What's new in pediatric intensive care

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Purpose: To provide an update on new developments in the field of pediatric intensive care.

Results: Pediatric intensive care and acute medicine continues to grow internationally with improving intensive care unit mortality rates (2.4% in the United States) and a positive effect on child survival from the leading causes of death in the developing and developed world (sepsis and trauma, respectively). New approaches have developed for the practicing clinician in the use of hypothermia, helium, surfactant, glucose, insulin, hydrocortisone, fluid resuscitation and fluid removal, superior vena cava oxygen saturation, goal-directed, coagulation, immune modulation, and multiple-organ extracorporeal support (MOSES) therapies. Some old drugs have fallen out of favor (propofol and etomidate) while new drugs are being evaluated with favorable (calfactant) and yet to be described effects (activated protein C). New diagnostic tests (troponin and brain natriuretic peptide levels) are being used to aid in diagnosis of heart dysfunction, and a new drug class of Ca^{++} sensitizers holds promise for recalcitrant heart dysfunction (levosimendan).

Conclusion: The field is alive, successful, and progressing across the globe. (Crit Care Med 2006; 34[Suppl.]:S183–S190)

KEY WORDS: pediatric intensive care; sepsis; trauma; surfactant; hypothermia; corticoidsteroids; extracorporeal life support

Garber et al. (1) linked hospital discharge records in 2001 and reported that 480,000 children were admitted to intensive care in the United States, with the incidence being highest in infants (57/1000) compared with older children (2.3/1,000 aged 5–9 yrs; 5/1,000 aged 1–4 yrs). Remarkably, the hospital mortality rate in these patients was 2.4% (n = 11,600). If we estimate and assume that one of two children who survived with intensive care would not have done so without intensive care, then approximately 240,000 children were saved. Further extrapolation, using national vital statistic data, shows that intensive care was likely responsible for a five-fold reduction in infant and child mortality rates. For example, if infant mortality rates were 6/1,000 and an estimated 28.5/1,000 were saved by intensive care, then mortality was reduced nearly five-fold.

This effect on child health is very close to that previously estimated and reported by Frank Shann in Melbourne, Australia, when he evaluated the number of admissions to the Royal Children's Hospital intensive care units (ICUs) and compared it with the number of infants and children who lived and died in Victoria. The cost of this care in the United States in 2001 was $19,300 per patient, of which $16,400 per patient was ICU costs. The cost per life saved could therefore be estimated as $40,000 (assuming one out of two would have lived without it). This amounts to approximately $1,000 per life year saved (assuming a 40-yr lifespan). It is no wonder that while pediatric hospital beds have been decreasing, ICU beds have been increasing, presently accounting for one of five children's hospital beds nationwide. When one compares the cost of common therapies in adults as cost per life year saved, pediatric intensive care is not only an effective way to reduce child mortality, it is also a relative bargain.

Intensive Care Reduces Death from Severe Sepsis, the Leading Cause of Mortality in Children Worldwide

The World Health Organization lists the leading causes of death in infants and children as pneumonia, diarrhea (including Dengue), malaria, measles, and bacterial sepsis. Remarkably, all of these diseases are caused by infection. These diseases are termed "severe" by the World Health Organization when the child develops tachypnea, acidosis, and hypotension. The World Health Organization uses different definitions than the American College of Critical Care Medicine, which defines this condition as severe sepsis and shock. Bang et al. (2) showed that administration of oral and intramuscular antibiotics by rural health workers to babies with tachypnea, poor feeding, or diarrhea reduced all-cause mortality five-fold, and studies of children with pneumonia, malaria, measles, and bacterial sepsis have all shown beneficial effect of antibiotic therapy. Intensive care has similar effects on the outcome of patients who do not respond to antibiotics alone.

Two randomized trials in Dengue shock performed in Vietnam have shown that time-sensitive crystalloid or colloid fluid resuscitation through intravenous access can attain 100% survival (3, 4). This intervention is even more cost-effective than antibiotics alone! Maitland et al. (5) have shown that fluid resuscitation with albumin reduced mortality from severe malarial shock from 15% to 3%. Bacterial sepsis and septic shock remains a common cause of death in the developing and developed world. Investigators at Saint Mary's Hospital showed that implementation of rapid fluid resuscitation and inotropic support reduced mortality in children with meningococcal disease from 22% to 2% (6). Based on these and other studies, the American College of Critical Care Medicine developed evidence-based clinical practice parameters for resuscitation of septic shock (7) (Figs. 1 and 2).
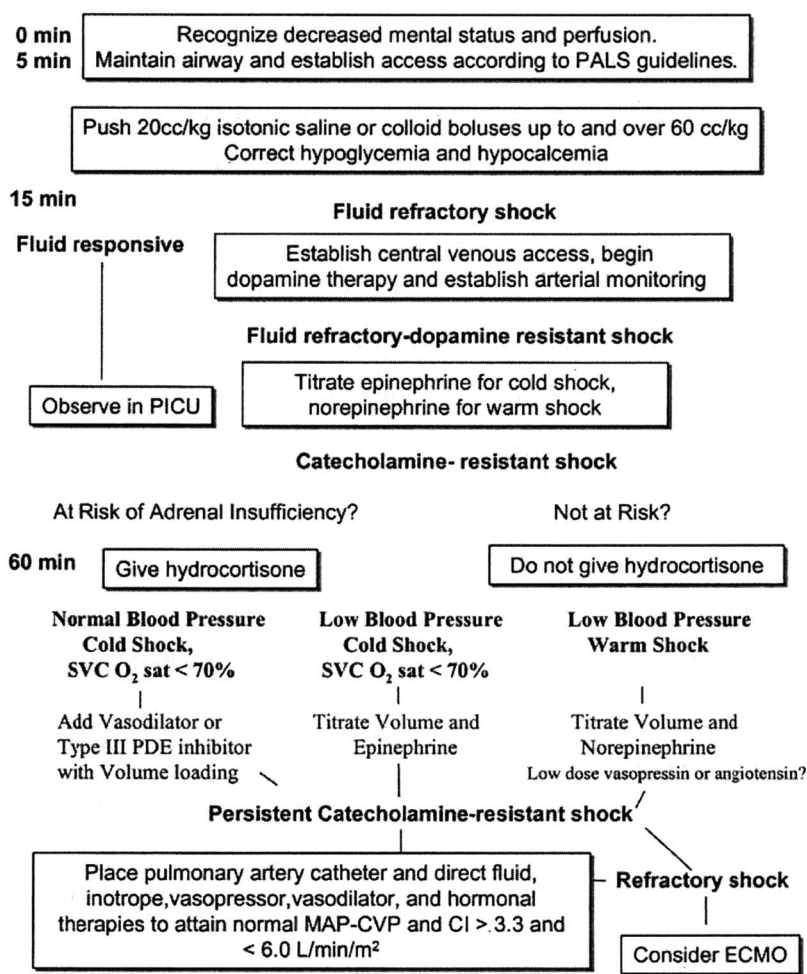
Figure 1. Recommendations for stepwise management of hemodynamic support in infants and children with goals of normal perfusion and perfusion pressure (mean arterial pressure–central venous pressure [*MAP-CVP*]). Proceed to next step if shock persists. *PALS*, pediatric advanced life support; *PICU*, pediatric intensive care unit; *SVC O₂*, superior vena cava oxygen; *PDE*, phosphodiesterase; *CI*, cardiac index; *ECMO*, extracorporeal membrane oxygenation. Reproduced with permission from Carcillo et al (7).

Important age-specific physiologic differences are demonstrated in these guidelines. Newborns tend to have persistent pulmonary hypertension and right heart failure and respond to right ventricular afterload reduction agents, such as inhaled nitric oxide, and to total cardiopulmonary support with extracorporeal membrane oxygenation (ECMO).

Children differ from adults, with an age-specific insensitivity to dopamine/dobutamine and mortality caused by poor cardiac output rather than low systemic vascular resistance. Hence, epinephrine and afterload reduction is more commonly needed in children than adults. Goal-directed therapies are used with targets of superior venous cava oxygen saturation of >70% and normal perfusion pressures (mean arterial pressure–central venous pressure). Oliveira et al. (8) recently reported a randomized controlled trial using continuous superior vena cava oxygen saturation monitoring that found a reduction in mortality in fluid refractory septic shock patients from 40% to 12% with use of American College of Critical Care Medicine clinical practice parameters.

Pediatric Intensive Care Reduces Death from Trauma, the Leading Cause of Mortality in Children in the Western World

In developed nations, trauma, not infectious shock, is the most common cause of child death. Regionalized trauma care and shock trauma centers have been considered the optimal approach for these patients. Although there are no randomized controlled trials, case control studies suggest that outcomes are better in hospitals with designated trauma centers. Head trauma in particular is the leading cause of death in children. Unlike adults, penetrating trauma is rare. The hallmark of resuscitation of children with trauma is time-sensitive reversal of shock. Intensive care management of severe traumatic brain injury (Glasgow Coma score of <9) has now been reviewed in evidence-based clinical practice parameters published in *Pediatric Critical Care Medicine* (9) (Figs. 3 and 4). Goal-directed therapies are recommended, with maintenance of cerebral perfusion pressures as the hallmark. Invasive procedures have become more standard. Extraventricular drains are used not only for measurement of intracranial pressure but also for therapeutic removal of cerebrospinal fluid for intracranial pressure of >20 mm Hg. Emergent craniotomy and craniectomy are also performed to reverse intractable intracranial hypertension, despite extraventricular drain and medical therapies. Although there have been no randomized controlled trials evaluating these clinical practice parameters, some of the authors of this article have evaluated a registry and reported improving outcomes in children with traumatic brain injury as aggressive intensive care management has become more commonplace.

Hypothermia Is Cool

The late Peter Safar popularized the idea that moderate therapeutic hypothermia (32–34 degrees centigrade) is an effective measure to protect against brain injury after hypoxic or traumatic brain injury. Two adult investigators who worked in Dr. Safar's animal laboratory went home to Australia and Austria and simultaneously performed two separate landmark studies that showed a 50% good neurologic outcome in adult cardiac arrest victims who were treated with postresuscitation mild/moderate hypothermia for 12–24 hrs (10, 11). Based on these findings, mild/moderate hypothermia has become standard of care in adult cardiac arrest patients. Neonatal investigators from New Zealand, Australia, and elsewhere also performed "cool cap" (head temperature maintained at 34 degrees centigrade) and whole-body hypothermia studies in newborns with asphyxia neonatorum. The results are being interpreted by many, but they seem to show some benefit to newborns with
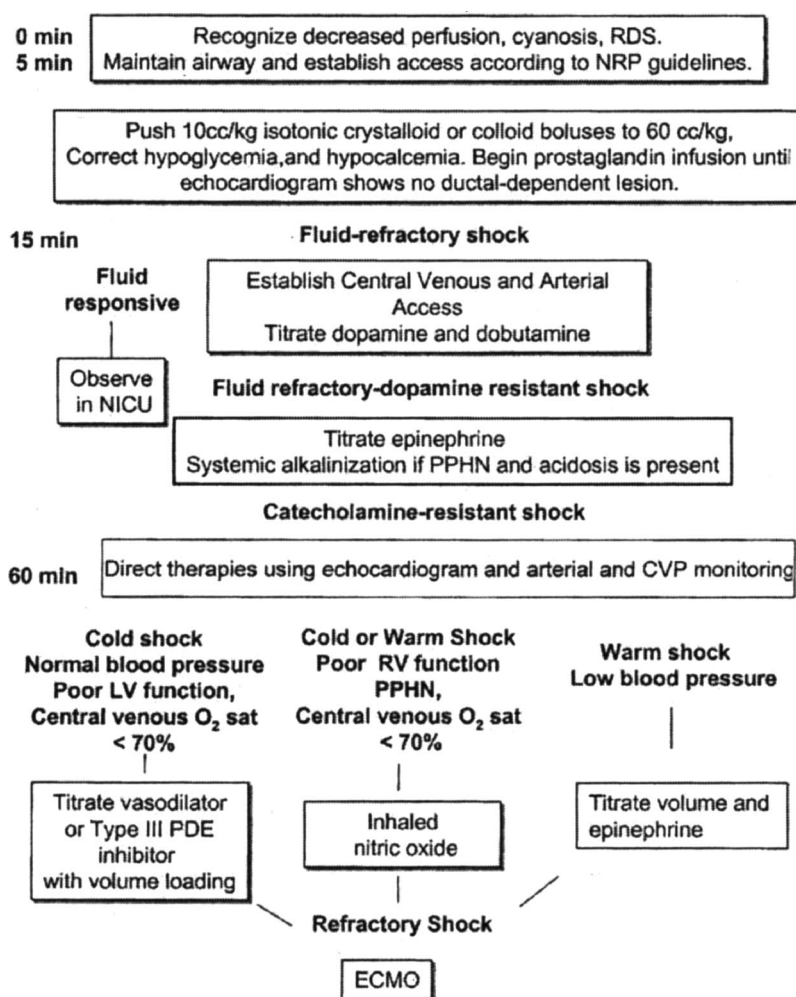
Figure 2. Recommendations for stepwise management of hemodynamic support in term newborns with goals of normal perfusion and perfusion pressure (mean arterial pressure–central venous pressure) and preductal and postductal oxygen saturation difference of <5%. Proceed to next step if shock persists. *RDS*, respiratory distress syndrome; *NRP*, neonatal resuscitation program; *NICU*, neonatal intensive care unit; *PPHN*, persistent pulmonary hypertension of the newborn; *CVP*, central venous pressure; *LV*, left ventricular; *RV*, right ventricular; *PDE*, phosphodiesterase; *ECMO*, extracorporeal membrane oxygenation. Reproduced with permission from Carcillo et al (7).

mild/moderate injury but none to those with severe injury (12). Further trials are being planned to evaluate hypothermia for pediatric cardiac arrest.

Interpretation of randomized controlled trials of mild/moderate hypothermia for traumatic brain injury are also ongoing. In an initial single-center adult study, hypothermia protected those with moderate injury but had no effect on those with severe injury. The follow-up multiple-center trial was disappointing, with no effect rendered by hypothermia therapy. Discussion has centered on whether lack of effect was related to differential handling of known side effects of hypothermia in the various units. An initial single-center pediatric trial is now complete, and a second multiple-center randomized trial is ongoing. Similar to the adult studies, although hypothermia is one effective method to reduce intracranial pressure, its effects on outcomes are not yet clear cut (13).

Thinner than Air in the Amazon Jungle

Helium is everywhere in the pediatric ICU. Compared with nitrogen, this gas reduces turbulent flow and is helpful in reducing work of breathing and delivery of gas past airway obstruction. Anecdotal reports have now been confirmed with randomized controlled trials for the use of helium–oxygen mixtures for just about every airway obstructive disease from croup to status asthmaticus. The use of high-flow, humidified, heated air has also become "new." Reports of nasal septum necrosis with high-flow nasal cannulae oxygen/air when the gas had not been humidified or heated are now a thing of the past. Babies have a great deal of airway obstruction from the nasopharyngeal passages and a high chest wall compliance that can lead to airway collapse during periods of respiratory distress. High-flow, heated, and humidified nasal cannula oxygen can deliver continuous positive airway pressure and improve functional residual capacity without causing septal necrosis. When helium is added to the gas mixture (heliox), babies with bronchiolitis and respiratory distress feel so much better. Add inhaled nitric oxide to the mixture and children with pulmonary hypertension and sickle cell patients with chest syndrome can benefit as well.

Surfactant Is for Kids!

Willson et al. (14) recently reported the results of a randomized, placebo-controlled calfactant trial for acute respiratory distress syndrome in children. The average oxygenation index ($FIO_2 \times$ mean arterial pressure) in the two groups of children was 20. The remarkable finding was a reduction in mortality with two doses of calfactant in the first 24 hrs. Not even the neonatal studies showed this robust effect on survival. The adult studies have shown no benefit at all with surfactant. What could possibly explain these differences? Here are some possibilities. First, the drug is different. Calfactant has a high concentration of collectin, the protein that collects bacteria and contributes to bacterial killing. Second, the population characteristics are different. Neonates with hyaline membrane disease were always more likely to have bronchopulmonary disease than death; hence, the greater effect on chronic lung disease than survival is understandable. As for the adult studies, they predominantly have had an indirect lung injury population sample. When *post hoc* analysis has been done only in the group of adults with direct lung injury (e.g., pneumonia, pneumonitis, aspiration pneumonia), there has been a trend toward benefit with surfactant. Dr. Willson assures me that he is hopeful that a follow-up study will be performed to evaluate whether children with chronic lung disease (who had been excluded in the above study) can also benefit from this therapy
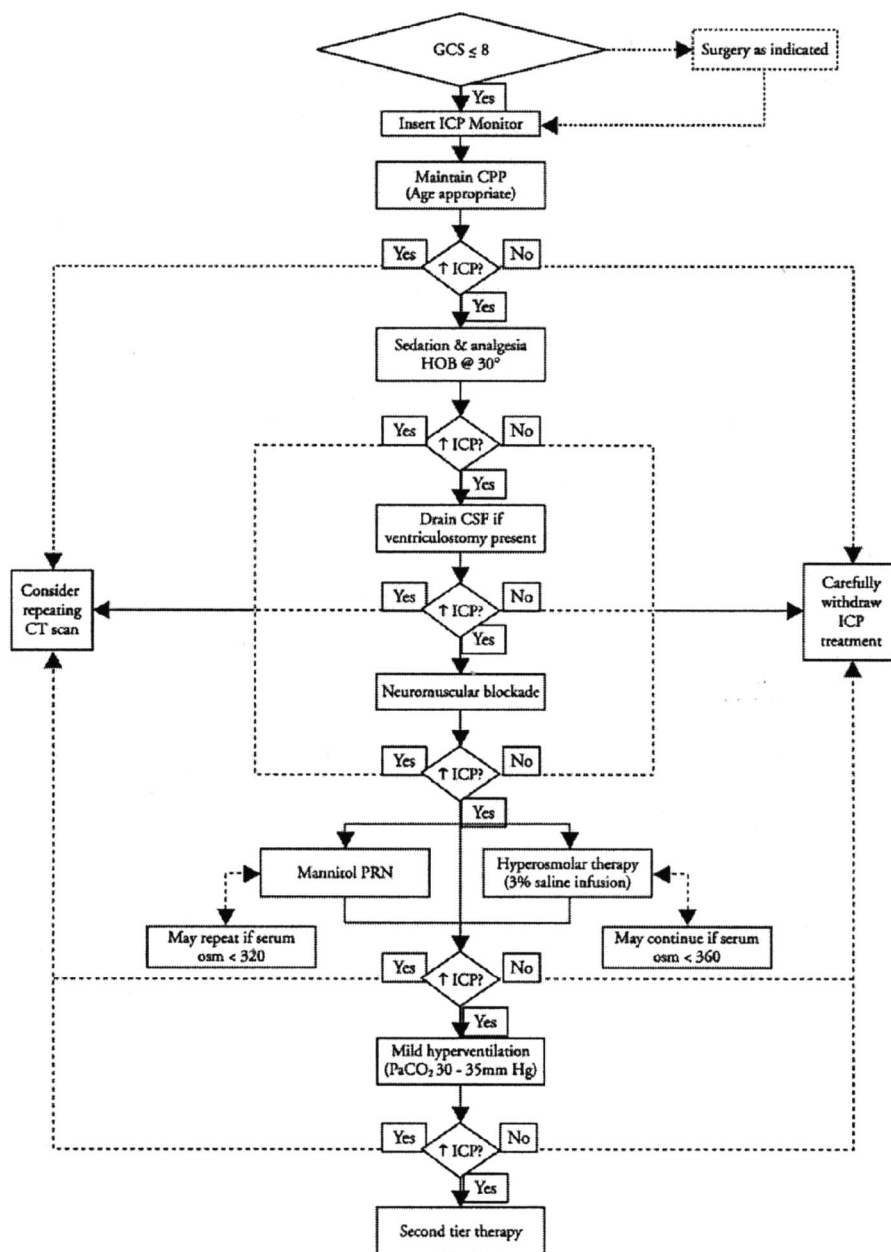
Figure 3. First-tier traumatic brain injury guidelines. *GCS*, Glasgow Coma Scale; *ICP*, intracranial pressure; *CPP*, cerebral perfusion pressure; *HOB*, head of bed; *CSF*, cerebrospinal fluid; *CT*, computed tomography; *PRN*, as needed. Reproduced with permission from Adelson et al (9).

sure and high-frequency strategies may be most effective at reducing volutrauma/barotrauma in indirect injury (increased extravascular lung H_2O), but surfactant may be more effective in direct lung injury (surfactant inactivation). Beware! Although I love to use the drug, I recommend that you remain at the bedside when it is given. I have found that compliance and oxygenation can go down with initial application.

Children Are So Sweet

We have argued for years about the need for glucose control in children in the ICU. Pediatricians are well versed on the management of diabetic ketoacidosis and know the hazards of untreated hyperglycemia in children who do not make insulin, but what about children who make insulin but have extreme insulin resistance? The clues have been there. A glucose of >200 mg/dL is associated with mortality in the Pediatric Risk of Mortality (PRISM) score. Anand and Hickey (15) reported a dramatic reduction in mortality in neonates undergoing cardiac surgery when high-dose sufentanil was added to the halothane–morphine regimen. The reduction in mortality was wholly attributable to a reduction in the rate of severe hyperglycemia and secondary sepsis after surgery. What sense could this possibly make? Hyperglycemia and, particularly, cortisol-induced hyperglycemia are immune suppressive and prothrombotic. This is well known; however, hyperglycemia from severe stress and insulin resistance also means that glucose is not getting into the Krebs cycle. The heart in particular depends on insulin-dependent type II and IV glucose transporters to get glucose into the Krebs cycle. Dr. Van den Berghe understands this well (16). She has now published a randomized controlled trial in an adult surgical unit in which she randomized patients to a 10% dextrose–containing intravenous fluid solution at maintenance rate with subsequent use of insulin for those who developed a glucose of >120 mg/dL. With this approach, she noted a two-fold reduction in mortality in surgical patients, all from prevention of sepsis. Ten-percent dextrose-containing solutions at maintenance fluid provides the glucose delivery needed, regardless of age, and insulin therapy for hyperglycemia ensures that this glucose indeed is delivered into the Krebs cycle.

when they develop acute respiratory distress syndrome.

Why do I think it works? Here is why. A myriad of investigators, most notably those from Toronto, have shown that overdistention of the alveolus with volutrauma releases interleukin-6. This cytokine in turn is associated with immune paralysis, secondary infection and death from infection, unremitting pneumonia, and multiple organ failure. A number of ventilatory modes can be used to combat this phenomenon, including volume limitation to 6 mL/kg tidal volume with use

of positive end-expiratory pressure, and use of high-frequency or oscillatory ventilation to capture functional residual capacity. These approaches minimize the chance of overdistension of alveoli and are indeed common in pediatrics. However, the pathophysiology of acute respiratory distress syndrome is surfactant inactivation when it is caused by direct lung injury with infection or chemical agents. The whole point to surfactant is that it equalizes surface tension among alveoli of different sizes. I and others think that positive end-expiratory pres-
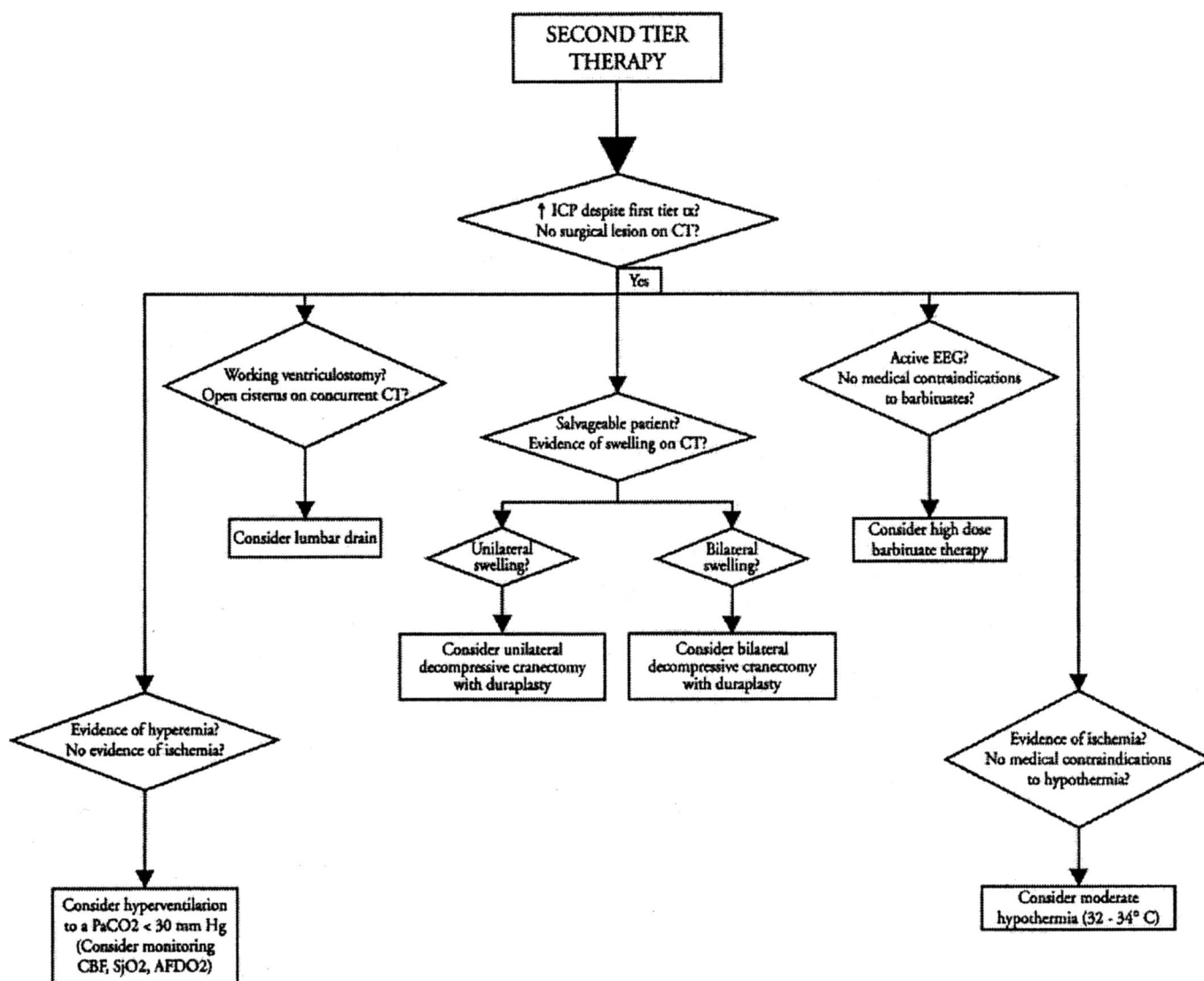
Figure 4. Second-tier traumatic brain injury guidelines. *ICP*, intracranial pressure; *CT*, computed tomography; *EEG*, electroencephalogram; *CBF*, cerebral blood flow; *SjO2*, jugular venous oxygen saturation; *AJDO2*, arterial-jugular venous difference in oxygen content. Reproduced with permission from Adelson et al (9).

Clinicians are now grappling with the data, hoping that they do not need such "tight" control or "so much" glucose for their patients. Pediatricians are worried that tight control causes hypoglycemia. Here is what I know from ongoing work in our unit. Insulin resistance is greatest for the first 18 hrs, some patients need >1.0 unit·kg^{-1}·hr^{-1} of insulin and other patients need <0.05 unit·kg^{-1}·hr^{-1} of insulin to attain euglycemia. Hence, no simple formula such as that used with diabetic ketoacidosis patients (0.1 units·kg^{-1}·hr^{-1} for everyone) will suffice. You have to be there with the patient and adjust accordingly. At 18 hrs, we observe that insulin needs can go down rapidly. Randomized controlled trials in children are being planned in three continents to address how sweet children really should be.

Steroids, the Staff of Life

Randomized controlled pediatric trials now confirm the role of dexamethasone for croup and methylprednisolone for asthma. The new "old" steroid is hydrocortisone, which has glucocorticoid and mineralocorticoid effects. Clinicians need to get used to the dosage of hydrocortisone because it always sounds too high. The conversion factor for dexamethasone is hydrocortisone × 30, and for methylprednisolone, the conversion factor is hydrocortisone × 6. So, a dosage of 0.5 mg/kg dexamethasone every 8 hrs is the equivalent of 45 mg·kg^{-1}·day^{-1} hydro-

cortisone, and 2 mg/kg methylprednisolone every 6 hrs is the equivalent of 48 mg·kg^{-1}·day^{-1} hydrocortisone. Absolute secondary or primary adrenal insufficiency is quite common in pediatric critical care. Many patients have previously received steroids, some have central nervous system anomalies or injury, many have reduced cytochrome P450 activity, and a few have Waterhouse-Friderichsen syndrome. These patients can require between 2 mg/kg (stress dose) and 50 mg/kg (shock dose), depending on their condition.

New interest has been generated by Annane et al. (17), who have described a state of relative adrenal insufficiency in adults who have a baseline cortisol of

>20 μg/dL and a reduced response to adrenocorticotropic hormone stimulation of <9 μg/dL. Adult patients with this condition who also have septic shock with a vasopressor requirement are treated with hydrocortisone and fludrocortisone (equivalent of 6 mg·kg^{-1}·day^{-1} hydrocortisone), with a 10% reduction in 28-day mortality. Several investigators have demonstrated that approximately one quarter of children with septic shock have this condition, but it remains unknown whether they would benefit from steroid therapy. Randomized controlled trials in children with septic shock are in planning stages.

Give Fluid Often. Remove Fluid Often

Fluid resuscitation is the hallmark of hypovolemic and septic shock reversal. However, this fluid may leak into the extravascular space. This causes edema and secondary organ dysfunction. In our initial report of aggressive fluid resuscitation for children with septic shock, we neglected to report that all patients received furosemide and sequential diuretic management after their initial fluid resuscitation. Indeed, many received diuretics during their resuscitation. The importance of fluid removal has been underlined in two recent studies. Introduction of a Dengue shock protocol that uses furosemide and subsequent peritoneal dialysis for children who were unable to diurese after fluid resuscitation was associated with an improved survival (18). Similarly, Foland et al. (19) recently reported the continuous renal replacement therapy (CRRT) registry in the United States and found that early implementation of CRRT before there was a 10% increase in fluid overload was associated with improved survival compared with late implementation of CRRT after a 10% increase in fluid overload was observed. The take-home message from these studies is that when children do not self-diurese after aggressive volume resuscitation, then implementation of diuretics and extracorporeal fluid removal is warranted to prevent fluid overload of >10%.

Superior Vena Cava Oxygen Saturation, the Fifth Vital Sign

This has become the new goal of the century in pediatric critical care. After a great deal of consternation about "balancing the circulation" of babies with single-ventricle physiology, the consensus is that the original observation described by Parr et al. (20) is correct. This group found that a cardiac index of <2.0 L·min^{-1}·m^{-2} or a mixed venous oxygen tension of <30 mm Hg is associated with mortality in infants after cardiac surgery. Maintenance of a threshold mixed venous oxygen tension, or superior cava oxygen saturation, reduces this mortality risk. The superior vena cava oxygen saturation can be as much a 9% higher than the mixed venous oxygen saturation because the coronary sinus empties after the superior vena cava. Thus, threshold goals of 70% (minimal mixed venous oxygen saturation of 61%) are considered the minimal threshold central venous oxygen saturation target at this location. Because children with shock, including those with septic shock, die of low oxygen delivery and cardiac output, the superior vena cava or mixed venous oxygen saturation has become the fifth vital sign of intensive care.

Low venous saturation can be corrected by increasing hemoglobin concentration or by increasing cardiac output. When oxygen delivery is low, venous oxygen saturation is low (wide arteriovenous oxygen content difference). When oxygen delivery is normal, venous oxygen saturation is >70% (normal arteriovenous oxygen content difference). Cardiac index is improved by the combination of inotropes and vasodilators. Epinephrine has always been king, but the new predominance of vasodilator therapy is "what's new in pediatric critical care." Inhaled nitric oxide, nitroprusside, nitroglycerin, enoximone, milrinone, amrinone, pentoxifylline, prostacyclin, and levosimendan are commonly used in critically ill children and remain rarely used in critically ill adults.

Clotting and Bleeding: Ouchie, Mommy!

We know that when Johnnie or Susie cut their finger on the playground, that they bleed, get a bandage, and then clot. But why, when a child is in the ICU, does he or she clot and then bleed. The secrets of the paradox have now been revealed. When vasculature is focally injured by a laceration on the playground, the focal endothelium at the point of injury, normally antithrombotic and profibrinolytic, becomes prothrombotic and antifibrinolytic, allowing the bandage to get all the credit. In critical illness, systemic inflammation–induced endotheliopathy causes all the endothelium to become prothrombotic and antifibrinolytic. Systemic antithrombotic factors (protein C and antithrombin III) are consumed until they become low enough that prothrombotic factors take over and are systemically consumed in clots. When enough prothrombotic factors are consumed in this manner, then spontaneous hemorrhage occurs. An armamentarium of anticoagulants (e.g., heparin, antithrombin III, protein C, argatroban), procoagulants (e.g., activated factor VII), fibrinolytics (e.g., tissue plasminogen activator, activated protein C), and antifibrinolytics (e.g., Amicar, tranexamic acid) are now available to the physician. Unfortunately, clinical tests that might guide the clinician as to which specific therapy to use are not readily available in most clinical laboratories. One can sometimes see bleeding, but how does one know if the patient may have systemic thrombosis precedent to bleeding? You should think about it in any patient who develops new-onset thrombocytopenia and multiple organ failure. These patients are likely to be consuming platelets in microvascular fibrin or platelet clots. If the child has a prolonged prothrombin time/partial thromboplastin time and low fibrinogen, then it is likely to be disseminated intravascular coagulation pathophysiology, and if the child has a normal or high fibrinogen, then it is likely to be thrombotic thrombocytopenic purpura pathophysiology. Plasma exchange is an effective therapy for reversal of coagulopathy from either condition because it corrects any and all abnormalities (21).

Immune Modulation

Look around the literature and you will see that patients in pediatric intensive care are increasingly immune suppressed. Transplant patients, cancer patients, patients with autoimmune disease, and even those with common disease including asthma, croup, and dermatitis are bathed in immune-suppressive therapies. Here's what is new. If these children have an infection and are sick enough to be admitted to the ICU then *hold* the immune suppression until you eradicate the infection. Why do you think this population is 67 times more likely to develop sepsis than other children? It's the immune suppression. Do they reject their organs or relapse their cancer if you hold immune suppression while you kill the infection? No, they do not. Growth

factors are now being used in these patients as well, including granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor. They work best if immune suppression is concomitantly held.

Children who do not receive immune-suppressive therapies can develop critical illness stress-induced immune suppression. Increased cortisol levels cause hyperglycemia and lymphopenia and lymphoid depletion. Hyperglycemia can be reversed with insulin. However, there are no good therapies to maintain lymphocyte counts and function during stress. Endotoxin tolerance–induced immune paralysis also occurs and results in a reduced ability of macrophages and monocytes to kill infection. Low-dose granulocyte-macrophage colony-stimulating factor therapy may be helpful in these patients.

Drugs That Have Recently Fizzled

Propofol has fizzled as a drug for prolonged sedation in the pediatric ICU (PICU). The manufacturer reported that a stepwise increase in use of $0 \times$ propofol, $1 \times$ propofol, and $2 \times$ propofol in three PICUs was associated with a stepwise increase in mortality (4%, 7%, and 10%), leading the Food and Drug Administration to recommend against its use in the young PICU population. Apparently, the drug inhibits complex II in mitochondrial respiration. Etomidate has fizzled as an intubation drug for patients with septic shock. Even one dose has been associated with increased mortality in children and adults, leading two respected adult journals to recommend against its use for emergency intubations (22, 23). The recommended choices of these journals are thiopental for head trauma and ketamine for septic shock. Activated protein C (drotrecogin alpha [activated]) did not reduce mortality or time to organ failure resolution in a now completed phase III trial in children.

New Drugs That I Think Could Shine, Maybe

Calfactant has already been discussed and is the first drug shown to decrease mortality in the PICU. It is unknown whether other surfactants are as effective. Dexmedetomidine is the newest sedative. Clinicians have always appreciated the utility of the alpha-2 agonist, clonidine,

but never had an intravenous form. Dexmedetomidine seems to be an effective intravenous alpha-2 agonist sedation agent with a reasonable risk profile. Recombinant activated factor VII has drawn much attention as the new drug to use to stop bleeding without causing deleterious thrombosis. Although the recombinant drug is expensive, its use in life-threatening bleeding is bound to continue to gain popularity. Levosimendan is my inside tip on the hottest drug in the near future, although it is among the most expensive inotrope/vasodilators available. This drug sensitizes troponin to Ca^{++} binding, inhibits type III phosphodiesterase, and further improves afterload reduction through K^+ channel–induced hyperpolarization. Just as inhaled nitric oxide reduced the need for ECMO for persistent pulmonary hypertension of the newborn and right heart failure, my guess is that levosimendan in combination with epinephrine will reduce the need for ECMO for low cardiac output syndrome caused by sepsis and cardiac disease alike.

Finally, Something New from the Clinical Laboratory

In my first 15 yrs of critical care medicine, no new tests arrived from the clinical laboratory to aid critical care. However, in the last 5 yrs, two tests, the troponin level and the brain natriuretic peptide level, have become available and quite useful. The troponin level is increased when cardiac cells either leak from cellular inflammation or die of ischemia or viral-induced necrosis/apoptosis. If troponin levels are increasing, be very concerned. In asthmatics, this can mean too much β_2-agonist toxicity. Diastolic hypotension (β_2 effect) and tachycardia (β_2-agonist spillover to the β_1 receptor) can lead to decreased diastolic filling and ischemia. Back off on the β_2 agonist. In patients with myocarditis, increasing troponin levels after admission can be an ominous warning sign of need of extracorporeal support. For meningococcal septic shock patients, troponin levels mirror cardiac function.

Have you ever noticed all those puffy children you have in the PICU who just cannot get off the ventilator? They have a high central venous pressure but diuretics just are not making them better. Many of these children have occult congestive heart failure, which can now be diagnosed by increased brain natriuretic peptide levels. The echocardiogram is

mostly normal because diastolic function is difficult to assess with this test. Brain natriuretic peptide levels decrease with dobutamine, afterload reduction, and diuretics, followed by transition to angiotensin-converting enzyme inhibitors and Aldactazide. We need to have more useful tests like these available to us. It would be nice to have measures of thrombosis (F 1 + 2) and fibrinolysis (plasmin α_2 antiplasmin) in addition to the often useless prothrombin time/partial thromboplastin time, measures of brain injury (SB-100 and neuron specific enolase) to augment the Glasgow Coma Scale, and measures of immune function (monocyte HLA-DR expression, whole blood ex vivo TNF response to LPS) to help us understand when to give immune modulation to reverse critical illness stress-induced immune suppression in patients with severe sepsis.

Wholly MOSES! *M*ultiple *O*rgan *S*ystem *E*xtracorporeal *S*upport

Pediatric critical care has been built on machines, and one machine in particular, the ventilator. We have continued to be at the forefront of this technology. Our adult colleagues are still asking what is high-frequency oscillator ventilation? But, what's new in the PICU? Extracorporeal machines in tandem! The following machines have become commonplace: ECMO for cardiorespiratory support, CRRT for renal support, MARS (molecular adsorbent recirculating system) for liver support, plasma exchange for coagulation support, leukapheresis for hematologic support, and whole blood exchange and plasmapheresis for immunologic support. Amazingly, these machines are now commonly used in combination to support patients with multiple organ failure.

Initially used extensively in neonates and occasionally in children and adults, ECMO is now becoming popular in older patients as well. Several breakthroughs have contributed to this. First, investigators at Eggleston Children's Hospital reported that venovenous ECMO can be effective not only in those with respiratory failure but also in those with some degree of cardiac failure (24). These authors pointed out the importance of a second venous cannulae to improve flow in older patients. Those who did not respond to venovenous ECMO were switched to veno-arterial, but the majority did well with venovenous ECMO alone. Second,

the importance of unrecognized hemolysis in older patients is becoming appreciated. With higher flows required, hemolysis is more likely. In the days before the membrane and hollow-fiber oxygenator, multiple organ failure was commonly seen in patients exposed to the hemolysis of bubble oxygenators for more than a few hours. Free hemoglobin scavenges nitric oxide, adenosine, and ADAMTS 13, leading to microvascular vasoconstriction and platelet thrombosis and ensuant multiple organ failure. Free hemoglobin levels of <10 avoid this problem. Careful attention must be paid to appropriate catheter sizes and positions, second venous cannulae, and avoidance of overzealous flow to prevent free hemoglobin levels from rising above this level.

In patients with renal failure and oliguria, CRRT can be performed in line with the ECMO circuit by adding a hemofiltration filter. In patients who are not receiving ECMO support, CRRT is most commonly performed using continuous venovenous hemofiltration rather than continuous arteriovenous hemofiltration. Initially used to provide gentle hemodialysis for a 24-hr period rather than a 1- to 2-hr period, it is now being used to rapidly remove extravascular fluid and cytokines immediately after cardiopulmonary bypass. High-flux CRRT (hemofiltration rate of >60 mL/kg/h) is now being used to remove cytokines in children with acute respiratory distress syndrome. An ongoing multinational, multicentered trial has been organized by Joe DiCarlo in cancer patients with this condition.

MARS has now been successfully used to support children with liver failure. This hemofiltration/dialysis machine hemodialyzes blood against albumin, removing albumin-bound toxins and drugs. The albumin is then reconditioned and reactivated through a second column so that the albumin can be continuously recycled rather than wasted. Each treatment lasts several hours and is then followed by conventional CRRT. In this manner, the patient has removal of both protein-bound (e.g., bilirubin) and free (e.g., ammonia) molecules. Plasma exchange therapy can also be successful in these patients, correcting complex co-

agulopathy without fluid load. Plasma exchange is equally effective in children with disseminated intravascular coagulation, thrombotic thrombocytopenia purpura, or liver failure coagulopathies (20).

Leukopheresis reverses multiple organ failure by removing malignant neutrophils and lymphocytes from children with leukemia and proliferating lymphocytes from children with critical pertussis. This lifesaving therapy reverses pulmonary leukosequestration and pulmonary hypertension. Whole blood exchange reverses multiple organ failure in sickle cell patients by removing sickle cells, in newborns by reversing ABO incompatibility and systemic hemolysis, and in cerebral malaria by removing parasites and increasing hemoglobin. Plasmapheresis reverses multiple organ failure in rheumatologic and autoimmune crises by removing antibody–antigen immune complexes.

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