

Hemodynamic Support in Fluid-refractory Pediatric Septic Shock

Gary Ceneviva, MD*‡; J. Alan Paschall, MD||¶; Frank Maffei, MD‡; and Joseph A. Carcillo, MD, FAAP*‡§||

ABSTRACT. *Objective.* Assess outcome in children treated with inotrope, vasopressor, and/or vasodilator therapy for reversal of fluid-refractory and persistent septic shock.

Design. Survey; case series.

Setting. Three pediatric hospitals.

Patients. Fifty consecutive patients with fluid-refractory septic shock with a pulmonary artery catheter within 6 hours of resuscitation.

Interventions. Patients were categorized according to hemodynamic state and use of inotrope, vasopressor, and/or vasodilator therapy to maintain cardiac index (CI) >3.3 L/min/m² and systemic vascular resistance >80 dyne-sec/cm⁵/m² to reverse shock.

Outcome Measures. Hemodynamic state, response to class of cardiovascular therapy, and mortality.

Results. After fluid resuscitation, 58% of the children had a low CI and responded to inotropic therapy with or without a vasodilator (group I), 20% had a high CI and low systemic vascular resistance and responded to vasopressor therapy alone (group II), and 22% had both vascular and cardiac dysfunction and responded to combined vasopressor and inotropic therapy (group III). Shock persisted in 36% of the children. Of the children in group I, 50% needed the addition of a vasodilator, and in group II, 50% of children needed the addition of an inotrope for evolving myocardial dysfunction. Four children showed a complete change in hemodynamic state and responded to a switch from inotrope to vasopressor therapy or vice versa. The overall 28-day survival rate was 80% (group I, 72%; group II, 90%; group III, 91%).

Conclusions. Unlike adults, children with fluid-refractory shock are frequently hypodynamic and respond to inotrope and vasodilator therapy. Because hemodynamic states are heterogeneous and change with time, an incorrect cardiovascular therapeutic regimen should be suspected in any child with persistent shock. Outcome can be improved compared with historical literature. *Pediatrics* 1998;102(2). URL: <http://www.pediatrics.org/cgi/content/full/102/2/e19>; *inotropes, vasodilators, vasopressors, septic shock, hemodynamics.*

ABBREVIATIONS. PALS, pediatric advanced life support; CO, cardiac output; MAP-CVP, mean arterial blood pressure-central venous blood pressure; SVR, systemic vascular resistance; PCWP, pulmonary capillary wedge pressure; CI, cardiac index; SVRI, systemic vascular resistance index; ANOVA, analysis of variance; PICU, pediatric intensive care unit.

From the Departments of *Anesthesiology and Critical Care Medicine and †Pediatrics, and the ‡Center for Clinical Pharmacology, University of Pittsburgh, Pittsburgh, Pennsylvania; the §Department of Anesthesiology and Critical Care Medicine, Children's National Medical Center, Washington, DC; and the ¶Department of Pediatric Critical Care Medicine, Mary Bridge Children's Hospital, Tacoma, Washington.

Received for publication Jun 18, 1997; accepted Apr 14, 1998.

Reprint requests to (J.A.C.) Division of Critical Care Medicine, Children's Hospital of Pittsburgh, 3705 5th Ave, Pittsburgh, PA 15213.

PEDIATRICS (ISSN 0031 4005). Copyright © 1998 by the American Academy of Pediatrics.

We described previously the use of aggressive fluid resuscitation (60 mL/kg) in children with septic shock.¹ The high incidence of capillary leak syndrome, vasodilatation, and decreased fluid intake in children with sepsis causes a relative hypovolemia and a decreased preload. Pediatric advanced life support (PALS) guidelines recommends 60 mL/kg fluid resuscitation during treatment of septic shock²; however, fluid-refractory shock frequently occurs because sepsis also impairs cardiac and vascular function.¹

Cardiac and vascular function can be assessed using the equation $Q = P/R$, in which Q = flow, P = pressure, and R = resistance. In this model, the flow of fluid through a tube increases if the change of pressure across the tube is increased or the resistance of the tube is decreased. This equation can be transformed to $CO = MAP-CVP/SVR$, with CO = cardiac output, $MAP-CVP$ = mean arterial blood pressure-central venous blood pressure, and SVR = systemic vascular resistance. CO increases with an increase in $MAP-CVP$ and or a decrease in SVR . CO decreases with a decrease in $MAP-CVP$ or an increase in SVR . Shock occurs when CO and/or SVR are abnormal.³⁻⁵

Threshold values of CO and SVR have been associated with improved outcome in sepsis. Pollack and colleagues^{6,7} reported that maintenance of CO (3.3 to 6.0 L/min/m²) was associated with increased survival in children, and Parker and associates⁸⁻¹⁰ reported that a decreased SVR was associated with increased mortality in adults with septic shock. Cardiovascular therapy for shock is directed according to the relative contribution of abnormal CO and/or SVR . When decreased CO contributes to shock, inotropic support is used to increase CO . If a high SVR contributes to a decreased CO , then the addition of a vasodilator to inotropic therapy is used to increase CO . When decreased SVR contributes to shock, vasopressor therapy is used to increase SVR ; if this decreases CO , then addition of an inotrope may be used to improve CO .

To our knowledge, evaluation of systemic hemodynamics and outcome in pediatric septic shock has not been reported after implementation of PALS recommendations for aggressive volume resuscitation. Because adult septic shock is commonly associated with the hyperdynamic-low vascular tone state, vasopressor therapy remains a mainstay;¹¹ however, age-dependent differences in cardiovascular mechanics may render this approach less appropriate in children. In the present study, we examined 50 children with septic shock unresponsive to 60 mL/kg fluid resuscitation. We report systemic hemodynamics, the use of cardiovascular therapies to maintain

prognostically favorable CO and SVR parameters, and outcome in children with fluid-refractory septic shock.

METHODS

Fifty consecutive children with fluid-refractory septic shock and a pulmonary artery catheter placed within 6 hours of resuscitation for a minimum of 48 hours, who were admitted to three pediatric intensive care units over a 4-year period (Children's National Medical Center, Washington, DC; Children's Hospital of Pittsburgh, Pittsburgh, PA; Mary Bridge Children's Hospital, Tacoma, WA) were observed. Need for signed informed consent was waived by the respective institutional review boards, and all confidentiality was maintained. All patients received aggressive fluid resuscitation with a minimum volume of 60 mL/kg in the first hour. Patients with shock refractory to fluid and the addition of inotropic or vasoactive support had pulmonary artery, central venous, and arterial catheters inserted within 6 hours of admission. All decisions to place catheters and obtain hemodynamic variables were made by housestaff and attending staff who were unaware that the study was being performed. All patients included in the study had full hemodynamic monitoring, and the smallest patient to receive a pulmonary artery catheter weighed 5 kg. All patients had either a positive blood culture finding or a strong clinical suspicion of infection based on the presence of fever or hypothermia, leukocytosis or leukopenia, and a source of infection. Pulmonary artery wedge pressure readings in patients were performed off positive pressure ventilation without measurable adverse outcomes. Ionized calcium concentrations were normalized in all patients. Cardiac outputs were measured in triplicate by thermodilution using a normal saline injectate. All hemodynamic variables using measurement of CO were indexed for body surface area.

Shock was defined as blood pressure <2 SD units below the mean for age and/or fulfilling at least three of the following criteria for decreased perfusion: 1) decreased peripheral pulses; 2) mottled or cool extremities; 3) tachycardia (heart rate >180 beats per minute for infants and >160 beats per minute for children); or 4) urine output <1 mL/kg/h if <30 kg and <0.5 mL/kg if >30 kg.^{6,7} Adequate volume loading was defined as a pulmonary capillary wedge pressure (PCWP) >8 and <16 mm Hg.¹ Fluid refractory shock was defined as ongoing shock after fluid resuscitation (≥ 60 mL/kg) had accomplished a PCWP >8 and <16 mm Hg. Persistent shock was defined as shock that persisted beyond the first 6 hours.

Children with septic shock were considered to have a significant cardiogenic abnormality contributing to the shock state if the cardiac index (CI) was <3.3 L/min/m² (normal range; 3.3 to 5.5 L/min/m²), and a significant vascular tone abnormality contributing to the shock state if the systemic vascular resistance index (SVRI) was <800 dyne-sec/cm⁵/m² (normal range; 800 to 1600 dyne-sec/cm⁵/m²).^{3-7,12} The use of the three classes of cardiovascular therapy to reverse shock and maintain CO and SVR was defined according to the following criteria. Inotrope use was defined as the use of dopamine between 5 and 10 μ g/kg/min dobutamine, amrinone, milrinone, epinephrine <0.3 μ g/kg/min or >0.3 μ g/kg/min with a vasodilator (ie, nitroprusside, nitroglycerin, or phentolamine) to increase CI and reverse shock in children with a CI <3.3 L/min/m² after fluid resuscitation.^{2,12-18} Vasopressor use was defined as the use of dopamine ≥ 10 μ g/kg/min, norepinephrine, phenylephrine, or epinephrine >0.3 μ g/kg/min to increase SVRI and reverse shock in children with an SVRI <800 dyne-sec/cm⁵/m² after fluid resuscitation.^{2,12-15} Vasodilator use was defined as the use of nitroprusside, nitroglycerin, or phentolamine to decrease SVRI and reverse shock in children with a CI <3.3 L/min/m² and a SVRI >1600 dyne-sec/cm⁵/m² after fluid resuscitation.^{12,19}

The children were categorized into three groups according to hemodynamic state after fluid resuscitation, placement of the pulmonary artery catheter, and initial adjustment of cardiovascular therapy. Group I had a low CI state (CI <3.3 L/min/m²) that initially responded to inotrope with or without vasodilator therapy. Group II had a low SVRI state (SVRI <800 dyne-sec/cm⁵/m²) that initially responded to vasopressor therapy alone. Group III had combined cardiac and vascular dysfunction that initially needed a combination of inotrope and vasopressor therapy to maintain CI and SVRI within normal range.

Hemodynamic variables in groups I, II, and III were analyzed after fluid resuscitation and pulmonary artery catheter placement, and every 8 hours for the first 48 hours after fluid resuscitation. Twenty-eight day and discharge from the pediatric intensive care unit (PICU) mortality rates were recorded. Kruskal-Wallis and Dunn tests (nonparametric distribution) were used to compare differences in CI and SVRI between groups after fluid resuscitation. Repeated-measures analysis of variance (ANOVA) was used to measure differences within groups over time. The Fisher's exact test was used to evaluate addition of a different class of cardiovascular therapy (ie, addition of vasodilator to children receiving inotrope therapy or addition of inotrope to children receiving vasopressor therapy) to reverse persistent shock. Logistic regression analysis was used to determine the influence of epidemiologic characteristics on hemodynamics and outcome. A *P* value <0.05 was considered significant.

RESULTS

Fifty children were diagnosed with septic shock refractory to ≥ 60 mL/kg fluid resuscitation and initial cardiovascular support over the 4-year PICU study. The age of the children was 6.7 ± 5.8 years (mean \pm SD; range, 2 months to 18 years). Forty-four of the 50 had culture-positive sepsis. Pathogens included Gram-positive bacteria (26%) and Gram-negative bacteria not including meningococcus (34%), meningococcus (18%), fungus (6%), and virus (4%). Of the 50 children, 29 had no underlying illness; 21 had a chronic illness including malignancy ($n = 9$), transplantation ($n = 4$ [2 bone marrow and 2 solid organ]), cerebral palsy/neurologic ($n = 4$), sickle-cell disease ($n = 2$), and spina bifida ($n = 2$). All patients had a PCWP >8 mm Hg at the time of evaluation of CI and SVRI.

All children were receiving cardiovascular therapies at the time of pulmonary artery catheter placement. After assessment of hemodynamic measurements, changes in therapy were directed to improving hemodynamic variables in 44 of 50 patients. Therapeutic maneuvers included 1) a complete change in cardiovascular therapy strategy (ie, change from vasopressor therapy to inotrope therapy in a patient with a low CO/high SVR state, or inotrope to vasopressor therapy in high CO/low SVR state); 2) the addition of a different class of cardiovascular therapy (ie, the addition of a vasodilator to a patient with a high SVR); 3) the addition of direct-acting catecholamines (ie, the addition of norepinephrine to a patient with dopamine-resistant low SVR or epinephrine to a patient with dobutamine-resistant low CO); and 4) an increase in dosage of an existing class of therapy (ie, an increase in dobutamine dose) (Table 1). The cardiovascular agents used to reverse fluid-refractory shock are shown in Table 2.

Inotropic therapy (with or without a vasodilator) was used to reverse shock in 58% of the children (group I), vasopressor therapy alone was used to reverse shock in 20% of the children (group II), and a combination of vasopressor and inotrope therapy was used to reverse shock in 22% of the children (group III). Group I had a lower CI and a higher SVRI than did groups II and III ($P < .05$; Kruskal-Wallis with Dunn's test) (Table 3).

Thirty-six percent of the children needed the addition of a different class of cardiovascular therapy to reverse persistent septic shock. By 48 hours, 68% of children in group I needed a vasodilator to reduce SVRI, maintain CI >3.3 L/min/m², and reverse persistent shock ($P < .05$, Fisher's exact test) (Table 4). CI

TABLE 1. Changes in Cardiovascular Therapies Instituted After Initial Evaluation of CI and SVRI

	Added Vasodilator	Added Catecholamines	Changed Therapy Regimen	Increased Class of Therapy
Group I	<i>n</i> = 8 Nitroprusside	<i>n</i> = 3 Epinephrine	<i>n</i> = 5 Changed from vasopressor to inotrope	<i>n</i> = 8 Increased or added new inotrope
Group II		<i>n</i> = 3 Norepinephrine	<i>n</i> = 2 Changed from inotrope to vasopressor	<i>n</i> = 4 Increased or added new vasopressor
Group III		<i>n</i> = 4 Epinephrine	<i>n</i> = 2 Changed from inotrope alone or vasopressor alone to inotrope and vasopressor	<i>n</i> = 1 Increased inotrope
		<i>n</i> = 2 Norepinephrine		<i>n</i> = 2 Increased vasopressor

TABLE 2. Dose Ranges of Cardiovascular Agents Used After Fluid Resuscitation and Initial Therapy Adjustment

	Inotrope ($\mu\text{g}/\text{kg}/\text{min}$)	Vasopressor ($\mu\text{g}/\text{kg}/\text{min}$)	Vasodilator ($\mu\text{g}/\text{kg}/\text{min}$)
Dobutamine	11.2 \pm 1.6 [5–40] (<i>n</i> = 26)		
Dopamine ^a	4.9 \pm .92 [4–8] (<i>n</i> = 11)	16 \pm 1.2 [12–20] (<i>n</i> = 13)	
Epinephrine ^b	0.13 \pm .04 [.05–.2] (<i>n</i> = 9)	.48 \pm .22 [0.3–2.0] (<i>n</i> = 9)	
Norepinephrine		.56 \pm .35 [0.1–3.0] (<i>n</i> = 8)	
Nitroprusside			2.2 \pm .7 [0.1–5.0] (<i>n</i> = 8)

Mean \pm SEM [range]; *n* = patients. Amrinone (*n* = 2), milrinone (*n* = 1), isoproterenol (*n* = 1), phenylephrine (*n* = 1), phentolamine (*n* = 1), and nitroglycerin (*n* = 1) were also used.

^a Dopamine inotrope range, 5–10; vasopressor range, >10 $\mu\text{g}/\text{kg}/\text{min}$.

^b Epinephrine inotrope range, <0.3 $\mu\text{g}/\text{kg}/\text{min}$ or >0.3 $\mu\text{g}/\text{kg}/\text{min}$ in presence of vasodilator.

TABLE 3. CI (L/min/m²) and SVRI (dyne/sec/cm⁵) in Groups I, II, and III After Fluid Resuscitation, Initial Therapy Adjustment, and 48 Hours

	After Fluid Resuscitation	After Initial Therapy Adjustment	48 Hours
Group I (<i>n</i> = 29)			
CI	3.06 \pm .26	3.3 \pm .16*	4.0 \pm .2**
SVRI	1794 \pm 176	1758 \pm 158*	1178 \pm 65**
Group II (<i>n</i> = 10)			
CI	8.51 \pm 1.1	6.3 \pm .75	5.06 \pm .41**
SVRI	622 \pm 184	919 \pm 99	1090 \pm 91**
Group III (<i>n</i> = 11)			
CI	3.93 \pm .28	4.37 \pm .26	5.07 \pm .29**
SVRI	922 \pm 87	904 \pm 65	1089 \pm 92

Values = mean \pm SEM.

* *P* < .05 difference group I versus group II and group III after fluid-resuscitation and initial therapy adjustment (Kruskal–Wallis with Dunn’s tests).

** *P* < .05 difference in hemodynamic variables over time within group compared with baseline after fluid resuscitation (repeated-measures ANOVA with Student Neuman–Keuls test).

increased and SVRI decreased when additional vasodilator therapy was used in this group of children (*P* < .05, repeated-measures ANOVA) (Table 3). Fifty percent of the children in group II needed the addition of inotropic therapy to maintain CI >3.3 L/min/m² and reverse persistent shock (*P* < .05, Fisher’s exact test) (Table 4). CI decreased but was maintained within the normal therapeutic range when inotrope therapy was added in this group of children (*P* < .05, repeated-measures ANOVA) (Table 3). Group III received no additional classes of therapy; however, vasopressor use decreased over the next 48 hours (Table 4). Systemic vascular resistance was maintained within the normal range, and CI increased with decreased use of vasopressor therapy in this group (*P* < .05, repeated-measures ANOVA) (Table 3).

TABLE 4. Classes of Cardiovascular Therapy Used After Fluid Resuscitation and Initial Therapy Adjustment, and Over First 48 Hours in Groups I, II, and III

Group I	After Fluid Resuscitation and Initial Therapy Adjustment 21 patients inotropes alone, 8 patients inotropes + vasodilators After 48 hours* (<i>P</i> < .05 addition of vasodilators, Fisher’s exact test) 8 patients inotropes alone, 19 patients inotropes + vasodilators, 1 patient inotrope + vasopressor, 1 patient vasopressor only
Group II	After Fluid Resuscitation and Initial Therapy Adjustment 10 patients vasopressor only After 48 hours (<i>P</i> < .05 addition of inotropes, Fisher’s exact test) 5 patients vasopressor only, 2 patients vasopressor + inotrope, 2 patients inotrope alone, 1 patient inotrope + vasodilator
Group III	After Fluid Resuscitation and Initial Therapy Adjustment 11 patients inotrope + vasopressor After 48 hours 6 patients inotrope + vasopressor, 5 patients inotrope alone

Four children with persistent shock showed a complete change in hemodynamic profile over 48 hours. One child evolved from a low CO/high SVR state to a high CO/low SVR state, and 3 children evolved from a high CI/low SVR state to a low CI/high SVR state and responded to appropriate changes in class of cardiovascular therapies (Table 4).

Of the children, 80% survived 28 days, and 78% survived to discharge from the PICU. The 1 patient who survived to 28 days but not PICU discharge died from resistant nocardia pneumonia and unremitting acute myelocytic leukemia. The 28-day mortality rate in group I was higher (8/29, 28%) than in group II (1/10, 10%) and group III (1/11, 9%). The mortality rate was 33% (6/18) in children who needed treatment with a different class of therapy to reverse persistent shock. Microbial etiology and

health status had no influence on hemodynamic state, response to cardiovascular therapies, or mortality.

DISCUSSION

To our knowledge, this is the first report examining hemodynamic variable-directed inotrope, vasopressor, and vasodilator therapy in children with fluid-refractory septic shock after a minimum of 60 mL/kg volume resuscitation. The standard measure of pulmonary artery wedge pressure documented the adequacy of fluid resuscitation in these children. All patients received cardiotoxic or vasoactive infusions through central venous access at the time of fluid resuscitation when it was apparent that shock was refractory to volume replacement. Refractory shock prompted placement of pulmonary artery catheters. The standard measures of CO and SVR documented the adequacy of directed cardiovascular therapy regimens in these children with fluid refractory and/or persistent septic shock. Analysis of hemodynamic variables after fluid resuscitation showed that 9 children were receiving incorrect cardiovascular therapy regimens. Changes in cardiovascular therapy regimens resulted in resolution of shock in these children. Life-threatening pericardial tamponade ($n = 2$) and suprasystemic pulmonary artery hypertension ($n = 1$) were diagnosed in 3 children. Pericardiocentesis and the use of inhaled nitric oxide contributed to resolution of shock in these patients.

After initial therapeutic adjustments, children with fluid-refractory shock were found to have heterogeneous hemodynamic states. In contrast to adult reports,¹¹ the majority of children were hypodynamic and needed inotropic support. Many needed the addition of vasodilators to decrease SVR, increase CI, and improve perfusion. Findings from two previous pediatric studies are consistent with our findings. Reynolds et al reported that pediatric burn patients with fluid refractory shock had decreased left ventricular stroke work and responded to inotropic support with increased cardiac output and resolution of shock.²⁰ Feltes and colleagues reported that echocardiographic analysis showed decreased systolic function and increased afterload in 5 of 10 children studied with septic shock and in none of 5 with sepsis without shock.²¹

The differences observed between pediatric and adult reports could represent an age-related phenomenon. Parker and colleagues reported that adults with septic shock have decreased ejection fraction but increased CO through ventricular dilatation and increased heart rate.⁸⁻¹⁰ Feltes et al did not observe ventricular dilatation in children with septic shock.²¹ The relative ability of children to increase CO with heart rate changes may be limited. An adult can increase resting heart rate from 60 to 100 beats per minute, but a proportionate increase in an infant from 140 to 220 beats per minute is not sustainable. It also is possible that differences in patient selection explain the predominance of the hypodynamic state in our study. Children refractory to fluid resuscitation who responded to initial cardiovascular thera-

pies with normal perfusion, urine output, and resolution of metabolic acidosis did not receive pulmonary artery catheters in our intensive care units. If adult intensive care units tend to place pulmonary artery catheters in patients with fluid-refractory septic shock when cardiovascular therapies are effective, then their patient population could differ from ours. It is possible that we selected for children with more severe cardiac dysfunction, if children with predominant vascular dysfunction responded to volume loading and children with predominant cardiac failure did not.

A smaller number of children with fluid-refractory shock presented with vascular failure. Approximately 1 of 5 fluid-refractory children were hyperdynamic, with diminished SVR that responded to vasopressor support without a decrease in CI below normal thresholds; another 1 of 5 required a combination of inotropic and vasopressor support to reverse shock. The hyperdynamic state is the hallmark of cardiovascular pathophysiology in adult sepsis. Systemic vascular resistance decreases as the vasculature becomes increasingly less responsive to catecholamines,¹⁹ in part, from intrinsic biochemical alterations in α -adrenergic receptor signal transduction mechanisms.²² If the patient is volume-loaded, the decrease in afterload is accompanied by an increase in CO and the "hyperdynamic state."^{23,24} Without volume-loading, an increase in CO is not possible because preload is decreased.^{21,25,26} The hyperdynamic state is characterized by an elevated CO; however, significant myocardial depression can be present^{9,27} and contribute to a variable CO response to vasopressor therapy. As with adults,²⁸⁻³⁰ the majority of children with hyperdynamic sepsis were able to maintain CO during vasopressor therapy; however, some children needed the addition of an inotrope to maintain CO and reverse shock.

Common adjustments in therapy that reversed fluid-refractory shock included the use of epinephrine or norepinephrine to reverse dobutamine/dopamine-resistant septic shock. The direct-acting catecholamines were added to regimens in 12 patients with dobutamine/dopamine-resistant septic shock after initial evaluation of CI and SVRI, and 14 other children were already receiving epinephrine or norepinephrine at the time of placement of the pulmonary artery catheter.^{17,28,30} Dopamine and dobutamine have been reported to be potentially less effective in infants³¹⁻³⁴ than in adults. Vasodilators were effective in reversing fluid-refractory shock in children with cardiac dysfunction and increased vascular resistance. Because vasodilators cause hypotension when a child is not adequately volume-loaded, these agents were added in our population after increased SVR and adequate PCWP were documented.

Shock persisted in more than 1 of 3 children. Evolving hemodynamic changes required the addition of different classes of cardiovascular therapy. Progressive myocardial dysfunction appeared to be a significant cause of persistent shock. There was a need for additional vasodilator therapy in children with the low CO/high SVR state, and inotropic ther-

apy in children who initially had a high CO/low SVR state. The hypodynamic state has been reported in children and adults with meningococcal septic shock as well as with septic shock from multiple etiologies.^{6,7,35,36} Experimental studies suggest that cytokines including tumor necrosis factor and end-effector molecules including nitric oxide can depress myocardial function directly.³⁷

Some children showed a complete change in class of drug needed to treat persistent shock (ie, from inotrope to vasopressor or from vasopressor to inotrope). Animal models have shown that hypodynamic or hyperdynamic septic shock can be attained with different methods of endotoxin or bacterial infusion.³⁸ Early studies showed that acute models (using bolus endotoxin or bacterial infusions) and chronic models (using chronic endotoxin infusion or peritoneal clot infections over 24 to 48 hours) resulted in low CO states.³⁹ It was only after the use of aggressive volume resuscitation (~60 mL/kg) that the chronic endotoxin infusion and peritoneal clot models were found to exhibit the high CO/low SVR state and improved survival.^{23,40} Volume resuscitation had little effect on the acute bolus models, because the low CO/high SVR state persisted despite restoration of adequate preload.³⁸ We reported previously a volume-resuscitated (60 mL/kg) swine model of septic shock in which an intraperitoneal bolus infusion of *Escherichia coli* resulted in low CO/high SVR state 6 hours after infusion. The animals survived if they received 60 mL/kg volume resuscitation at the onset of hypotension (1 hour after infusion). Twenty-four hours later, the animals showed a change to a high CI/SVR state, with a 50% mortality rate.⁴¹ The experimental animal data and our clinical findings suggest that any patient who shows persistent shock should be assumed to be receiving an incorrect cardiotoxic and/or vasoactive regimen until proven otherwise.

Studies in humans suggest that low CO and/or low SVR is deleterious to organ perfusion and survival during septic shock.^{3,6,8,35-37,42-44} Pollack et al examined children with septic shock and reported a 32% overall survival but noted that patients who maintained a CI between 3.3 and 6.0 L/min/m² had a higher rate of survival (67%).⁶ On the basis of these findings, they recommended maintenance of this CI range as a therapeutic goal in septic shock. In our study, we adhered to PALS fluid resuscitation guidelines and the recommendations of Pollack et al⁶ and observed an overall survival of 80% in children with fluid-refractory septic shock. As predicted by Pollack et al, we observed the highest mortality in the group of children with decreased CO after fluid resuscitation. Use of inotrope and vasodilator therapies was associated with an increase in CI toward the target goal of 3.3 to 6.0 L/min/m² and a 72% survival rate. Parker et al had reported that adults with septic shock had decreased survival in the presence of diminished SVR,⁷ and Groeneveld and colleagues reported that adults who died of septic shock had a persistent defect in peripheral vascular tone (SVR) regardless of CO.^{3,44} In our study, children with decreased vascular tone were treated with vasopres-

sors, and CI was maintained endogenously or with inotropes. The SVRI was maintained within the therapeutic goal range of >800 dyne/sec/cm⁵, and survival was >90%.

Children with persistent shock had a higher mortality rate (33%). Five of the 6 children in this group exhibited evolving myocardial dysfunction as the cause of persistent shock. The one child with persistent shock who developed a hyperdynamic-low systemic vascular resistance state died of unrecognized and untreated candida sepsis. Adult studies suggest that evolving vascular failure is associated with death in septic shock,^{3,8,11,44} however, evolving cardiac dysfunction was associated with mortality in our children with persistent septic shock. Attention to maintenance of cardiac output may be of greater importance to improved survival in children with fluid-refractory shock.

Limitations of our study include experimental design. We attempted to evaluate prospectively hemodynamic states and effectiveness of different classes of cardiovascular therapy in fluid refractory shock; however, the institutional review board stated that stopping cardiovascular therapy for the purpose of documenting hemodynamic states and randomizing classes of cardiovascular therapy to prove effectiveness was not ethical in children with shock. Therefore, we used an observational case series design in which existing therapies were directed to abnormal hemodynamic variables. The study shows data within 6 hours of admission to the intensive care unit rather than at the time of fluid resuscitation, because the insertion of the pulmonary artery catheter in children is a time-consuming process. The study also uses definitions of vasopressors and inotropes¹³⁻¹⁶ and normal ranges of CI and SVRI¹²⁻¹⁶ that, although based on published tables in standard pediatric intensive care textbooks, can be questioned. For example, because dopamine and epinephrine have mixed β - and α -adrenergic qualities, it is not necessarily true that epinephrine infusions <0.3 μ g/kg/min or dopamine infusions <10 μ g/kg/min have no vasopressor effect. Likewise, the inodilators amrinone and milrinone have inotrope and vasodilator qualities; therefore, classification as inotropes and not as vasodilators is arbitrary. The study population was heterogeneous with varied organisms and disease states. Although there were no apparent differences in hemodynamics, use of specific classes of cardiovascular agents, or mortality in the different groups of patients, our small sample size precludes any conclusion about responses in homogeneous patient populations. Greater numbers of children will be required to determine any differences in these subgroups.

Despite the inherent limitations in study design, several important clinical observations were made in our population of fluid-refractory septic shock patients. Children with fluid-refractory shock in three pediatric centers had varied hemodynamic profiles that responded to directed inotrope, vasopressor, and vasodilator therapy, with reversal of shock, maintenance of CI and SVRI goals, and improved outcome compared with findings in the historical liter-

ature. Common therapeutic maneuvers that resulted in reversal of fluid-refractory shock included use of the correct class of cardiovascular agent for cardiac or vascular failure (inotrope or vasopressor, respectively), direct-acting catecholamines for dopamine or dobutamine-resistant shock (norepinephrine or epinephrine, respectively), and vasodilators for the high SVR/low CO shock state. In contrast to adult reports, decreased cardiac output was a predominant contributor to fluid-refractory shock, evolving persistent shock, and possibly mortality in our pediatric population. Because hemodynamic profiles were heterogeneous and changed during all stages of fluid-refractory septic shock, we suggest that it is prudent to assume that refractory or persistent shock is secondary to an inappropriate cardiovascular support regimen rather than an inexorable pathophysiologic state until otherwise proven. It appears that outcome in children with fluid-refractory septic shock can be improved compared with findings in the historical literature.

ACKNOWLEDGMENTS

This work was supported by 3M01RR00056GCRC (University of Pittsburgh).

We thank Francie Siegfried for editorial assistance. We also thank Richard Orr, MD, and Shekhar Venkataraman, MD, for critical review of the manuscript.

REFERENCES

- Carcillo JA, Davis AL, Zaritsky A. Role of early fluid resuscitation in pediatric septic shock. *JAMA*. 1991;266:1242-1245
- Fluid therapy and medications. In: Chameides L, Hazinski MF, eds. *Textbook of Pediatric Advanced Life Support*. Dallas, TX: American Heart Association; 1994:1-618
- Groeneveld ABJ, Bronsveld W, Thijs LG. Hemodynamic determinants of mortality in human septic shock. *Surgery*. 1986;99:140-152
- Perkin RM, Levin DL. Shock in the pediatric patient. I. *J Pediatr*. 1982;101:163-169
- Perkin RM, Levin DL. Shock in the pediatric patient. II. Therapy. *J Pediatr*. 1982;101:319-332
- Pollack MM, Fields AI, Ruttimann UE. Distributions of cardiopulmonary variables in pediatric survivors and nonsurvivors of septic shock. *Crit Care Med*. 1985;13:454-459
- Pollack MM, Fields AI, Ruttimann UE. Sequential cardiopulmonary variables of infants and children in septic shock. *Crit Care Med*. 1984;12:554-559
- Parker MM, Shelhamer JH, Natanson C, Alling DW, Parrillo JE. Serial cardiovascular variables in survivors and nonsurvivors of human septic shock: heart rate as an early predictor of prognosis. *Crit Care Med*. 1987;15:923-929
- Parker MM, Shelhamer JH, Bacharach SL, et al. Profound but reversible myocardial depression in patients with septic shock. *Ann Intern Med*. 1984;100:483-490
- Parker MM, Ognibene FP, Parrillo JE. Peak systolic pressure/end-systolic volume ratio, a load independent measure of ventricular function, is reversibly decrease in human septic shock. *Crit Care Med*. 1994;22:1955-1959
- Carcillo JA, Cunnion RE. Septic shock. *Crit Care Clin*. 1997;13:553-574
- Krovetz LJ, McLoughlin TG, Mitchell MB, Schiebler GL. Hemodynamic findings in normal children. *Pediatr Res*. 1967;1:122-130
- Zaritsky A, Chernow B. Use of catecholamines in pediatrics. *J Pediatr*. 1984;105:341-350
- Notterman DA. Cardiovascular support—pharmacologic. In: Holbrook PR, ed. *Textbook of Pediatric Critical Care*. Philadelphia, PA: WB Saunders Co; 1993:288-315
- Steinberg C, Notterman DA. Pharmacokinetics of cardiovascular drugs in children: inotropes and vasopressors. *Clin Pharmacokinet*. 1994;27:345-367
- Notterman DA. Inotropic agents: catecholamines, digoxin, amrinone. *Crit Care Clin*. 1991;7:583-613
- Moran JC, O’Fathartagh MS, Peisach AR, Chapman MJ, Peppard P. Epinephrine as an inotropic agent on septic shock: a dose profile CCM 1993;21:70-77
- Barton P, Garcia J, Kouati A, et al. Hemodynamic effects of i.v. milri-
- none lactate in pediatric patients with septic shock. A prospective, double-blinded, randomized, placebo controlled, interventional study. *Chest*. 1996;109:1302-1312
- Cerra FB, Hassett J, Siegel JH. Vasodilator therapy in clinical sepsis with low output syndrome. *J Surg Res*. 1978;25:180-183
- Reynolds EM, Ryan DP, Sheridan RL, Doody DP. Left ventricular failure complicating severe pediatric burn injuries. *J Pediatric Surg*. 1995;30:264-270
- Feltes TF, Pignatelli R, Kleinert S, Mariscalco MM. Quantitated left ventricular systolic mechanics in children with septic shock utilizing noninvasive wall-stress analysis. *Crit Care Med*. 1994;22:1647-1658
- Roth BL, Suba EA, Carcillo JA, et al. Alterations in hepatic and aortic phospholipase C coupled receptors and signal transduction in rat intraperitoneal sepsis. In: Roth BL, Nielson TB, McKee AE, eds. *Progress in Clinical and Biological Research. Vol 286. Molecular and Cellular Mechanisms of Septic Shock*. New York, NY: Alan R Liss; 1989:41-59
- Carroll GJ, Snyder JV. Hyperdynamic severe intravascular sepsis depends on fluid administration in cynomolgus monkey. *Am J Physiol*. 1982;243:R131-R141
- Rackow EC, Kaufman BS, Falk JL, Astiz ME, Weil MH. Hemodynamic response to fluid repletion in patients with septic shock: evidence for early depression of cardiac performance. *Circ Shock*. 1987;22:11-22
- MacLean LD, Mulligan WG, McLean APH, Duff JH. Patterns of septic shock on man—a detailed study of 56 patients. *Ann Surg*. 1967;166:543-562
- Krausz MM, Perel A, Eimerl D, Cotev S. Cardiopulmonary effects of volume loading in patients with septic shock. *Ann Surg*. 1977;185:429-434
- Parrillo JE, Burch C, Shelhamer JH, Parker MM, Natanson C, Schuette W. A circulating depressant substance in humans with septic shock. *J Clin Invest*. 1985;76:1539-1553
- Meadows D, Edwards JD, Wilkins RG, Nightingale P. Reversal of intractable septic shock with norepinephrine therapy. *Crit Care Med*. 1988;16:663-666
- Gregory JS, Binfiglio MF, Dasta JF, Reilley TE, Townsend MC, Flancaum L. Experience with phenylephrine as a component of the pharmacologic support of septic shock. *Crit Care Med*. 1991;19:1395-1400
- Desjars P, Pinaud M, Potel G, Tasseau F, Touze MD. A reappraisal of norepinephrine therapy in human septic shock. *Crit Care Med*. 1987;15:134-137
- Lang P, Williams RG, Norwood WL, Castaneda AR. The hemodynamic effect of dopamine in infants after corrective cardiac surgery. *J Pediatr*. 1980;96:630-634
- Outwater KM, Treves ST, Lang P, Castaneda AR, Crone RK. Renal and hemodynamic effects of dopamine in infants following cardiac surgery. *J Clin Anesth*. 2:253-71990
- Perkin RM, Levin DL, Webb R, Aquino A, Reedy J. Dobutamine: a hemodynamic evaluation in children with shock. *J Pediatr*. 1982;100:977-983
- Martinez AM, Padbury TF, Thio J. Dobutamine pharmacokinetics and cardiovascular response in critically ill neonates. *Pediatrics*. 1992;89:47-51
- Mercier JC, Beaufils F, Hartmann JF, Azema D. Hemodynamic patterns of meningococcal shock in children. *Crit Care Med*. 1988;16:27-33
- Monsalve F, Rucabado L, Salvador A, Bonastre J, Cunat J, Ruano M. Myocardial depression in septic shock caused by meningococcal infection. *Crit Care Med*. 1984;12:1021-1023
- Quezado ZMN, Natanson C. Systemic hemodynamic abnormalities and vasopressor therapy in sepsis and septic shock. *Am J Kidney Dis*. 1992;20:214-222
- Green EM, Adams HR. New perspectives in circulatory shock: pathophysiologic mediators of the mammalian response to endotoxemia and sepsis. *J Am Vet Med Assoc*. 1992;200:1834-1841
- McDonough KH, Brumfield BA, Lang CH. In vitro myocardial performance after lethal and nonlethal doses of endotoxin. *Am J Physiol*. 1986;250:H240-H246
- Natanson C, Fink MP, Ballantyne HK, MacVittie TJ, Conklin JJ, Parrillo JE. Gram-negative bacteremia produces both severe systolic and diastolic cardiac dysfunction in a canine model that simulates human septic shock. *J Clin Invest*. 1986;78:259-270
- Hoban LD, Paschall JA, Eckstein J, et al. Awake porcine model of intraperitoneal sepsis and altered oxygen utilization. *Circ Shock*. 1991;34:252-262
- Weil MH, Nishijima H. Cardiac output in bacterial shock. *Am J Med*. 1978;64:920-922
- Vincent JL, Gris P, Coffernils M, et al. Myocardial depression characterizes the fatal course of septic shock. *Surgery* 1992;111:660-667
- Groeneveld ABJ, Nauta JJP, Thijs LG. Peripheral vascular resistance in septic shock: its relation to outcome. *Intensive Care Med*. 1988;14:141-147

Hemodynamic Support in Fluid-refractory Pediatric Septic Shock

Gary Ceneviva, J. Alan Paschall, Frank Maffei and Joseph A. Carcillo

Pediatrics 1998;102:e19

DOI: 10.1542/peds.102.2.e19

Updated Information & Services

including high resolution figures, can be found at:
<http://pediatrics.aappublications.org/content/102/2/e19>

References

This article cites 39 articles, 1 of which you can access for free at:
<http://pediatrics.aappublications.org/content/102/2/e19#BIBL>

Subspecialty Collections

This article, along with others on similar topics, appears in the following collection(s):

Correction

<http://www.aappublications.org/cgi/collection/correction>

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:

<http://www.aappublications.org/site/misc/Permissions.xhtml>

Reprints

Information about ordering reprints can be found online:

<http://www.aappublications.org/site/misc/reprints.xhtml>

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®



PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Hemodynamic Support in Fluid-refractory Pediatric Septic Shock

Gary Ceneviva, J. Alan Paschall, Frank Maffei and Joseph A. Carcillo

Pediatrics 1998;102:e19

DOI: 10.1542/peds.102.2.e19

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/102/2/e19>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 345 Park Avenue, Itasca, Illinois, 60143. Copyright © 1998 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®

