A Contemporary Approach to Septic Shock in Children

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During the past several years there has been a progressive increase in the incidence of shock secondary to sepsis and the mortality rate remains in excess of 50 percent. This has occured despite a better understanding of this entity, the use of newer treatment regimens and the development of more potent antimicrobial agents (1, 20).

While septic shock is a syndrome of circulatory in-sufficiency which can be caused by a variety of illnesses it may result in prostration, hypotension, pallor, diaphoresis, cool skin and oliguria.

The terms bacteremia and septicemia refer to the presence of bacteriae and their toxins in the blood. Bacteremia is used when bacteriae are recovered from blood cultures of a patient who does not appear to be seriously ill and who may be afebrile. In contrast, septicemia implies that blood cultures are positive and that the patient appears seriously or critically ill. In some patients bacteremia or septicemia may be related to focal infection (e.g. pneumonia, osteomyelitis, endocarditis, meningitis) the presence of which can be suspected or confirmed rapidly by history, physical examination and roentgenographic or other laboratory studies. In such cases, bacteremia or septicemia may be suspected with a high degree of likelihood (5, 13, 17).

In shock the circulatory abnormalities change with time thus careful, often invasive, physiologic monitoring is necessary to evaluate and treat the spesific hemodynamic, respiratory and metabolic abnormalities (5, 10).

According to the pathophysiologic mechanisms there are four major types of shock: (I) hypovolemic (II) cardiogenic (III) obstructive and (IV) distribute. The chief abnormality in hypovolemic shock is, decreased intravascular volume, which may occur as a result of loss of blood or plasma, hence fluid and electrolytes. These losses may be exogenous or endogenous (17).

The chief abnormality in cardiogenic shock is abnormal cardiac function due to dysrhythmia, pump failure or valvular dysfunction.

The chief abnormality in obstructive shock is an impediment to filling of the right or left ventricle, which means the decreasing of preload. If decreased filling is sufficiently severe, the resulting fall in cardiac output causes shock. Obstruction may occur in the systemic circulation (e.g. obstruction of vena cava) or pulmonary circulation (e.g. massive pulmonary embolus) or may be due to pericardial disease (eg. cardiac tamponade) or cardiac disease (e.g. atrial myxoma).

The chief abnormality in distributive shock is abnormal distribution of vascular volume due to changes in vascular resistance or permeability. The end result is a decrease in ventricular filling that leads to inadequate cardiac output. The derangement of vascular volume characterizing distributive shock may occur as a result of sepsis, anaphylaxis or neurogenic shock (5, 10, 11).

Septic shock is the shock syndrome complicating infectious disease (6). There is the association of septic shock with bacteremias caused by gram-negative bacteriae in about two-thirds of the patients in whom this complication develops in the hospital environment. Septic shock is theoretically related to the release of exotoxins which many strains of Staphylococci and Streptococci (but not pneumococci) are known to procedure. The hemodynamic changes that occur are different from those seen in septic shock due to gram-negative organisms (17).

ETIOLOGY

The most frequent causative organisms are gram-negative and gram-positive bacteriae; although any agent capable of producing infection (including viruses, parasites, fungi and rickettsiae) may initiate septic shock (17). The most frequent source of gram-

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Table — 1

Classification of Shock by Pathophysiology

Hypovolemic shock
- Loss of blood
- Loss of plasma
- Loss of fluid and electrolytes

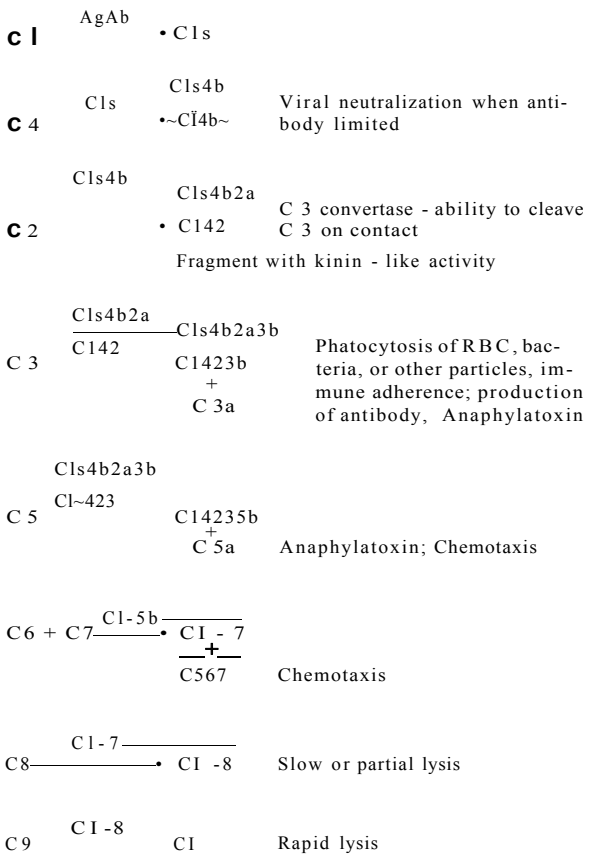
Cardiogenic shock
- Dysrhythmia
- Pump failure
- Valvular disfunction

Obstructive shock
- Pericardial tamponade or consriction
- Pulmonary emboli and pulmonary hypertension
- Cardiac tumor
- Left atrial mural trombus

Distributive shock
- Anaphylactic shock
- Septic shock
- Neurogenic shock
- Vasodilator drugs
- Acute adrenal insufficiency

Table — 2

Classic Pathway of Complement Activation:
The initiation antigen (Ag) can be erythrocyte, bacteria, virus, other cell, or any other antigen, the antibody (Ab) can be IgG$_1$, IgG$_3$, IgG$_2$, or IgM A bar over the compoment indicates that the component has acquired enzymatic or other biologic activity.



negative infections is the genitourinary system; almost half of the patients usually have undergone an associated operation or instrumentation of the urinary tract. The second most frequent site of origin is the respiratory system and many of the patient have an associated tracheostomy. Next in frequency is the alimentary system with diseases such as peritonitis, intra-abdominal abscesses and biliary tract infections and the diseases of the integumentary; including burns and soft tissue infections. Indwelling venous catheters for monitoring and hyperalimentation are an increasing source of contamination, particularly with prolonged use. The reproductive system continues to be a significant source of infections (principally from septic abortion and postpartum infections) although the incidence is variable, depending on the hospital population (11, 13).

Predisposing factors include diabetes mellitus, cirrhosis, leukemia, lymphoma or disseminated carcinoma, transplantation and its associated immunosuppression, childbirth, a variety of surgical procedures and antecendent infections (11).

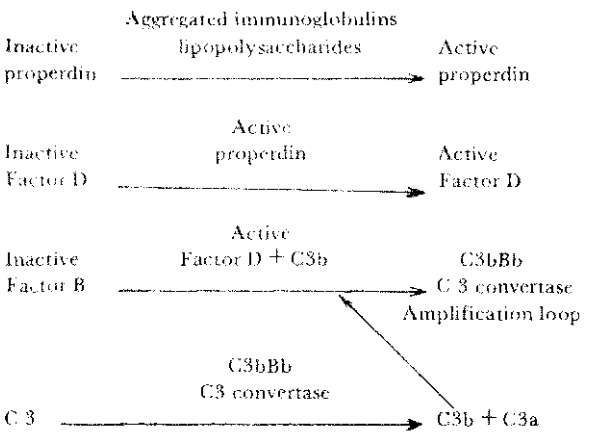
PATHOPHYSIOLOGY

Gram-negative shock has a more complex pathophysiology than hypovolemic shock, but the end result is the same; progressive cellular damage leading to cell death and eventually death of the organism. Septic shock results from a violent struggle between the body's defense mechanisms and bacteriae by-products rather than the direct action of the infective agent. The process appears to have a primarily immunologic basis, leading to the release of substances that have a profound effect on the blood vessels and cells (13, 20).

Host defense plays an essential role in the pathophiysiology of gram-negative shock. As bacteria enter the body, two basis mechanisms; one humoral and the other cellular are activated to eliminate the invading agents. Humoral defenses involve antibodies which are immunoglobulins produced by plasma cells. When a microorganism enters the body, it is recognized as a foreign antigen and is bound to a specific immunoglobulin. The resulting complex activates the effector arm of the humoral defense mechanism; the classical complement system (7,8).

Table - 3

Alternative Pathway of Complement Action: The Initiating Substance May Be Endotoxin, Yeast Cell Wall, Bacterial Capsule Or IgA



The cascade of reactions begins with CI, the first protein in the sequence and ends with C9. The resulting complement products insert themselves into the bacterial cell membrane causing lysis and death.

Phagocytosis and intracellular killing of bacteria is the second and most important method of combating acute bacterial infections. The principal phagocytic cell is the polymorphonuclear leukocyte. The white blood cell is attracted to the site of the bacterial invasion by elements of the complement system, particularly C3 and C5, in a process known as chemotaxis. Leukocytes next must recognize bacteriae and ingest them. These processes are facilitated by opsonisation, which is the bingd of immunoglobulin or complement particles to the microorganisms. It appears that the alternate or properdin complement pathway rather than the classic pathway is the principal mechanism for the production of opsonins (13)

As bacteria are killed, endotoxin which is a lipopolysaccharide derived from the cell membrane, accumulates in the circulation. The body elimenates endotoxin by combining it with antibodies, white blood cells and platelets. These reactions also require activating of the complement system. The bound endotoxin is then phagocytosed by the reticuloendotelial system, the major site of detoxification. As the reticuloendotelial system becomes overwhelmed, increasing amounts of endotoxin accumulate in the body. Endotoxin contributes to the overall effects of gram-negative sepsis by causing direct damage to the cells and also by initiating adverse immunologic reactions (1, 5, 13).

Both the alternate and classic complement pahtways are maximally activated by the clash between invading bacteriae and the patient's defense mechanisms. Active complement particles are relaased into the circulation and travel throughout the body, affecting cells and blood vessels. The two complement proteins, C3a and C5a trigger the release of histamine and heparin. Stimulation of the complement system leads to activation of the kinin-bradykinin and coagulation systems, with the release of vasoactive and clothing substances. Platelet aggregation and destruction occurs in the presence of complement and endotoxin and leads to the release of serotonin, adenosine diphosphate (ADP), PGE, and I'GF; and histamine. With the rupture of lysosomal membranes, proteolytic enzymes injurious to the cell are released into the circulation (11, 12).

Although endotoxin and proteolytic enzymes may cause direct ejHular injury, inadequate perfusion **as** in hypovolemic shock, is even more damaging to cell. Low flox results from (i) obstruction and rerouting of the microcirculatory flow, (iil reduction of circulating blood volume and (iii) reduction of cardiac output. With platelet aggregation and destruction, platelet fragments are swept, into the microvasculature producing widespread blockade. Increased platelet adhesiveness results in the adherance of platelets to small blood vessels, reducing flow. Other platelet substances initiate further aggregation, vasoconstriction or vasodilatation and capillary leak. As the coagulation system is activated diffuse disseminated intravascular coagulation may occur. Vasoactive compounds released by kinin bradykimn and complement system cause arterial vasoconstriction and opening of arteriovenous shunts (7, 8, 13, 1 5. 20).

otasis and pooling of blood in the capillary bed leads to reduction of the circulating blood volume. Vasoactive substances cause pooling of blood in the venous system. Proteolytic enzymes and histamine increase capillary membrane permeability. Water, electrolytes and proteins leak from the capillaries into the nonfunctional interstitial space. With high protein, edema develops in the interstitial space, thus the circulating blood volume falls.

Myocardial dysfunction develops progressively **as** the shock state worsens, owing partly to the decreased venous return. The principal explanation for the failure of the cardiac function appears to be; inadequate coronary perfussion and inadequate delivery of oxygen and cellular substrates to the cardiac musculature.

CLINICAL MANIFESTATIONS

Gram-negative infections are often recognized initially by the development of chills and elevated

rectal temperature above 38.3 C. The onset of shock may be abrupt and coincident with the signs and symptoms of sepsis and may occur several hours to days after recognition of an established infection (1).

A syndrome of early septic shock occurs in patients who are normovolemic prior to onset of sepsis and exhibit a hyperdynamic circulatory pattern characterized by; (I) hypotension (which is under 90 mmHg of systolic pressure). (II) high cardiac output, (HI) normal or increased blood volume, (TV) normal or high centra! venous pressure, (V) low peripheral resistance, (VI) warm, dry extrémités, (VII) hyperventilation, (VIII) respiratory alkalosis and (IX) oliguria.

A typical patient with this pattern is the young, previosly healthy person with a septic abortion or an infant with septic peritonitis. The high cardiac output is often associated with a decreased in oxygen utilization per unit flow. These findings can be explained by any of the several mechanisms, but the two most likely possibilities are arteriovenous shunting and a primary cellular defect in the utilization of oxygen due to a direct effect of sepsis (5).

In contrast, if septic shock develops in a patient who is hypovolemic, a hypodynamic pattern emerges characterized by: (I) hypotension, (II) low cardiac output, (III l high peripheral resistance, (IV) low central venous pressure, (V) cold, cyanotic extrémités, and (VI) oliguria. This response is typically seen in a patient with strangulation of the small bowel and a moderate to severe extracellular fluid and plasma volume deficit (13).

All of patients have fever, erytroderma and mucous membrane hyperemia (excepting vaginal) by the day of admission and most have vomiting or diarrhea (11, 21). Jaundice occurs occasionally and signifies infection in the biliary tree, intravascular hemolysis or toxic hepatitic (20).

As shock progresses; oliguria persists and heart failure, respiratory insufficiency and coma supervene. Death usually occurs from pulmonary edema, generalized anoxemia secondary to respiratory insufficiency, cardiac rysrhythmias, disseminated intravascular coagulation with bleeding, cerebral anoxemia or a combination of these factors.

Laboratory data in bacteremia and septic shock vary greatly and depend in many instances on the cause and stage of hemodynamic decompensation. Leukocystosis of between 15.000 and 30.000 WBC7 cumm with a left shift is usually present. However relative or absolute leukopenia may be present in severe cases. The platelet count usually decreases. In urinanalysis the urine density increases initially but if oliguria persists, isosthenuria may develop. The BUN and creatinin increase and the creatinin clearance declines. Electrolytes vary considerably with a trend toward hyponatremia and hypochloremia Potassium may be low or high, depending upon the intact functional ability of the kidneys. Respiratory alkalosis with a low $pC0_2$ and increased arterial pH is present early and compansates for lactic acidemia. As shock progresses, metabolic acidosis supervenes. Anoxemia with $p0_2 < 70$ mmHg is common. The electrocardiogram shows depressed ST segments with T wave inversions (1, 5, 9, 10).

PRINCIPLES IN TREATMENT

The treatment of septic shock involves control of infection and restoration of adequate tissue perfusion. While the treatment of infection is the keystone; a combination of antibiotics providing wide-spectrum coverage is administered intravenously in high doses from the beginning (20). Furthermore the ill stage and the consequences brought along with the septic shock is advised to be managed as follows:

Maintaning airway and ventilation is mandatory. Oxygen may be given by nasal prongs or mask. Stridor is listeden for, as well as other evidences of upper airway obstruction. Keeping intratracheal intubation or ericothyrotomy equipment readily at hand is wise, especially in children.

Insertion of a large-bore intravenous catheter and obtaining a venous blood sample for whole blood counts with differential platelet count, prothrombin time, partial thromboplastin time, electrolyte studies, renal and liver function test while intravenous fluids are administered. A Swan-Ganz catheter for hemodynamic evaluation can be very useful.

Obtaining arterial blood gas and pH measurements to evaluate the status of blood acid-base balance is beneficial. Respiratory alkalosis may be present early in septic shock but usually progresses to metabolic acidosis.

Monitoring cardiac rhythm while obtaining a 12-lead electrocardiogram can show worsened myocardial ischemia and heart faliture along with the septic shock. But one must also keep in mind that, shock of any cause may predispose to cardiac dysrhythmias due to electrolyte and acid-base abnormalities (10, 11).

Volume Replacement

Since elimination of infection is ultimately determined by the effectivenes of the host's defenses and that prematurity, stress, trauma, operation, anesthesia, certain drugs, starvation and infection reduce the humoral and cellular defenses against infection reduce the humoral and cellular defenses

Table - 4

The Clinical Response to Septic Shock

	Blood Volume	Blood Pressure	Cardiac Output	CVP	Peripheal Resistance	Extremities
Hyperdynamic Shock	Normal or ↑	↓	↑	Normal or ↑	↑	Warm Dry
Hypodynamic Shock	↑	↑	↑	↑	↓	Cold Cyanotic

against infection, an attempt to provide additional host defense, blood and blood byproducts can be lifesaving.

The administration of fresh frozen plazma and fresh whole blood transfusions will increase the elements of the classic and alternate complement pathways ar J the level of circulating immunoglobulins to bind bacteriae and serve as opsonins for white blood cells and other phagocytic cells. Fresh whole blood transfusions have been effective in treatment severe group B-streptococcal sepsis of the newborn (9) Blood which is rich in opsonic antibodies for streptococci, given in volume greater than 40 percent of the whole blood volume, enhances the fight against causative organisms.

Exchange transfusions of fresh whole blood provide complement and immunoglobulins in addition to viable white blood cells. Removing the patient's blood and infusion fresh donor blood may have the added benefit of removgni circulation infectious components such as live bacteriae, vasoactive substances, platelets, white blood cell aggregates and endotoxins. Exchange transfusions are also useful when disseminated intravascular coagulation (DIC) occurs during the course of septic shock. They appear to be more effective than heparin because of the removal of fibrin split-products and the replacement of depleted clotting factors (7, 13)

The chronic hypovolemia of gram-negative sepsis is treated with blood or plasma as part of the initial resuscitation regimen. These colloid containing fluids are used not only for their positive oncotic pressure effect but rather for their immunologic factor content that need to be replaced because of the patient's comprimised host defense.

Crystalloid solutions will improve blood pressure and urine output (5). One can use the crystalloid solution in a dose of 0.2 g/Kg to 10 g/Kg and can be delivered as a bolus infused over several hours or over a 24 hours period (6).

In infants a bolus of 1.5 g/Kg of human albumin causes an immediate marked elevation of colloid oncotic pressure lasting about 20 minutes and then levelling off to a moderate elevation. Elevation colloid oncotic pressure can also be produced by infusing 2.5 percent albumin in an electrolyte solution, 2.5 to 3 g/Kg/24 h (20).

After the initial period of rapid fluid resuscitation total fluid requirement is evaluated, a rise in arterial, central venous and pulmonary wedge pressure, an increase in urine output, a slowing pulse in the older infant and child, an increase in pulse rate in the neonate, a decrease in metabolic acidosis and a rise in cardiac output suggest that the fluid deficit has been corrected and that the circulatory system is functioning effectively. Occasionally, Central venous and pulmonary wedge pressure increase but arterial hypotension persists and there is continued oliguria and metabolic acidosis. These findings suggest that 'fluid resuscitation is adequate but shock persists because of cardiac failure In these instances cardiac output measurements are particularly helpful in confirming the diagnosis.

Correction of acidosis by giving sodium bicarbonate is a must. If blood measurements are not available, 0.5-1 mEq/Kg dose of $NaHC0_3$ is required. If blood tensions are available the dose can be calculated as follows; mEq $NaHC0_3$ = 0.3 x weight (kg) x base deficit (mEq/L) for the pediatric patient (12)

The use of-inotropic-agents-are inevitable. Dopamine should be used if shock can not be relieved by fluid replacement therapy alone (11, 17, 20). Dopamine is presently the drug of first choice among the septic shock because it increases myocardial contractility, redistributes blood flow to central viscera, and can be titrated to obtain different pharmacologic effects. The agent has alpha and beta effects midway between dose of isoproterenol and epinephrine. An infusion of 1.5 /ig/Kg/min increases

Table — 5

The Dosage, Method of Application and Incompatibilities of Dopamine

iv onset	: 2 to 4 minutes
duration	: 10 minutes
dosage	: 1-2 /Jg/kg/min = dopaminergic effect 2-10 /ig/kg/min = predominantly beta effect 10 /ig / kg/ m = predominantly alpha effect 20 g/kg/min = same effects as norepine phrine
incompatibilities	: Alkalosis and oxidizing agents decompensa drag (HCO_3 and aminaphylline), ampicillin.

cardiac output, renal blood flox and urine output. With large doses, up to 30 /ig/Kg/min there is a further increase in cardiac output (12, 13, 17). For infants and children, a solution of dopamine (0.8 /Ug/ml) in five percent dextrose-in-water is prepared. The infusion is adjusted to run at a rate of 1 to 3 /ig/Kg/min, The dose is gradually increased if urine output and hemodynamic function do nat improve (3, 12).

SPECIAL DRUGS

The beneficial actions of corticosteroids in patients with septic shock include stabilization of lysosomal and cell membrane activity, inhibition of complement-induced granulocyte aggregation, improved myocardial performance, a rightward shift in the oxygen-hemoglobin dissocitation curve, and improvement in metabolic defects (19, 21).

Some conditions causing septic shock (e.g. meningococemia with adrenal hemorrhage) are associated with glucocorticoid deficiency and replacement therapy is warrented. one must be aware of the fact that, cordicosteroids are not a substitute for adequate supportive and antibiotic therapy. If administered, cordicosteroids are to be given early, in large doses and continued for no longer than 24 hours (4, 20).

The clinical data about the corticosteroid doses, are clearly different from each other; 15-150 mg/Kg/-day of methylprednisolone or 6-10 mg/Kg/day of dexamethasone or 50-100 mg/Kg of hydrocortsone have been recommended (3, 4, 5, 11, 21). The drugs must be given intravenously in 10 minutes and can be repeated 4 times in a day if shock persists (2, 13, 21). Some patients can develop a complication due to the high dose of corticosteroids such as hyperglycemia, superinfections and gastrointestinal bleeding (2, 4).

Corticosteroids do nat improve the overall survival of patients with sever e late septic shock but may be helpful early in course and only in certain groups of patients.

50-100 Units/Kg heparin is given intravenously initially followed by 500-1000 Units every hour by continuous intravenous drip. Response to heparin is indicated by slowing of factor V and VIII and of fibrinogen. Platelet counts may rise at a slower rate. Heparin therapy is discontinued when the cause of DIC is corrected and coagulation factors are restored to homeostatic levels (13, 20).

Preliminary animal and clinical trials have shown that administration of narcotic antagonists such as naloxone may reverse the hypotension associated with septic shock. Administration of naloxone 1 mg/Kg as an intravenous bolus, followed by 0.7 mg/Kg/h by continuous intravenous infusion has been suggested (18).

Prostacyclin or prostaglandin 1_2 ($PG\ I_2$) and thromboxane A_2 ($TX\ A_2$) are members of the prostaglandin family that have an important cardiovascular regulatory function in healt and disease. It was 20 years ago when researchers first discovered that nonsteroid anti-inflammatory agents protected against some effects of endotoxic shock (2, 11).

Gram-negative sepsis and shock frequently occur in older patients with congestive failure or may precipitate cardiac failure in patients with limited cardiac reserve. In these instances digitalis can be administered cautiously in full doses, although toxicity may occur if the patient is hypokalemic (19). In addition, the urine output of these patients should be increased, preferably with intravenous frosemide (11).

An urinary catheter is placed in the bladder to monitor the urine output. The catheter is removed once the patient's condition stabilizes; usually in 12-24 hours.

ANTIBIOTIC TREATMENT

Examination throughly and rapidly of the patient for an obvious source of infection is essential. A special attention has to be paid to the following sites;

- skin and nails
- all joints and vertebrae
- presence of signs of meningeal irritation
- presence of heart murmurs or abnormal lung sounds are checked for, while examination of the abdomen and rectum can surface underlined infections

Table 6

Suggested Empiric Antibiotics in Septic Shock

Suspected Site of Infection or Predisposing Factor	Common Pathogens	Antibiotics (doses are under the table)
Genitourinary tract.	Aerobic gram-negative bacilli (E. cob. Klebsiella, Proteus, Pseudomonas); group D streptococci	Ampicillin 4- aminoglycoside
Respiratory tract	Streptococcus pneumoniae; Staphylococcus aureus; aerobic gram-negative bacilli; anaerobes	Penicillin G or clindamycin 4- aminoglycoside
Below the diaphram Intra-abdominal abscess; decubitus ulcers; pelvic or perirectal abscess	Aerobic, gram-negative bacilli; anaerobes (including Bactcriodes rraqilis)	Clindamycin + aminoglycoside
Biliary tree-	Aerobic gram-negative bacilli, group D streptococci; anaerobes	Ampicillin 4- aminoglycoside (clindamycin may be added)
Skin, bone or joint	S. aureus, streptococci; aerobic gram-negative bacilli; Clostridium or other anaerobes	Natcillin, oxacillin or methieillin; aminoglycoside or clindamycin may be added.
Immunocompromised host (immunosuppressive drugs; corticosteroids, cancer)	Aerobic gram-negative bacilli (including Pseudomonas); staphylococci; yeast (especially Candida albicans)	Cefotaxime 4- aminoglycoside
Unknown	S. pneumoniae. S. aureus; Neisseria meningitis, aerobic gram-negative rods	Ampicillin r aminoglycoside (Nafciliin may be added)

Doses are lor patients with normal renal and hepatic function:
Ampicilhn : 150-200 mg/kg/c! iv. in 4 divided doses
Gentamicin or tobramycin : 5-6 mg/kg/d iv. in 3 divided doses
Penicillin G : 20-24 million units iv, in 6 divided doses
Clindamycin : 30-40 mg/kg/d iv. in 3 divided doses
Cefazolin : 100 mg/kg/d iv. in 3 divided doses
Nafciliin, oxacillin or methieillin : 150 mg/kg/d iv. in 4 divided doses
Cefotaxime : 200 mg/kg/d (up to 12 g) iv. in 4 divided doses

— bimanual pelvic examination must be performed in ill female patients.

Antibiotic treatment should be specific for the infecting organism verified by aerobic and anaerobic culture techniques. However the causative agent is frequently not known when the patient presents for treatment. Empiric antibiotic therapy chosen on the basis of "an-educated-best-guess" about the possible causative organisms may be used until the infectious agent is positively identified.

Provision of the surgical treatment as required will be most helpful. Antibiotics and volume replacement are fruitless if the physician fails to incise and drain abscesses or débride infected necrotic tissue. Thereforepossible sources of sepsis (e.g. intra-abdominal abscesses, biliary obstruction with cholangitis, perirectal abscesses, septic abortion) must be identified and dealt with surgically as well (19, 20).

DISCUSSION

Many studies show that the average complication rate in septic shock is around 55 percent (1, 3, 5, 9, 11, 20, 21).

Patients are also evaluated for complication of septic shock, including the respiratory-distress syndrome (diffuse bilateral pulmonary infiltrates and hypoxemia), gastro-intestinal bleeding, acute renal failure, disseminated intravascular coagulation and acute myocardial infarction (typical ECG and cardiac enzymatic changes). Complications may be determined by pathologic evidence found at autopsy as well (9, 11, 13, 18, 21).

The overall mortality in septic shock ranges from 50 to 90% (3, 5, 9, 13, 20, 21). If mild to moderate lactic acidemia is present, the prognosis is better than the severe types. Poor results often follow due to the failure to institute therapy soon enough O ce severe lactic acidemia and decompasated metabolic acidosis become established, shock is often irreversible despite therapy. Since most patients who are likely to develop septic shock are in the hospital before the symptoms and signs of shock appear, this grave complication of infection is often avoidable by aggressive care.

Sprung has noted that girls with septic shock syndrome showed a trend toward less severe illness than boys commonly based on to the hormonal structure of RES and immunologic basis suggested by the presence of a locus on the X-chromosome involved with immunoglobulin synthesis (19).

In the treatment of neonatal sepsis, the succesful use of unmatched granulocyte transfusions has been reported by Laurenti et al. (7, 8). In the past, it was believed that white blood cell transfusions were effective only if the donor cells matched these of the recipient.

Saba and coworkers reported that reticuloendotelial system plays an essential role in removing bacterial byproducts, particularly endotoxin from the circulation during infection (14). An alpha-2 opsonic glycoprotein must be present in the plasma for the cells of the RES to act as phagocytes. Since concentration of glycoprotein is reduced by trauma and infection and that cryoprecipitated plasma contains a high concentration of the opsonic glycoproteins, cryoprecipitated plasma may be used in the treatment of such infected patients. Thes also reported a reduction in septic complications in burnt patients. Reduced levels of opsonic glycoprotein were restored by infusion of cryoprecipitated plasma (14).

The efficacy of crystalloid versus colloid cantain ing solutions in resuscitation of the patient in shock is still controversial (1, 11, 13, 17). The two solutions most commonly compared are Ringer's lactate and five percent human albumin in normal saline or plasma. Colloid containing fluids have the advantage of increasing colloid oncotic pressure. However, Rowe suggested that initial fluid replacement should use crystalloid solutions such as balanced salt solutions, since capillary endotelial integrity is damaged and administration of colloid solutions may result in extravasation of protein into the interstitum, thus aggravating interstitial edema (13).

Isoproterenol as an inotropic agent counteracts arteriolar and venous constriction in the microcirculation by its direct vasodilating effect. In addition, the drug exerts a direct inotrophic effect on the heart. Cardiac output is increased by stimulation of the myocardium and by reduction of cardiac work as peripheral resistance decreases. The dose of isoproterenol is 2-3 *¡Jtg* per minute for children. Ventricular dysrhythmias may result from this drug, and shock may be aggravated if fluid administration does not keep pace with relieved vosoconstruction (5, 9, 11, 20).

Sprung has noted corticosteroids when given acutely in septic shock may not alter phagocytosis or the bactericidal activity of neutrophils, although monocyte function may be affected The negative effects are more pronounced when corticosteroids are given at high doses and forlong periods (19).

Sprung also reported that shock state was not improved by the use of methylprednisolone or dexamethasone in their patients. However, corticosteroids did result in short-term improvements in the first 24 hours of the recognized state andwere beneficial for certain groups of patients (19). It is also possible that corticosteroids only delay the ultimate mortality of patients in severe, late septic shock (4).

The ability of corticosteroids to improve ultimate survival may be related to several factors. The first is the requisition of average dopamine concentration of 21.0 jUg/Kg/min at the time of corticosteroid therapy (19). A second factor as reported by Sheagren; is that corticosteroids may be effective even late in septic shock (16). The third cause, noted by Sprung, is the corticosteroids' lack of efficacy in improving the survival of their patients that may be related to cardiac function (19).

Comparable pharmacologic doses of methylprednisolone (30 mg/Kg) and dexamethasone (6 mg/Kg) were equally effective in reducing the mortality among patients in septic shock (15). However methylprednisolone sodium succinate penetrates cellular compartments faster than dexamethasone phosphate, as noted by Wilson (22). Gn the other hand, dexamethasone acts for a longer period than methylprednisolone, therefore the patients treated with dexamethasone may have had a higher incidence of superinfection. However, there seems to be no difference in the overall mortality or reversal of shock between dexamethasone treated patients and methylprednisolone treated patients or in controls (4, 19, 22).

Prostacyclin or prostaglandin 1₂ (PG I₂) and thromboxone A₂ (TX A₂) are potent, endogenously produced, vasoactive substances that have been implicated as mediators in thepathophysiologic nature of septic shock. Carmona and coworkers investigated the contribution and production of PG 1₂ and TX A₂ in sepsis and septic shock, using an intact rabbit model and an invitro rabbit isolated cardiac perfussion model. Continuous hemodynamic

monitoring of both experimental models, along with serial radioimmunoassays of the metabolites of PG 1_2 and TX A_2 indicated that myocardial depression is a common finding in subjects with septic shock and that septic shock causes a suppression of PG 1_2 production while augmentation TX Aj production. In addition, PG I_2 and TX A_2 tere mediators of some cardiovascular changes in septic shock but were themselves not the toxic factor (s) responsible for the associated myocardial depression (2).

In the recent 10 years physiologists have admitted that there are endogen opiate antagonists (endorphines) in brain and blood circulation, which are located in the hypophysial ACTH secreting cells. Releasing of ACTH and endorphines follow the same stages of stress. Therefore it is though that the endorphine antagonist such as naloxone can treat the hypotension in septic shock, and the results are impressive (13, 18, 20).

Septic shock usually is recognized too late; too often after irreversible changes have already taken place since many patients who are likely to develop septic shock are in hospital surroundings; when signs and symptoms of shock appear, it is essential to watch patients closely who are candidates for the development of shock. One must treat the causative infections vigorously and early enough to perform appropriate surgery before catastrophic complications do occur. There is strong preliminary evidence that early therapy of septic shock improves the ultimate outcome.

Always beign ahead of the pathophysiological-expectant changes require a well trained and alert physician.

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