INTERNATIONAL JOURNAL OF PAEDIATRICS AND GERIATRICS

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Clinical profile of children aged between 1 to 15 years with acute systemic infections attending tertiary care hospital

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DOI: https://doi.org/10.33545/26643685.2020.v3.i1a.54

Abstract
Sepsis is a common, life-threatening condition in the pediatric ICU. Severe sepsis and septic shock occurs in all settings and age groups and many of these children often have associated co-morbidities such as prematurity or malignancy. However, in the community at large, recent epidemiologic data indicate that more than half the cases of severe sepsis occur in children without a predisposing condition.
Presence of two or more of the following symptoms, i.e. temperature instability (core temp >38.5/<36), tachycardia/bradycardia, tachypnea or mechanical ventilation, leukocytosis/leucopenia. Sepsis is SIRS with infection. Clinical features and laboratory parameters in patients with sepsis, viral hemorrhagic fever and other acute systemic infections were noted. Details of blood component therapy as administered to them were noted along with the reasons and indication for doing so. Of the total 178 cases included in the study, mortality was noted at 18.6% (33 patients). In the septicemia group, the mortality rate was higher (52.9%) as compared with the viral hemorrhagic group (13.1%) which was statistically significant ($P<0.001$).

Keywords: Clinical profile, children, acute systemic infections

Introduction

The majority of admissions in PICU, requiring blood component therapy in our study were due to viral hemorrhagic fever of which dengue infections are an important part. Dengue infection is a systemic and dynamic viral infection with a wide clinical spectrum-ranging from flu like illness to severe dengue-which can be fatal.

It is a transmitted by the bite of an infected female Aedes mosquito. The infection causes flu-like illness, and occasionally develops into a potentially lethal disease called severe dengue. Symptoms appear in 3-14 days (average 4-7 days) after the infective bite. It is a caused by a flavivirus with four distinct serotypes (DV-1, DV-2, DV-3, and DV-4).The exact pathophysiology of severe dengue infection (dengue hemorrhagic fever and dengue shock syndrome) is still an enigma, although it is now widely accepted that the host immune system, host genetic makeup, and pathogen virulence all contribute towards the rapid deterioration seen in some patients [1].

All the four dengue virus strains may cause the infection to be asymptomatic or may lead to undifferentiated fever, dengue fever (DF) or dengue haemorrhagic fever (DHF) with plasma leakage that may lead to hypovolemic shock and the dengue shock syndrome (DSS). The WHO reports that in 2012, dengue ranked as the fastest spreading vector-borne viral disease in the world, registering a 30-fold increase in incidence over the past 50 years [2].

The global incidence of dengue has grown dramatically in recent decades with over 2.5 billion people, comprising over 40% of the world's population, now at risk. The WHO currently estimates there might be 50-100 million dengue infections worldwide every year including 500,000 with severe dengue who require hospitalization of which, a large proportion are children. About 2.5% of those affected die. The disease is a major public health problem in our country. Epidemics closely follow seasonal climatic change with waves of cases following each rainy season. During an epidemic, thousands may be affected. Most of them recover from a simple febrile illness, but a small though significant proportion go on to develop the dengue shock state with associated fatalities. In many affected areas, this adds to a significant case fatality rate, predominantly among young children [3].

Dengue viruses cause symptomatic infections or asymptomatic seroconversion. Symptomatic dengue infection is a systemic and dynamic disease.

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It has a wide clinical spectrum that includes both severe and non-severe clinical manifestations. After the incubation period, the illness begins abruptly and in patients with moderate to severe disease, is followed by three phases-febrile, critical and recovery. Due to its dynamic nature, the severity of the disease will usually only be apparent around defervescence i.e. during the transition from the febrile to the afebrile phase, which often coincides with the onset of the critical phase [4].

Sepsis is a common, life-threatening condition in the pediatric ICU. Severe sepsis and septic shock occurs in all settings and age groups and many of these children often have associated co-morbidities such as prematurity or malignancy. However, in the community at large, recent epidemiologic data indicate that more than half the cases of severe sepsis occur in children without a predisposing condition.

Presence of two or more of the following symptoms, i.e. temperature instability (core temp >38.5/<36), tachycardia/bradycardia, tachypnea or mechanical ventilation, leukocytosis/leucopenia. Sepsis is SIRS with infection [5].

The vascular endothelium is both a source and target of injury in SIRS/sepsis. Injury may be due to toxins such as LPS (endotoxin) or from ischemia itself. Tissue factor release leads to amplification of the inflammatory response and to DIC via the thrombin pathway. Thrombin not only catalyzes fibrin formation but also causes leukocyte adhesion which leads to further endothelial damage. As DIC progresses, clotting factors such as pro-fibrinolytic and anti-thrombin factors are consumed and bleeding occurs and thereafter progresses to fibrinolysis & normal down-regulation of thrombin pathway. This phenomenon is both pro-inflammatory and pro-thrombotic [6].

Protein C depletion has been associated with increased mortality. In meningococcemia, protein C depletion can be profound and is associated with large vessel thrombosis (purpura fulminans) as well as mortality. This has led to a series of clinical trials utilizing protein C, activated protein C (APC), antithrombin III (AT-III), and tissue factor pathway inhibitor to try and disrupt this cycle. Activated protein C has in fact been shown to reduce mortality in severe sepsis in adult.

Inflammatory cytokines, such as produced in sepsis, play a major role in alterations in iron metabolism, leading to decrease serum iron levels. These inflammatory cytokines (TNF-a, IL-1β, and IL-6) also increase iron storage by the reticuloendothelial system, limiting the availability of iron for erythropoiesis. Anti-inflammatory cytokines, like IL-10, also play a role in iron metabolism by increasing heme degradation and iron storage in monocytes and, thus, contributing to iron retention in the reticuloendothelial system.

Serum erythropoietin is the growth factor responsible for erythropoiesis, and is produced in the kidneys. Erythropoietin levels below those expected for the degree of anemia have been demonstrated in septic and critically ill patients. There is evidence that inflammatory cytokines play an inhibitory role on erythropoietin production as well as a direct inhibitory effect on erythroid progenitor cell production in the bone marrow.

In addition to their significant contribution to all of the above pathogenic mechanisms in anemia, inflammatory mediators play other important roles in anemia of sepsis.

The proinflammatory cytokines decrease erythrocyte survival time. And quite often, functional and structural changes are found in erythrocytes. These changes are very similar to the changes that are present in naturally aged populations of erythrocytes, including decreased red blood cell deformability and antioxidant activity, decreased hemoglobin content, and increase in oxidatively modified lipids and proteins. Oxidative stress and free radicals that develop from inflammation in sepsis can also trigger RBC apoptosis by opening Ca2+- channels.

Methodology
Sample: All children between the age of 1 year to 15 years admitted to PICU at our teaching Hospital over a 24 month period with acute systemic infections were evaluated.

Group 1: Included those cases with clinical and laboratory evidence of viral hemorrhagic fever who had received blood component therapy

Group 2: Included those cases with clinical and laboratory evidence of sepsis who had received blood component therapy

Group 3: Included other systemic infections who had received blood component therapy

They were further subdivided into different age groups of 1-5yrs, 6-10yrs, 11-15yrs and a detailed analysis was made with regard to type and number of transfusions administered to these patients and their clinical outcome as determined by duration of hospital stay, mortality and significant morbidity.

Method of data collection
Clinical features and laboratory parameters in patients with sepsis, viral hemorrhagic fever and other acute systemic infections were noted. Details of blood component therapy as administered to them were noted along with the reasons and indication for doing so.

Inclusion criteria
All PICU admissions within the age of 1year to 15 years, who had features of acute systemic infection, as detailed below, were studied.

Exclusion criteria
- Post traumatic cases developing sepsis
- Hematological conditions which require component therapy Post-surgical cases
- Malignancies Metabolic diseases
- Children aged <1 year and >15 years
- Children of parents who did not consent for the study

Statistical methods
Descriptive statistical analysis was carried out in the present study. All the 178 patients were divided into three groups namely, the viral hemorrhagic group, the septicaemia group and other acute systemic infections.

Analysis of variance (ANOVA) has been used to find the significance of study parameters between three or more groups of patients, Chi-square/Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

Statistical software

The statistical software namely SPSS version 20.0, was used for the analyzing the data. Microsoft Excel was used to generate graphs, tables etc. Microsoft Word was used to draft and format the study.

Results

Table1: Age distribution of patients studied

Age in years	Diagnosis			Total
	VHF	Septicemia	Others	
1-5 years	42(27.3%)	9(52.9%)	4(57.1%)	55(30.9%)
5-10 years	53(34.4%)	3(17.6%)	2(28.6%)	58(32.6%)
10-15 years	59(38.3%)	5(29.4%)	1(14.3%)	65(36.5%)
Total	154(100%)	17(100%)	7(100%)	178(100%)

The age distribution of the entire study series was equally distributed among three subgroups. However, when correlating the age with the various diagnosis in the study, it was found that in VHF cases, a majority of the children were above 5yrs of age, while in the sepsis group a majority of the patients were below the age of 5. The difference was statistically significant (p=0.117).

Table 2: Gender distribution of patients studied

Gender	Diagnosis			Total
	VHF	Septicemia	Others	
Male	83(53.9%)	5(29.4%)	2(28.6%)	90(50.6%)
Female	71(46.1%)	12(70.6%)	5(71.4%)	88(49.4%)
Total	154(100%)	17(100%)	7(100%)	178(100%)

While observing the gender distribution in the series, the overall distribution of cases was found equal among both the sexes. However when analyzing the study under the various diagnosis, it was found that while males suffered more with VHF, it was female preponderant population who suffered from septicemia. The differences were again significant (p=0.075).

Table 3: Total duration of hospital stay

Total duration of stay	Diagnosis			Total
	VHF	Septicemia	Others	
≤2 days	17(11%)	5(29.4%)	4(57.1%)	26(14.9%)
2-5 days	21(13.6%)	3(17.6%)	0(0%)	24(13.8%)
6-10 days	103(66.9%)	4(23.5%)	2(28.6%)	109(62.6%)
11-20 days	13(8.4%)	5(29.4%)	1(14.3%)	19(10.9%)
>20 days	0(0%)	0(0%)	0(0%)	0(0%)
Total	154(100%)	17(100%)	7(100%)	178(100%)

Mean duration of stay in hospital was approximately 6-10 days in all three groups studied (P=0.361) i.e. viral hemorrhagic fever, septicemia and other acute systemic infections.

Table 4: Requirement of ventilatory support in the study group

Ventilatory support	Diagnosis at admission			Total
	VHF	Septicemia	Others	
Yes	25(16.2%)	11(64.7%)	4(57.1%)	40(22.5%)
No	129(83.8%)	6(35.3%)	3(42.9%)	138(77.5%)
Total	154(100%)	17(100%)	7(100%)	178(100%)

Of the total of 178 cases, ventilatory support was required in 40 cases (22.5%) of which a majority (64.7%) cases were in the septicemia group, indicating significant morbidity in this group of patients who required blood component therapy.

Table 5: Distribution of Mortality in the study group

Morality	Diagnosis			Total
	VHF	Septicemia	Others	
Yes	20(13.1%)	9(52.9%)	4(57.1%)	33(18.6%)
No	134(86.9%)	8(47.1%)	3(42.9%)	145(81.4%)
Total	154(100%)	17(100%)	7(100%)	178(100%)

Of the total 178 cases included in the study, mortality was noted at 18.6% (33 patients). In the septicemia group, the mortality rate was higher (52.9%) as compared with the viral hemorrhagic group (13.1%) which was statistically significant (*P*<0.001).

Discussion

All the children in this study series were equally distributed among three age subgroups. However, when correlating the age of these children with the various diagnosis in the study, it was found that in VHF cases, a majority of the children were above 5yrs of age, while in the sepsis group a majority of the patients were below the age of five. This is quite on expected lines, as younger children are more prone to infections due to their compromised immune status while VHF being an immunologically triggered disease is likely to occur in the more immuno competent older child.

While observing the gender distribution in the series, the overall distribution of cases was found to be equal among both the sexes. However, analyzing the study under the various diagnosis, it was found that while males suffered more with VHF, it was a female preponderant population who suffered more from septicemia. This is entirely explained by the realization that boys tend to sleep more outdoors and with lesser clothes in the summer heat than girls and hence expose themselves more to the dreaded mosquito bites [7].

Dengue Shock Syndrome (DSS) is a life threatening clinical manifestations of infection due to dengue virus. The clinical features of DHF/DSS are due to bleeding diathesis and increased capillary leak. The mechanisms of hemorrhagic manifestations in DHF/DSS are not well understood. The suggested factors contributing to bleeding include thrombocytopenia, coagulopathy and vasculopathy. Suggested mechanism for thrombocytopenia include maturation arrest of megakaryocyte production in the bone marrow, platelet destruction by the virus itself or Disseminated Intravascular Coagulation (DIC).

Dengue hemorrhagic fever (DHF) and Dengue shock syndrome (DSS) is characterized by increased capillary permeability, thrombocytopenia, and coagulopathy. Several studies have observed that the severity of thrombocytopenia does not predict bleeding and that other factors such as platelet dysfunction and a prolonged duration of shock leading to potentiation of the disseminated intravascular coagulation state may play important roles. There are no clear guidelines on the role of transfusions of platelet concentrates (PC) and/or fresh frozen plasma (FFP) in DHF/DSS. Nonetheless, these have been prescribed for many DHF/DSS patients with thrombocytopenia and coagulopathy, in an attempt to prevent bleeding. There is, however, no evidence to support that transfusions are of any benefit. On contrary, the risks of these therapies are fluid overload, prolonged hospitalization, and blood- borne infections. Hence, the liberal use of blood products in the

treatment of DSS increases the risk to life of the patient, in addition to the unnecessary cost and an incorrect focus in the treatment [8]

Blood products such as red blood cells (RBCs), fresh frozen plasma (FFP), and platelets are commonly used in septic patients as in other critically ill patients. Appropriate use is necessary in view of the limited supply and potential risk to patients. There are few clinical trials that specifically evaluate the use of blood products in patients with severe sepsis or septic shock.

Sepsis is very common lethal and the leading cause of death in non-coronary Intensive Care Units, and the tenth leading cause of death overall. Red blood cell transfusion is one of the most commonly used interventions in the ICU to treat severe anemia, which often occurs in sepsis. Several problems were documented with RBC transfusions earlier, such as infection, pulmonary complications such as TRALI and Transfusion-Associated Circulatory Overload (TACO), Transfusion-Related Immunomodulation (TRIM), multiorgan failure, and increased mortality.

The effects of RBC transfusion on the microcirculation in sepsis are numerous. Several studies have demonstrated that RBC rheology is impaired (increased aggregation, decreased deformability, alterations of RBC shape) in recipient RBCs in septic patients. The RBC in health acts as an oxygen sensor, which can modulate tissue oxygen flow by the release of the vasodilators, nitric oxide or ATP.

The release of vasodilators from RBCs during hypoxia could be impaired during storage and/or sepsis. Storage of RBCs decreases levels of 2, 3-diphosphoglycerate and Adenosine Triphosphate (ATP) with a resultant increase in oxygen affinity and a decrease in the ability of hemoglobin to offload oxygen. Morphological changes in erythrocytes occur during storage which may result in increased fragility, decreased viability, and decreased deformability of red blood cells. A number of substances are released during storage resulting in such adverse systemic responses as fever, cellular injury, alterations in regional and global blood flow, and organ dysfunction [9].

Most of these complications are partially explained by the volume of blood transfused as well as pathogenic factors of stored RBCs relating to 2, 3 DPG concentration, inflammatory mediators, nitric oxide, ATP concentration, RBC rheology, and RBC adhesion characteristics. These same factors are present in the RBCs of septic patients as well. RBC transfusions are truly indicated in patients with evidence of hemorrhagic shock. Otherwise a-restrictive‖ strategy of RBC transfusion (transfuse when Hb <7 g/dL) in patients with hemodynamically stable anemia is desirable. In the absence of acute hemorrhage, RBC transfusions should be given as single units.

Although the optimum haemoglobin for patients with severe sepsis has not been specifically investigated, data from the Transfusion Requirements in Critical Care (TRICC) trial suggests that a hemoglobin of 7-9 g/dl (70-90 g/L) is adequate for most critically ill patients. A transfusion threshold of 7 g/dl (70 g/L) was not associated with an increase in mortality rate. This recommended transfusion threshold contrasts with the target of a hematocrit of 30% in patients with low central venous oxygen saturation during the first 6 hrs of resuscitation of septic shock.

Routine use of FFP to correct laboratory clotting abnormalities in the absence of bleeding or planned invasive procedures is not recommended. FFP is indicated for coagulopathy due to documented primary or secondary deficiency of coagulation factors (increased prothrombin time, international normalized ratio, or partial thromboplastin time) in the presence of active bleeding or before surgical or invasive procedures [10].

FFP is often used in critically ill and septic patients to correct factor deficiencies that occur as a result of an acquired coagulopathy, such as disseminated intravascular coagulation (DIC), although clinical studies have not assessed the impact of FFP transfusion on critically ill patients. It would be far more beneficial if the triggering condition must be aggressively treated. The routine use of FFP to correct laboratory abnormalities in the absence of bleeding is not recommended. FFP transfusion is also appropriate if reversal of the warfarin (anticoagulant) effect is needed immediately. Doses of FFP should be chosen to achieve factor levels of 30% of normal values (usually 10-15 ml/kg).

Disseminated intravascular coagulation is a frequent complication of sepsis. Coagulation activation, inhibition of fibrinolysis, and consumption of coagulation inhibitors lead to a procoagulant state resulting in inadequate fibrin removal and fibrin deposition in the microvasculature. As a consequence, microvascular thrombosis contributes to promotion of organ dysfunction. Recently, three randomized, double-blind, placebo-controlled trials investigated the efficacy of antithrombin, activated protein C (APC), and tissue factor pathway inhibitor, respectively, in sepsis patients. A significant reduction in mortality was demonstrated in the APC trial.

Systemic inflammation during sepsis leads to the generation of proinflammatory cytokines that, orchestrate coagulation and fibrinolytic activation. Both coagulation activation as well as down-regulation of fibrinolysis are principally regulated by tumor necrosis factor (TNF), interleukin (IL)-1, and IL-6.The hallmark of the coagulation disorder in sepsis is the imbalance between intravascular fibrin formation and its removal [11].

Blood products such as red blood cells (RBCs), fresh frozen plasma (FFP), and platelets are commonly used in septic patients as in other critically ill patients. Appropriate use is necessary in view of the limited supply and potential risk to patients. There are few clinical trials that specifically evaluate the use of blood products in patients with severe sepsis or septic shock.

In the absence of extenuating circumstances and following resolution of tissue hypoperfusion, red blood cell transfusion should be targeted to maintain hemoglobin at 7.0 g/dL or greater. Erythropoietin is not recommended as a specific treatment for sepsis- associated anemia. Fresh-frozen plasma should be given for documented deficiency of coagulation factors and in the presence of active bleeding or before surgical or invasive procedures. Antithrombin administration is not routinely recommended. Specific platelet transfusion thresholds are based on the presence or absence of bleeding, significant risk for bleeding, and/or platelet count <10,000/mm3 [12].

Conclusion
Of the total 178 cases included in the study, mortality was noted at 18.6% (33 patients). In the septicemia group, the mortality rate was higher (52.9%) as compared with the viral hemorrhagic group (13.1%) which was statistically significant (P<0.001).

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