to the system (pre and post capillary sphincter relax)

ATP + H2O $\Rightarrow$ ADP + Pi + H+ + Energy

Acidosis results from the accumulation of acid when during anaerobic metabolism the creation of ATP from ADP is slowed.

H+ shift extracellularly and a metabolic acidosis develops.

ATP production fails, the Na+/K+ pump fails resulting in the inability to correct the cell electronic potential.

Cell swelling occurs leading to rupture and death.

Oxidative Phosphorylation stops & anaerobic metabolism begins leading to lactic acid production. (Ramana et al ., 2006).

b. In Case of Refractory Septic Shock (IS)
Vasodilatation is produced by:
- Microbial toxins: Endotoxins like lipopolysaccharide (LPS)
-Primary and secondary Inflammatory mediators as: Histamine, Kinine/ Bradikinine (TNF-α), (IL- pooling of blood (sludge) to the system (pre and post capillary sphincter relax) 1 , IL-6, Lysosome,, Prostaglandine, eicosanoids, cytokines, adhesion molecules, reactive free radicals, platelet-activating factor,
- NO (nitric oxide)
-Hypoxia
-Metabolic Acidosis Metabolic Acidosis -from stagnant waste products of cells, especially Lactic Acidosis
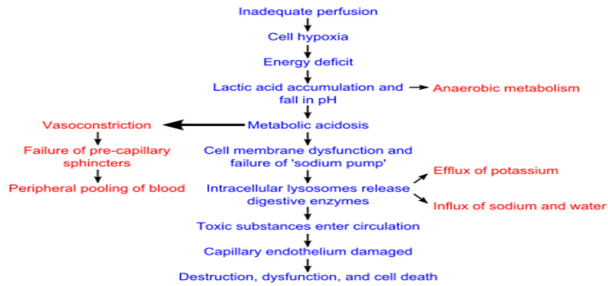- Pooling of blood (sludge) to the system (pre and post- capillary sphincter relax).

TABLE 1

Microcirculatory mechanisms are:

- Ischemic hypoxia stage
- Stagnant hypoxia stage
- Refractory stage has these Cellular and molecular mechanisms:

In the Microcirculation System the following phases are observed in Refractory Shock the following features are observed to:

-Relaxation of post-capillary sphincters

-Loss of Peripheral Vascular Resistance.

-Acidosis is a local accumulation of metabolic products because of, Alteration of hemorheology,

Endotoxins, Effects of humoral factors (Looney et al., 2006; Coimbra et al., 2006). In these cases have:

Effective circulating blood volume is diminished↓ ↓, temporarily has an increased of Blood flow resistance ↑ ↑, is diminished blood pressure ↓ ↓, is diminished Blood supply for vitals and dysfunctional.

1. In case of Ischemic hypoxia stage (compensatory stage) has: Microcirculatory changes, Small blood vessel constriction, Precapillary resistance↑↑ > postcapillary resistance↑, Closed capillary↑, Blood inflows vein by straightforward pathway and A-V shunt.

Characteristics of inflow and outflow: inflow and outflow↓↓; inflow < outflow.

2. In case of Stagnant hypoxia stage (reversible decompensated stage) has: Acidosis derived from Local accumulation of metabolic products, Endotoxins, Effective circulating blood volume is diminished ↓ ↓:
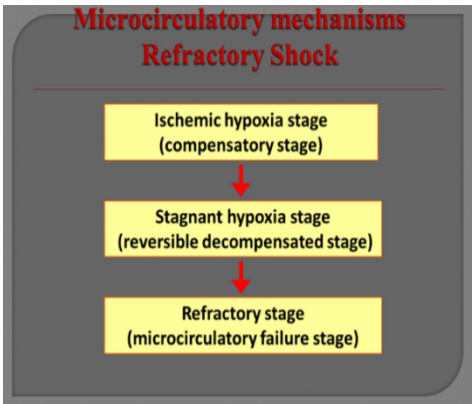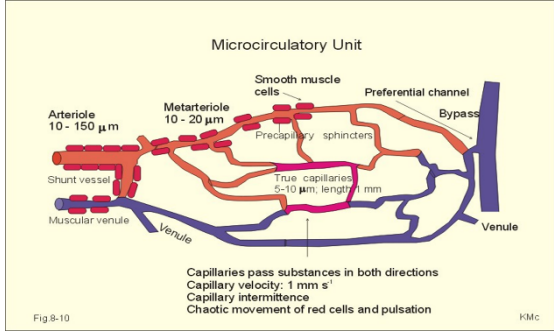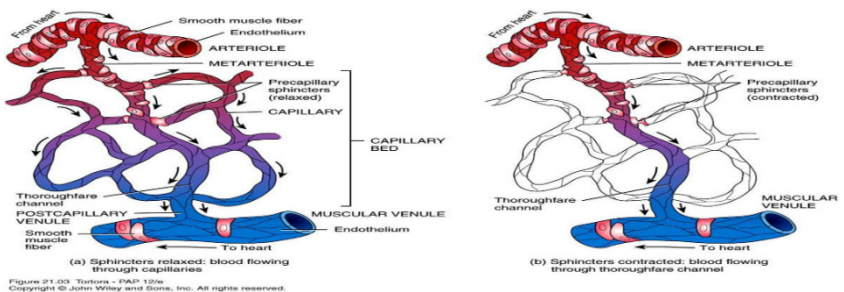
(See the tables: 2,3, 4 and 5):

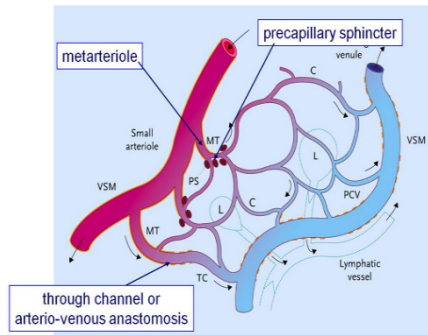**TABLE 2**

TABLE 3

TABLE 4

TABLE 5

Clinical manifestations

Is essential to monitor Vital signs During Refractory Shock patient is in very grave condition:

- Cardio-vascular system: Tachycardia and dysrhytmias, hypotension,
- Pulmonary System: Tachypnea, Superficial respirations, dyspnea,
- Mental Status: Changes, is frightened, anxiety, confusional condition, and coma.
- Skin e mycoses: Patient is pale, with cold extremities, and cyanosis
- Diuresis: Oliguria
- Thermoregulation: Hypothermia, but during hyperkinetic phases of Septic Shock can be high temperature,
- Lactic Acidosis.
- Cardiac Output - diminished
- PAOP - increased
- SVR - increased
- Left ventricular stroke work (LVSW) – DIMINUISHED
- Coronary Perfusion Pressure
- Coronary PP = DBP - PAOP
- Coronary perfusion = Δ P across coronary a.

So is necessary t is essential to monitor symptoms to understanding their disease, to describe the patient's physiologic status, to facilitates diagnosis and treatment of shock, and continuing monitoring of Vital Signs. See the Tables 6, 7, and 8:

Type	PAOP	C.O.	SVR
HYPOVOLEMIC	↓	↓	↑
CARDIOGENIC	↑	↓	↑
DISTRIBUTIVE	↓ or N	varies	↓
OBSTRUCTIVE	↑	↓	↑

Note: PAOP – Pulmonary Artery Occlusion Pressure; C.O.- Cardiac Output; SVR - Systemic Vascular Resistance

TABLE 6

Clinical Signs of Three Category of Shock

Skin		CVP	UO	BP	HR	Temp
IS	- warm, red, dry/clammy - cold, pale, clammy	↓	N → ↓	N → ↓	↑	↑ → ↓
HS	cold, clammy and pale	↓	↓	N → ↓	↑	↓
	CScold, clammy and pale	↑	↓	↓	↑↓	↓

- CUT OFF FOR ↑HR AND SYST IS 90-100; FOR ↓HR IS 60, DOWN TO 40 IN ATHLETES;
- DYSRHYTMIAS/IHD AND AGITATION/CONFUSION/RESTLESSNESS DENOTE;RESPECTIVELY CARDIAC AND BRAIN HYPOXIA (ADVANCED CS/IS) OR IRRITATION (IS).;
- MET. AC. WITH - BE AND ↑ LACTIC ACID IS UNIVERSALLY PRESENT IN ANY SHOCK;
- COAGULOPATHY IS AN OMINOUS FEATURE OF ADVANCED, LATE, LAST;STAGE SHOCK OR UNTREATED, REFRACTORY OR PERSISTING HYPOTHERMIA.;
- HYPOTHERMIA IS CHARACTERISTIC OF SHOCK STATE EXCEPT IS FROM SEPSIS INITIAL;HYPERDYNAMIC STATE WHERE ENDOTOXINS TRIGGER HYPERTHERMIA

Note: **IS**-Inflamatory Shock; **HS** – Hemorrhagic Shock; **CS**-Cardiogenic Shock
CVP-Central Venous Pressure; **UO** – Urine Output; **BP** – Blood Pressure;
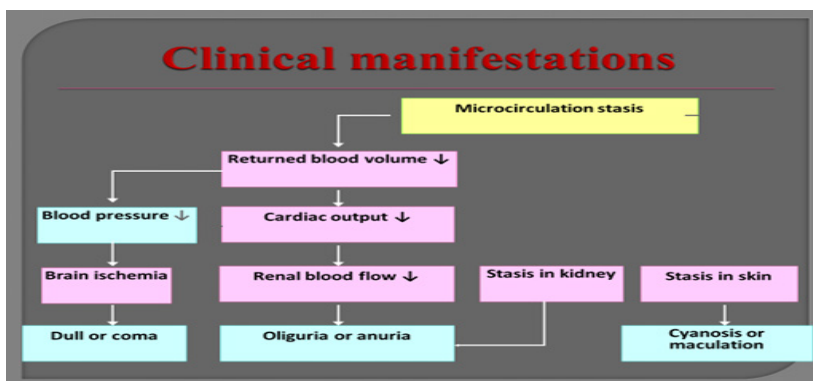**HR** – Heart Ritm;

TABLE 7

TABLE 8

Signs of Refractory Septic Shock are:
± cardiac output
±PAOP
SVR - diminished
Signs of Refractory Cardiac Shock are:
 Cardiac Output - diminished
PAOP - increased
SVR - increased
Left ventricular stroke work (LVSW) – Diminished
Coronary Perfusion Pressure
Coronary PP = DBP - PAOP
coronary perfusion = BP across coronary (Trzeciak et al., 2007)

Diagnosis of Refractory Shock

Evaluation should focus on the identification of the primary cause and reversible secondary contributors, such as hypovolemia, pump failure, or obstruction that is causing shock. Patients must be placed on continuous cardiopulmonary monitoring (Bernard et al., 2001) The following labs should be monitored: Complete blood count with differential (CBC-d), basic metabolic profile with liver function test, disseminated intravascular coagulation (DIC) panel, arterial blood gas, urinalysis, and pan cultures (blood, urine, wound, tracheal if intubated). Inflammatory markers, including C-reactive protein or procalcitonin and lactate levels, should be monitored. A chest x-ray should be obtained to monitor the degree of ARDS.

Differential Diagnosis
Differential Diagnosis must be done with: Septic shock, Vasodilatory shock and cardiogenic shock. Is necessary to evaluate these parameters (Krejci et al., 2016):

Measured	Calculated
Blood pressure	Mean BP
Pulmonary A. pressure	Mean PAP (Pulmonary Artery Pressure)
Heart rate	Cardiac Index
Cardiac Output	Stroke volume index
Stroke volume	Mean BP
Wedge pressure	SVRI (systemic vascular resistance index)
CVP (Central venous pressure)	LVSWI (Ventricular Stroke Work Index, Left) BSA (body surface area)

It is necessary to evaluate during diagnostic and therapy oxygen delivery and hemodynamic calculations of the patient in ICU as well (see the tables 9, 10, 11, and 12).

Att Phys :
PITT COUNTY MEMORIAL HOSPITAL

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**************************************************************************
*                        Hemodynamic Calculations                        *
*                                                                         *
*              units        :             units       :          units    *
*                           :                         :                   *
* C.O.    5.70 l/min        :                         : C.I.    2.50 l/min/m2 *
* HR        89 bpm          : SV    64.0 ml           : SI      28.1 ml/m2    *
* ABP  S   100 mmHg         : SVR    800 DS/cm5       : SVRI   1823 DSm2/cm5   *
* ABP  D    49 mmHg         : PVR    253 DS/cm5       : PVRI    576 DSm2/cm5   *
* ABP  M    68 mmHg         : LCW    5.3 kg-m         : LCWI    2.3 kg-m/m2    *
* PAP  S    49 mmHg         : LVSW  59.2 g-m          : LVSWI   26.0 g-m/m2    *
* PAP  D    24 mmHg         : RCW   2.64 kg-m         : RCWI    1.16 kg-m/m2   *
* PAP  M    34 mmHg         : RVSW 29.61 g-m          : RVSWI  12.99 g-m/m2    *
* PAWP      16 mmHg         :                         :                   *
* CVP  M    11 mmHg         :                         :                   *
*                           :                         :                   *
* Height    64 in           :                         : Calculation Time: *
* Weight 130.0 kg           : BSA(D)  2.28 m2         :     29 JAN 02  3:57 *
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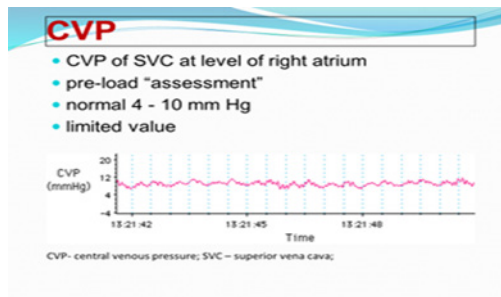
TABLE 9

CVP
- CVP of SVC at level of right atrium
- pre-load "assessment"
- normal 4 - 10 mm Hg
- limited value

CVP- central venous pressure; SVC – superior vena cava;

TABLE 10

Hemodynamic Calculations

Parameter	Normal
Cardiac Index (CI)	2.8 - 4.2
Stroke Volume Index (SVI)	30 - 65
Sys Vasc Resistance Index (SVRI)	1600 - 2400
Left Vent Stroke Work Index (LVSWI)	43 - 62

TABLE 11

TABLE 12

Monitoring and Stroke work as well:

LVSWI = (MAP-PAOP) x SVI x 0.0136
normal = 43 - 62
VSWI describe how well the ventricles are contracting and can be used to identify patients who have poor cardiac function.
ventricular stroke work = Δ pressure x vol. ejected

Important is monitoring, Pulmonary Artery Catheter as: Indications, volume status, cardiac status. Is important to evaluate and to prevent the complication of pulmonary artery catheterization: technical, anatomic, physiologic.

Special Problems during Diagnostic and Therapy
Oxygen Delivery (DO2I)
O2AVI = CI x CaO2 x 10
Normal values suggests that the heart & lungs are working efficiently to provide oxygen to the tissues. < 400 is bad sign. Is necessary to evaluate:
Oxygen Consumption
VO2I = CI x (CaO2 - CvO2)
If VO2I < 100 suggest tissues are not getting enough oxygen (Bagshaw et al.,2006), (Slade et al., 2003)

Diagnostic Mistakes
-   JVP is low CS and HS
-   Central Cyanosis is not eligible in HS
-   Elderly patients with ATS and HPT can be in shock with a Systolic pressure of 120-130 mHg

- Pts β-blockers or antidysrhythmic drugs do not manifest reflex tachycardia and can be in shock with normal HR.
- Steroids mask septic Shock signs
- Hypoglycemia, drunkness, not lethal carbon monoxide poisonings, syncope and vaso-vagal attacks can mimick shock initial skin changes
- Cocaine abusers are bradycardic or do not exhibit reflex tachycardia
- Caffeine intake before shock onset and phosphodiesterase inhibitors can deceive its recognition and assessment by causing tachycardia.

Treatment in General:
Goals of Shock Resuscitation are:
Restore blood pressure
Normalize systemic perfusion
Preserve organ function
CI = 4.5 L/min/m2
DO2I = 600 mL/min/m2
VO2I = 170 mL/min/m2
Critically ill patients who can respond
Oxygen Therapy (mecanical ventilation)
Improve microcirculation, Volume replacement, Acidosis correction, vasoactive drugs application, Treatment of DIC, Blockage of humoral factors, Cell protection, Organ protection.

Treatment of Refractory Cardiac Shock:
Coronary PP > 50 mm Hg
Improve myocardial function, C.I. < 3.5 is a risk factor, 2.5 may be sufficient.
Fluids first, then cautious pressors
Remember aortic DIASTOLIC pressures drives coronary perfusion (DBP-PAOP = Coronary Perfusion Pressure)
If inotropes and vasopressors fail, intra-aortic balloon pump
Temporary circulatory support with extracorporeal membrane oxygenation (ECMO)
Sol. Natri Bicarbonici 8.4% (PH ≤7.2)
Despite recent advances, therapeutic options are limited, and RCS is almost uniformly fatal when emergency circulatory support cannot be initiated in a timely manner.
This strategy based on temporary circulatory support in specialized and experienced centers; up to 40% of the patients with RCS can survive to hospital discharge in various pathophysiological situations.

Patients requiring CPR for cardiac output and the elderly, most probably cannot benefit from circulatory support, in this context. (Carlson et al., 2006), (Gary et al., 1998).

Nonetheless, this strategy is currently restricted to a very limited number of tertiary-care centers with specialist capabilities for instituting and supporting ECMO.

In remote hospitals, however, without ECMO capability, management of RCS patients is considerably more difficult, as transfer to tertiary centers is often essential to save the patient but is often not feasible in such medically unstable patients (Jaski et al ., 2010).

If such patients can be stabilized by extracorporeal membrane oxygenation (ECMO), possible outcomes include (Combes et al., 2008) *:*

(i) ECMO weaning to recovery (bridge to recovery),

(ii) heart transplantation (bridge to transplantation),

(iii) implantation of a long-term assist device (bridge to bridge).

- Vasopressors & Inotropic Agents
- Dopamine: δ-agonist-8-20 mcg/kg/min
- Norepinephrine: α-agonist -adrenergic- 1 – 100 mcg/min
- Epinephrine: α-adrenergic - 1 - 10 mcg/min
- Amrinone: 0.75 -1.5 mg/kg - 5 - 10 mcg/kg/min drip, esterase inhibitor, positive inotropic and vasodilatory effects.
- Dobutamine: α –β- agonist-5 - 20 mcg/kg/min.
- ACS CoT ATLS - restoration of vital signs and evidence of end-organ perfusion
- Swan-guided resuscitation

C.I. ≥ 4.5, DO2I ≥ 670, VO2I ≥166

- Lactic Acid clearance
- Gastric Ph

Current treatments used to manage septic shock

This therapy can be used to the Sepsis, Anaphylactic, Acute adrenal insufficiency, Neurogenic.

Therapy is:

Oxygen Therapy (mecanical ventilation)

Prompt volume replacement - fill the tank

Early antibiotic administration - treat the cause

Inotropes - first try Dopamine

If MAP < 60 mmHg:

Dopamine = 2 - 3 mcg/kg/min

Norepinephrine = titrate (1-100 µg/min

Sol.Natri Bicarbonici 8.4% (PH ≤7.0)

Steroids –Fludrocortisone 50 µg po q day; Hydrocortisone 200-300 mg/day in divided doses for 7 days

Treating septic shock is a complex clinical task that requires an accurate assessment of the patient's clinical stage on the bacteremia–refractory septic shock continuum. Current therapies are tailored to the distinct stages involved in refractory septic shock development. In the first stage–bacteremia, antibiotics are used as a first line of defense to control the infection [. Although this is administered early, it has a very limited efficacy in controlling immune dysregulation that occurs due to the bacterial infection.

The majority of current therapeutics target the late phase of refractory septic shock development. In the late stages, vasopressor therapy is routinely used however recent literature has shown that although this method can restore systemic blood flow it also results in decreased microcirculatory and mesenteric perfusion. This causes blood flow to divert away from the jejunum and pancreas, which leads to an adverse effect as decreased blood supply to the gastrointestinal system results in cell death. In addition, other therapeutics used to treat severe sepsis include the use of antioxidants, which have proven to be more effective due to their limited side effects. Investigations of antioxidant vitamin therapy by Carlson et al. showed that administration of Vitamins A, C, and E resulted in a significant decrease in the activation of the innate immune system (mediated by the proinflammatory transcription factor family, NF-κB). This in turn, decreased cytokine release, thereby minimizing inflammatory damage and resulting in improved myocardial contractile function. Other adjuvant therapies are also used, such as recombinant human activated protein C (rhAPC). A study by Looney et al. showed that administering rhAPC had an anti-coagulant, anti-inflammatory, anti-apoptotic and profibrinolytic effect, but the exact mechanism through which rhAPC exerts its benefit in severe sepsis is unclear.

Therapies used during the septic shock stage are targeted at restoring systemic circulation and treating failing components of individual organ systems. Fluid resuscitation is first used to maintain blood flow to organ systems and prevent further damage. In addition, mechanical ventilators are used to assist the patient in breathing if the respiratory system fails resulting in acute respiratory distress syndrome (ARDS). Furthermore, complications associated with the hematological system (such as disseminated intravascular coagulation) are treated with anti-thrombotic medications to prevent blood clotting.

If the symptoms of sepsis are prolonged, the patient's condition continues to deteriorate and the patient ultimately develops refractory septic shock. During

refractory septic shock localized therapies are administered to increase tissue perfusion however prognosis at this stage is bleak and most patients undergo multiple organ failure.

Possible treatments to manage refractory septic shock

Early management in the bacteremia—refractory septic shock pathway is crucial in order to effectively prevent the development of refractory septic shock. Upon identification of a positive blood culture, anti-LPS molecules can play a key role in preventing the progression into the next stage. Bosshart et al. used cationic lipids and poly-L-histidines to successfully prevent the formation of the LPS-LBP complex. As cationic lipids or histidine coils surround and sequester LPS, the LPS molecule is unable to bind LBP, and is therefore inactive and unable to stimulate the release of TNF-α. This prevents the activation of additional pro-inflammatory mediators which can cause further injury through the release of tissue factors (namely leukotrienes and platelet activating factors).

During the septic stage therapeutic interventions might also improve the clinical outcome. A study by Ranmana et al. recently noted that inflammatory signaling and cytokine generation during sepsis is dependent on the enzyme aldose reductase. They concluded that down-regulation of this enzyme using interfering ribonucleic acid (RNA) or a pharmacological inhibitor (sorbinil) decreases the activation of the NF-κB nuclear factor and prevents TNF-α release.

Other Intensive Treatment in ICU

In addition to the above treatments in the ICU these medications can also be used:

1. Methylene blue- loading-dose of 1.5 mg/kg and continuous infusion (1.5 mg/kg/h for 12 h, then 0.75 mg/kg/h for 12 h)-(decreasing vasodilation and increasing responsiveness to vasopressors);
2. Vasopressin Arginine- continuous infusions of 0.04 units/min (with Cardiac Index ≤ 2.5-3);
3. Xigris (drotrecogin alfa (activated) is a recombinant form of human activated protein C: i/v infusion rate of 24; mcg/kg/hr (5 mg vials must be reconstituted with 2.5 mL).
4. Lenitral (Trinitrine) trinitrin the initial optimal dose of 0.39 +/- 0.22 mcg/kg/min;
5. Fentolamine- 5 +/- 3 mcg/kg/min;

6. Pentoxifylline (PTX). phosphodiesterase inhibitor,
7. TP (terlipressin) is an effective vasopressor agent (pediatrics) Doses (1– 4) µg/kg/min.
8. Using Cationic Lipids and Poly-L-Histidines to successfully prevent the formation of the LPS-LBP (lipopolysaccharide -LPS binding protein) complex
9. Antioxidant vitamin therapy by Carlson et al. showed that administration of Vitamins A, C, and E resulted in a significant decrease in the activation of the innate immune system (mediated by the pro-inflammatory transcription factor family, NF-κB);
10. Recombinant Human activated Protein C (rhAPC)- had an anti-coagulant, anti-inflammatory, anti-apoptotic and profibrinolytic effect;
12. Sorbinil -using interfering ribonucleic acid (RNA) decreases the activation of the NF-κB nuclear factor and prevents TNF-α release.

Complications
End organ dysfunction
Multi-organ failure
Death

Prognosis
Depend from:
Poor prognostic features in Sepsis syndrome
Age more than 60
Multiorganic failure
Renal failure
Respiratory Failure
Hepatic failure
Hypothermia or Leucopenia
HAI - hospital-acquired infection
DIC – Dissemination Intravascular Coagulation
Underlying Disease (Malignancy, Immunocompromised)

Mortality
Mortality in Sepsis: Mortality Bacteremia 15-20%; Bacteremia plus Shock = 30-40%; Shock plus ARDS=40-60% (Journal of Critical Care, Volume 38, April 2017, Pages 284-288).

Mortality in Refractory Cardiogenic Shock is 45.5% within first 30 days after treatment (American Heart Journal, Volume 158, Issue 4, October 2009, Pages 680-687).

Recomandation

Refractory shock which is mainly caused by cardiogenic shock and Septic shock are severe conditions which cause increased mortality in patients with such conditions.

Advances in the treatment of these serious conditions have enabled the healing of these patients and the relative reduction of Mortality.

It is important that the diagnosis of Shock conditions is made as soon as possible so that treatment is started immediately in order to avoid serious conditions such as Refractory Shock.

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