Insulin administration for treatment of pediatric diabetic ketoacidosis: Are lower rates of infusion beneficial?*

In this issue of *Pediatric Critical Care Medicine*, Drs. Al Hanshi and Shann report laboratory data from 67 children treated for diabetic ketoacidosis (DKA) (1). The data were collected retrospectively from the charts of 34 children treated with an insulin infusion of 0.1 unit/kg/hr and 33 children treated with an insulin infusion of 0.05 unit/kg/hr. The treatment protocols were not randomly assigned, and the authors used analysis of covariance methods to compare the two groups on laboratory values obtained approximately 12 hrs after initiation of treatment, controlling for age and for laboratory values obtained at presentation. The authors conclude that effective osmolality declined more gradually in children treated with the lower rate of insulin infusion, despite similar rates of resolution of acidosis and ketosis.

The etiology of DKA-related cerebral edema, and the optimal protocol for treatment of pediatric DKA (which is greatly focused on the prevention of cerebral edema) has been and continues to be a subject of controversy. There are very few data in the literature comparing treatment regimens, and treatment recommendations are mainly based on expert opinion and physiologic principles. Prospective data from randomized trials in pediatric DKA are almost nonexistent. In the current study, Drs. Al Hanshi and Shann present information on an important topic. However, the study is limited by the lack of randomization of treatment protocols and resulting issues with the analytical methods used to compare treatment groups, so the findings must be interpreted with caution. Furthermore, the authors' premise that cerebral edema is a result of changes in serum osmolality is not uniformly accepted, and contrary to what the authors state, recent data (2–4) suggested that the pathophysiology of DKA-related cerebral edema may involve cerebral hypoperfusion and reperfusion leading to vasogenic edema.

Previous studies (5) have demonstrated that the decline in serum glucose concentration during DKA treatment is dependent on the rate of insulin infusion across a range of insulin dosages from 0.01 unit/kg/hr to 1.0 unit/kg/hr. The finding that a lower rate of insulin infusion might lower the plasma glucose more slowly, therefore, is not surprising. Other factors, however, also influence the rate of decline in serum glucose concentration, including the initial degree of compromise in renal function caused by dehydration, rate of infusion of intravenous fluid, and the timing and amount of dextrose administration. These and other factors may have a substantial impact on the initial and subsequent serum glucose concentrations. The severity of dehydration and rate of rehydration may have a particularly important effect on the decline in serum glucose concentration during the early stages of treatment. It is, therefore, important to note that intravenous fluid therapy was not standardized among patients in the study. In addition, it is unclear how many patients received glucose infusions, which is common during the first 12 hrs of DKA therapy. This would also affect the data and results of the analysis.

As noted by the authors, the lack of randomization in the choice of insulin dosages means that only very tentative comparisons can be made regarding the observed associations. Important confounders, both known and unknown, may partially or fully account for the observed between-group differences. The analysis of covariance model specified by the authors, which is well suited for comparing randomized treatment groups on posttreatment outcomes, is not optimal for between-group comparison of overtime changes in laboratory values when treatment group is not independent of pretreatment laboratory values, a phenomenon known as "Lord's Paradox." This phenomenon is named after a famous demonstration that analysis of covariance can produce statistically significant treatment effects even when treatment groups do not differ in mean changes from baseline (6–8). Hence, the p values reported in their Table 2 must be interpreted with caution, as their pertinence to the changes in laboratory values that they accompany requires that treatment be independent of initial values, a questionable assumption for nonrandomized data. Absent this assumption, the p values pertain only to whether, after adjusting for the initial value and patient age, the treatment groups differ in posttreatment values, an analysis that could be confounded by many factors that differ between the groups (6–9).

According to the data presented in Table 1 in the study by Drs. Al Hanshi and Shann, at least one fourth of the patients receiving high insulin dosages presented with glucose levels of >68 mmol/L. Although a formal statistical comparison was not made, the data in Table 1 suggest that the initial effective osmolality of patients in the higher insulin dosage group was higher than that shown for the patients in the lower dosage group. Given that osmolality would likely be within or close to the normal range at 12 hrs of treatment for most patients, it is also questionable whether the analysis of covariance model used to control for baseline differences was sufficient to adjust for the effects of between group differences in initial effective osmolality, as the model specifies only a linear relationship between initial and final values of the outcome.

Nonrandomized assignment of treatment protocols may have resulted in other important differences between groups. Very high initial glucose concentrations in children with DKA are associ-

*See also p. 137.

Key Words: DKS; diabetic ketoacidosis; cerebral edema; diabetes.

Dr. Glaser is a partial owner of a company making insulin dosing aids for patients with diabetes. Dr. Kuppermann is the co-owner of "Insu Call", which helps patients with diabetes manage their insulin. The remaining authors has not disclosed any potential conflicts of interest.

ated with greater severity of dehydration and greater compromise in renal function. During rehydration and reestablishment of optimal renal perfusion, these patients often have substantial declines in glucose concentration, resulting from increased renal glucose elimination, separate from the effects of the insulin infusion. Furthermore, the authors note that endocrinologists at their institution were more likely to prefer a dosage of 0.1 unit/kg/hr, and intensive care physicians were more likely to prefer a dosage of 0.05 unit/kg/hr. If input from an endocrinologist were requested more often for patients with very high initial glucose and osmolality, this tendency could be problematic. These factors could contribute to correlation between laboratory values at presentation and treatment group, invalidating the analysis of covariance model used to compare treatment effects on study outcomes.

Although glucose decline is one effect of insulin action during DKA treatment, the more important effect of insulin treatment is to promote the resolution of ketosis and acidosis. Several lines of evidence suggest that ketosis may have direct adverse effects on the brain and other organs (10, 11), and level of consciousness during DKA correlates most strongly with acidosis (12). Furthermore, hyperventilation in response to acidosis has been associated with risk of DKA-related cerebral edema (CE), and therapeutic hyperventilation has been associated with poor outcomes of CE (13, 14). It seems logical to conclude that more rapid resolution of ketosis and acidosis may be beneficial. Unfortunately, this study by Drs. Al Hanshi and Shann (1) documents measures of acidosis and ketosis only at the beginning of treatment and at 12 hrs. Rapidity of resolution of ketosis and acidosis during the first 4, 6, or 8 hrs may be of greater relevance, but these data were not reported. Aside from manipulating insulin dosages, declines in glucose concentrations can be modulated by adding dextrose to the intravenous fluid infusion (15), and treatment protocols employing such methods provide a means for ensuring resolution of ketosis at the same time promoting gradual declines in glucose concentration in cases where this is of concern. It is, therefore, questionable whether protocols utilizing lower rates of insulin infusion are likely to be beneficial, particularly in comparison with protocols which modulate glucose concentrations via concurrent administration of insulin and dextrose.

Regardless of whether lower rates of insulin infusion result in more gradual declines in osmolality and/or equivalent resolution of acidosis compared with higher rates of infusion, the contention that slowing the rate of the decline in glucose or osmolality may reduce the risk of DKA-related CE is questionable. Although older studies (16–18) employing bivariable analyses suggested this possibility, more recent studies (13, 19) using appropriately controlled multivariable analyses have not found associations between CE and variables related to osmotic changes. Contrary to what the authors propose, recent data suggest instead that DKA-related CE does not simply result from osmotic shifts. Animal and human data suggest that the mechanism of DKA-related CE is complex and may be related to multiple factors, including cerebral hypoperfusion and reperfusion, activation of ion transporters in the blood brain barrier and in astrocytes, and direct effects of ketosis and hyperglycemia on the brain (2–4, 20).

As the authors point out, variations in rates of insulin administration for treatment of pediatric DKA have been studied very little. Additional data on this topic may be helpful, but the findings in this retrospective, nonrandomized study should be interpreted with caution. In many instances, analyses of observational data that do not adequately consider confounding variables have resulted in recommended therapies and interventions that either offer no benefit or even result in harm (21–25). Randomized, prospective, clinical trials remain a necessity for answering important clinical questions.

Dr. Glaser is part-owner of a company making insulin dosing aids for patients with diabetes-no relationship to DKA. Dr. Kuppermann is co-owner of a company called "Insu Call," which helps patients with diabetes manage their insulin. All other authors have not disclosed any potential conflicts of interest.

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The practice of mechanical ventilation in pediatrics: Science, art, or a simple routine?*

In this issue of *Pediatric Critical Care Medicine*, Wolfler and colleagues (1) present a study conducted by the Sistema de Información de los Servicios Públicos de Empleo (SISPE) Study Group, a consortium of pediatric intensive care physicians in Italy. The SISPE study is a prospective, observational, multicenter, cohort study that describes children treated with mechanical ventilation (MV) for at least 24 hrs in 17 Italian pediatric intensive care units (PICUs) and one neonatal intensive care unit over a 6-month period from November 2006 to April 2007. Two of the 18 units, however, collected data only for 3 consecutive months.

There are only two previous prospective studies (2, 3) about the practice of MV in children. The Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) study (2) was conducted in nine large North American PICUs during a screening of mechanically ventilated patients, who were intended to be included in a weaning trial (4). Data were collected during 6 months from November 1999 to April 2001, and patients (children, aged 0–18 yrs) had to remain on MV for at least 24 hrs. The International Group for Mechanical Ventilation in Children (IGMVC) study (3) was conducted in 36 PICUs mainly from Argentina and Spain. Data were collected during 2 months from April to May 1999; patients (children, aged 1 month–15 yrs) had to be ventilated for a minimum of 12 hrs. It is important to note that the PALISI study excluded children with poor prognosis and patients with life-support restrictions, whereas the IGMVC study missed the viral respiratory season when bronchiolitis is frequently diagnosed and did not include neonates. Due to these characteristics, the PALISI study represents a population of selected patients better suited for clinical trials, and the IGMVC represents a more typical population of PICU patients who receive MV (5). The SISPE study (1) also matches with this last criterion.

A comparative analysis of these three articles has already been presented by the authors of the SISPE study (1). Because there is a temporal gap of approximately 7 yrs between them, it is of great importance to analyze any difference that appeared during these years.

1. Indications for MV. Acute respiratory failure, mostly from respiratory infections and coma, continues to be the most important indication for MV. Acute respiratory distress syndrome (ARDS) is an uncommon diagnosis, except in the PALISI study, where cases of bronchiolitis-associated ARDS are included (2). However, it is not known if bronchiolitis that meets clinical criteria for ARDS also meets confirmatory histologic criteria. Besides, mortality due to this specific form of ARDS is rare (2, 6), perhaps explaining the differences in the mortality rate due to ARDS in the PALISI study (4.3%) as opposed to the others (SISPE, 16.7%; IGMVC, 50%).

2. Practice of MV. Conventional, invasive ventilation is the preferred form of respiratory support. Synchronized intermittent mandatory ventilation with pressure support continues to be the most frequently used ventilatory mode; other reports (7, 8) confirm this as well. The SISPE study fails to describe a ventilatory strategy for any disease (including ARDS) but confirms the current tendency toward more assisted, rather than controlled, ventilation; the use of newer modes like bilevel positive airway pressure and airway pressure release ventilation by Italian practitioners also favors this concept (1). Spontaneous breathing during MV has the potential to prevent diaphragm dysfunction (9) and improve gas exchange, systemic blood flow, and oxygen supply to tissues (10). Furthermore, assisted MV could counter the undesirable cyclic alveolar collapse in dependent lung regions and could reduce the need for sedation (10). These benefits could decrease the duration of MV, the length of stay in the PICU, and costs.

High-frequency oscillatory ventilation is five times more frequent in the PALISI study (11.8%) than in the SISPE study (2.1%), despite the 7 yrs that separate them. Although the reasons that explain this are unclear, one could argue that the Italian practitioners had more expertise with traditional MV and/or restricted access to this kind of ventilators as described in a European country (11). It is also difficult to conclude if this lack of implementation of high-frequency oscillatory ventilation is the cause of the difference in the PALISI study in terms of

***See also p. 141.**

Key Words: mechanical ventilation; pediatrics; children; respiratory failure; intensive care

The author has not disclosed any potential conflict of interest.

DOI: 10.1097/PCC.0b013e3181d9c71b

mortality caused by ARDS (2). Lack of access to oscillators is also a frequent problem in less-developed countries; gaining expertise in newer strategies with conventional MV would be the answer to this dilemma. It is generally accepted today that the strategy should include maintaining the peak inspiratory pressure level at <35 cm H_2O by reducing the tidal volume, allowing the $Paco_2$ to increase when the situation demands it (permissive hypercapnia), and using a sufficient level of positive end-expiratory pressure to prevent lung collapse (the open-lung, gentle ventilation approach) (12, 13). This strategy should keep the driving pressure (end inspiratory plateau pressure − positive end-expiratory pressure) to a minimum.

Noninvasive ventilation, although not included in the PALISI analysis, increased from the IGMVC study (1.5%) to the SISPE study (17.1% of the total number of patients requiring ventilatory support). This increase has been noted worldwide as an attempt to delay or prevent endotracheal intubation and the inherent complications of invasive MV (14). Several studies have documented its benefits in different clinical scenarios (12, 14). Unfortunately, the SISPE authors fail to show the outcomes of the patients who received noninvasive ventilation.

3. Weaning From MV. The SISPE study only mentions, as a method of weaning, a progressive reduction of the pressure support level at the same time maintaining at least one single synchronized intermittent mandatory ventilation breath as a sigh (1). It seems that, as in the majority of patients in the IGMVC study (3), a conservative approach for weaning is preferred in Italy (the gradual reduction of support), instead of more active methods currently proposed as in spontaneous breathing trials and protocol-driven weaning techniques (4, 8, 15, 16), although there is still no standard method of weaning (17). The SISPE study also does not mention the number of extubation failures and the outcomes of patients requiring reintubation.

4. Adjunctive Therapies. Although the IGMVC does not report the use of any adjunctive therapy, there are differences that appear in the 7 years between the PALISI (2) and the SISPE (1) studies. Alternative positioning, like the prone position, increased from 17.1% in 1999 to 79% in 2007. Prone positioning has the potential to improve lung mechanics and gas exchange in acute lung injury (8); however, a recent large, multicenter, randomized trial (18) in children with acute lung injury failed to show a difference in the outcomes. The use of surfactant also increased from 1.3% in 1999 to 7.9% in 2007 (ARDS was diagnosed in 35% of these last cases). A randomized controlled study (19) with calfactant showed improvements in oxygenation and mortality; these data could justify its use in some patients with acute lung injury. Finally, the use of nitric oxide decreased from 4.6% (17.4% in ARDS cases) in 1999 to 1.9% in 2007. Despite improvements in oxygenation, randomized controlled trials of nitric oxide in adults and children with ARDS have found no effect on mortality or duration of MV (12). Recruitment maneuvers are infrequently described in any of the studies. These maneuvers are generally considered safe and could be beneficial in some clinical situations (8).

As we can see, most of the questions about the practice of MV in pediatrics remain to be answered. Hopefully, the upcoming results of the Pediatric Acute Lung Injury Mechanical Ventilation Strategies (PALIVE) study (20), an epidemiologic multicenter study on MV management in children with acute lung injury, will contribute to improve our knowledge. The treatment of children requiring MV should be based on strategies proven to be effective and safe. These strategies should come from randomized trials, but objective evidence is still lacking. Therefore, clinical practice in MV, far from being a *simple routine*, must be implemented with all the possible pediatric scientific knowledge (*science*), with data carefully extrapolated from studies conducted in adults and newborns, and with the judicious application of professional experience (*art*), tailored for each individual patient and the available resources at each PICU.

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A framework for healing*

The death of a child is traumatic to critical care practitioners, no matter how many times we have had the experience. The lingering uncertainties and the sudden ending of a generally brief but often very intense relationship with family members can feel uncomfortable. Imagine then, the experience of the family: the unreality of the whirlwind of events, the strange and often incomprehensible environment (1), and the parade of caregivers and administrative personnel entering their lives at a time of extreme emotional distress (2). All of this is followed by a discharge home filled with the unimaginable absence of their child, the details of the funeral, and sleepless nights. Simultaneously, the parents are faced with a stream of questions from family, friends, and others. "What happened?" they ask. Most often, despite our best efforts to explain during the stress of their child's hospitalization, they do not know the answer but are too numb to try to find out in the immediate aftermath of the death. Gradually, the protective fog lifts and the specter of the unanswerable questions begins to loom large. Finally, the comforting call, "We'd like to invite you to meet with your child's care team, to answer your questions, to see how you are doing, to see how we can help, and to say a proper goodbye."

Although these experiences and needs are clearly identified by families, the invitation is too infrequently received (3–6). One of the reasons may be that exactly when and how to conduct this conversation and who should be present has been unclear. Perhaps we worry that we will be hurt by further contact or that we may hurt the family by "reminding them" (as if they could forget). Perhaps it is too hard to imagine what we could say that would be helpful in such a tragic circumstance. After all, we were not trained to have this conversation (7, 8); we have no role models, and there is no evidence base to prove the benefit of doing something that seems to be fraught with significant risk to ourselves and possibly the family, too.

Dr. Eggly and colleagues (6), partners in the Collaborative Pediatric Critical Care Research Network, have now provided practical guidance on conducting such postdeath follow-up meetings. Their suggestions comprise a flexible framework, based on evidence derived from interviewing parents, pediatric intensive care unit fellow trainees, and attending physicians at seven sites. Their conclusion is that these meetings are so beneficial to both parties that their occurrence should not be left to chance; in other words, the process of inviting parents to come to such a meeting should be so integral to critical care that it should be routine and systematic. Further, because it is not clear when the fog will lift, enabling parents to emotionally and practically benefit, the invitation should be extended numerous times and in numerous formats over the first year following the death. Other explicit suggestions include how to prepare and set expectations for the meeting; where it should be held; whom to invite among hospital staff and how to prepare them; what range of topics should be anticipated; and the structure of the meeting itself, including initial introductions and acknowledgment of loss, followed by elicitation of the parents' questions and concerns. Some useable phraseology is suggested to initiate and encourage the discussion, as well as more general tips for effective communication. Methods to close the meeting and suggestions for additional follow-up are provided, as well as suggestions for team and trainee debriefing after the meeting.

The framework suggested has face validity and is further supported by interview data. It meets a need long identified by parents and caregivers. The next step is to implement the framework in a robust way to determine whether it meets the objectives for which it was designed; to improve family bereavement outcomes, to improve the quality of care rendered based on parental input, and to improve professional satisfaction (9). I eagerly await the results of the framework implementation outcome study.

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*See also p. 147.

Key Words: care team; postdeath follow-up; parents
The author has not disclosed any potential conflicts of interest.

DOI: 10.1097/PCC.0b013e3181f268ae

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Renal function and extracorporeal membrane oxygenation: The crossroads of concurrent multiple organ support*

Acute kidney injury (AKI) is a common occurrence among critically ill pediatric patients with an incidence of 4.5%–82%, depending on the definition used (1–4). These reports indicate that the etiology of AKI in pediatric inpatients has shifted in recent decades from primary intrinsic renal disease to secondary AKI such as ischemia associated with sepsis and cardiopulmonary bypass. In a recent, single-center application of a consensus definition of AKI, renal dysfunction was present on admission to the intensive care unit in 42% of patients requiring mechanical ventilation and persisted beyond 48 hrs in 55% (4). Among patients undergoing corrective congenital cardiac surgery, AKI was present after cardiopulmonary bypass in as many as 28% of patients (5). Additionally, multiple studies have demonstrated an increased risk of mortality for pediatric patients with AKI during critical illness (6). Hence, the critically ill pediatric population is at significant risk for renal dysfunction, which conveys an increased risk for mortality.

The presence of kidney failure is a longstanding indication for continuous renal replacement therapy (CRRT), and in the recent decade, fluid overload (FO) has emerged as an indication for CRRT based on its association with mortality in critically ill patients. Early observational cohort studies first made this association evident, and the findings have been replicated in larger multicenter studies among both pediatric and adult patients (7–9). A recent publication from the Pediatric Prospective CRRT Registry group was able to demonstrate that reversal of acute FO was associated with an improved survival for patients receiving CRRT with multiple organ dysfunction (7). Similar associations of FO and outcomes during extracorporeal membrane oxygenation (ECMO) have been made going back to the 1990s. FO has been associated with longer duration of ECMO and reversal of FO associated with separation from ECMO (10, 11). Additionally, the inability to return to dry weight has been noted as an independent risk factor for mortality during ECMO (12). Currently, a general shift in practice is occurring in many centers, with patients receiving renal support for indications other than AKI, yet still we know very little about the outcomes of patients receiving concomitant multiple organ support such as CRRT and ECMO.

In the current issue of *Pediatric Critical Care Medicine*, Dr. Paden and colleagues (13) examine this intersection of CRRT and ECMO. In this single-center experience, the authors document, over a 3-yr period at Children's Healthcare of Atlanta at Egleston, the demographics and outcomes of 378 neonatal and pediatric patients on ECMO, of whom 250 survived to hospital discharge. Of these 378 patients, 154 received CRRT (continuous venovenous hemodiafiltration) during ECMO, with 44% surviving to discharge. The population described on ECMO with CRRT was similar to other institutional experiences except that 50% of the patients were categorized as having a pediatric respiratory indication as compared with 12% from a recent Extracorporeal Life Support Organization registry-based study (14). Additionally, the overall survival rates for ECMO (66%) are commensurate with yearly reported outcomes from the Extracorporeal Life Support Organization Registry International Summary (Ann Arbor, MI). This study did not address important questions such as the comparison of FO management strategy (hemodiafiltration vs. diuretics) and the impact on outcomes. Additionally the authors did not examine the effects of CRRT modality or dose on outcomes. These limitations are a function of the relatively small single-center cohort examined.

This excellent study, which to date is the largest study of patients receiving both CRRT and ECMO, provides two significant contributions to the current knowledge in the field. First, recovery of renal function occurred in 96% of the patients requiring CRRT on ECMO, corroborating previous findings from a smaller single-center study (15). Of the three patients in whom renal function did not return, all had consensus guideline level AKI rather than FO as an indication for CRRT, and all three patients had primary intrinsic renal disease diagnosed subsequent to the initial event. Such data contradict the anecdotal belief that CRRT induces AKI in patients supported for FO indications rather than AKI. Second, it appears that the renal dysfunction (AKI and FO), rather than CRRT initiation for such dysfunction, is the driving principle for mortality on ECMO in this group. Outcomes in this study for patients receiving CRRT on ECMO (44% survival) were similar to previous reports of patients with AKI on ECMO (45% survival) (12).

These findings from a large, single-center study are an important step in understanding the intersection of CRRT and ECMO, but further work is required. CRRT has been well studied in the general critically ill population by the Pediatric Prospective CRRT Study Group in a large multicenter data registry (16). Similar data collection is possible through the Extracorporeal Life Support Organi-

***See also p. 153.**

Key Words: extracorporeal membrane oxygenation; continuous venovenous hemofiltration; continuous renal replacement therapy; acute kidney injury; acute kidney failure

The author has not disclosed any potential conflicts of interest.

DOI: 10.1097/PCC.0b013e3181f4d46e

zation Registry (Ann Arbor, MI) and will reflect international experience, allowing for the largest possible patient accrual. The RRT on ECMO study group has formed and will examine important questions such as the effect of FO and AKI (as defined by modern consensus definitions) on ECMO outcomes. Additionally, RRT-specific factors such as dose and modality effects on outcome will be examined in detail. This will provide more in-depth understanding of patient and support variables that affect outcome and may be amenable to prospective multicenter trials in the future.

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Extracorporeal membrane oxygenation survivors and pulmonary function: Encouraging outcomes early in life*

The long-term pulmonary outcome of infants treated with extracorporeal membrane oxygenation (ECMO) for life-threatening respiratory failure has been of interest for many years. The few controlled studies suggest that in addition to providing a survival advantage, this heroic therapy decreases each individual infant's subsequent pulmonary morbidity presumably by minimizing oxidant stress and ventilator-induced lung injury (1). However, all infants meeting criteria for ECMO have been exposed to oxidant stress and ventilator-induced lung injury, and the use of ECMO may increase the burden of respiratory disease in older children by allowing more children to survive with greater degrees of acute lung injury and/or with more severe underlying abnormalities of lung structure. Cross-sectional studies of survivors of ECMO in infancy from 6 mos of age to adolescence (1–4) have consistently demonstrated an increased prevalence of fixed airway obstruction and minor alterations in lung volumes (typically hyperinflation). There is also a higher incidence of airway hyperreactivity even in individuals without the usual risk factors for asthma (3). Considering the extent of disease present at the time that ECMO is instituted, however, the prevalence and degree of pulmonary function abnormalities are surprisingly mild, and the respiratory morbidity reported (symptoms and exercise limitation) is similarly modest. Although it seems likely that most pulmonary sequelae result from ventilator-induced injury and hyperoxia as a consequence of the treatment of respiratory failure before the institution of ECMO, there are differences between subgroups of ECMO-treated children based on their underlying problem. For instance, in children who require ECMO for respiratory failure associated with congenital diaphragmatic hernia, hypoplasia of both ipsilateral and contralateral lungs probably results in a decreased surface area for gas exchange throughout life (5).

In this issue of the *Pediatric Critical Care Medicine*, Dr. Hofhuis and colleagues (6) report careful longitudinal measurements of pulmonary function and respiratory morbidity during the first year of life in a large group of survivors of

*See also p. 159.

Key Words: extracorporeal membrane oxygenation; respiratory failure; pulmonary function

The authors have not disclosed any potential conflicts of interest.

DOI: 10.1097/PCC.0b013e3181f268ce

ECMO in infancy. These data are, in general, consistent with findings of previous investigators but demonstrate that abnormalities present at 6 mos of age change only modestly later in the first year of life. As with all studies of pulmonary function in infancy and beyond, it is dangerous to speculate about what abnormalities of structure contribute to functional abnormalities; firm conclusions will need to await further refinements in measurements of pulmonary function and imaging. Nonetheless, put together with previous studies, it seems likely that the lungs of infant survivors of ECMO recover relatively quickly to a level of function that is modestly abnormal but then appear to remain relatively unchanged through adolescence. Whether one focuses on the fact that there are pulmonary function abnormalities present in these children as a group or on the remarkable degree of recovery from the devastating degree of respiratory failure and lung injury experienced by the majority as infants is a matter of personal choice!

How do these data direct the management by a physician for a child who has history of ECMO in infancy? First, clinicians should remember that each child is an individual as well as a member of the group of ECMO survivors. While many will have definite but modest pulmonary sequelae, others will have none and a few will have more severe underlying abnormalities. As a group, survivors of ECMO are likely to have a degree of fixed airway obstruction that would be expected to decrease respiratory reserve and amplify other treatable causes of airway dysfunction such as asthma or aspiration syndromes or genetic predispositions to lung dysfunction such as alterations in innate immunity that may underlie severe respiratory syncytial virus infections (7). This is especially likely to be true in the first year of life, when respiratory reserve is normally limited, as the lung is growing and developing. Many survivors will also have airway hyper-reactivity in the absence of the usual risk factors for asthma and may benefit from bronchodilator or anti-inflammatory therapy. It is especially important to consider preexisting abnormalities in children with congenital diaphragmatic hernia. In addition to the risk of abnormal alveolar development related to lung hypoplasia that may limit pulmonary reserve, the ipsilateral lung is likely to be less well perfused (5). In such children, a focal process that affects the contralateral lung such as a pneumothorax could be devastating. Furthermore, in all children with a history of ECMO in infancy, early and aggressive identification and treatment of underlying reversible causes of airway dysfunction and careful attention to immunizations and immunoprophylaxis are indicated.

The institution of ECMO for infants with severe but reversible respiratory failure remains a rescue therapy in general. The timing for employing this technology is not uniformly agreed upon, but in general ECMO is utilized when a child is believed to have life-threatening but reversible lung injury. Dr. Hofhuis and colleagues (6) demonstrate that ECMO patients survive with restoration of very good pulmonary function. The presumption is that all (or nearly all) of these children would have died if ECMO was not available, and thus these results are very encouraging. Dr. Hofhuis and colleagues (6) have also shown the value of careful longitudinal studies of lung function in ECMO survivors. Perhaps the most important longitudinal studies for these patients remain to be accomplished. Although the prospects for near-normal pulmonary function and little respiratory morbidity through adolescence is remarkably good for survivors of ECMO in infancy, the jury is still out on the implications for these individuals later in life. All of us lose lung function steadily with age, and it is possible that these individuals will lose function more quickly or arrive at a level of function that limits normal activity sooner than other adults. Longitudinal studies such as these, extended beyond childhood, will help answer the most important clinical question remaining about this interesting and challenging group of patients.

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Biomarkers for sepsis: PERSEVERE to the bitter end*

In our daily clinical practice, we use markers of biological function to assess and evaluate the severity of illness, prognosis, response to therapy, progression of disease, and outcome. We utilize clinical, laboratory, and radiologic parameters to allow us to make some sense of the clinical situation we are faced with, which enables us to make rational treatment decisions. These decisions are sometimes based on evidence but often are based on clinical experience.

These parameters, together with clinical evaluation, allow us to make a reasonable guess at the patient's likely outcome, plan therapeutic decisions, predict clinical course, and facilitate discussions with patients and families. We also use these parameters to determine eligibility and suitability for clinical trials.

Most intensivists assimilate this information subconsciously, without necessarily realizing what we are doing, and often not realizing that we are using "biomarkers" routinely in our everyday practice. For example, we routinely measure markers of infection and inflammation (such as peripheral white blood cell count or C-reactive protein) to try to understand disease progression, response to therapy, or evolution of disease. However, the typical intensivist thinks of a "biomarker" as a novel "test" that provides us with patient information that is not readily obtainable using our current diagnostic and monitoring tools.

Various definitions of a biomarker exist, with the most widely used being that proposed by the Biomarker Definitions Working Group in 2001, which states that a biomarker is "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic process, or pharmacologic responses to a therapeutic intervention" (1).

Several kinds of biomarkers have been defined and are discussed below.

Diagnostic biomarkers enable us to establish the presence or absence of a disease or other clinical condition (i.e., procalcitonin in bacterial infection). Diagnostic biomarkers are of greatest value within a specific clinical context and with the addition of adjunctive clinical or diagnostic tests.

Monitoring biomarkers provide information regarding the effectiveness of a given therapy for the purpose of titration (i.e., serial glucose measurements for the titration of insulin therapy).

Surrogates are biomarkers that are intended to substitute for a clinical end point, based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence. Few biomarkers are able to achieve this, so the use of surrogate end points in a clinical trial still requires clear specification of the clinical end point that is being substituted for, the class of therapeutic intervention being applied, and the characteristics of the population and disease state in which the substitution is being made. Biomarkers may be useful in the assessment of safety or efficacy or both.

Stratification biomarkers (staging biomarkers) serve to subclassify or stage diseases based on severity and/or outcome. Such stratification can be applied to individual patients or may be used in the context of a clinical trial. An effective stratification biomarker can identify higher-risk patients who would be eligible for more toxic, more aggressive, or higher risk therapy. In addition, they may identify patients who are predicted to have a good outcome with standard therapy and thereby protect patients from exposure to unnecessary or potentially harmful therapies.

The field of critical care medicine would benefit tremendously from the development of effective biomarker-based stratification strategies. The clinical syndromes of organ failure that we encounter daily in the pediatric intensive care unit are highly heterogeneous from both a clinical and a biological standpoint. However, our therapeutic approaches are highly homogeneous. We generally apply the same therapeutic approaches to heterogeneous syndromes such as acute lung injury or sepsis whatever the cause. We also conduct interventional clinical trials in the pediatric intensive care unit without directly addressing the heterogeneous nature of the study cohort.

In this issue of *Pediatric Critical Care Medicine*, Kaplan and Wong (2) describe the derivation of a pediatric sepsis biomarker risk model (PERSEVERE: PEdiatRic SEpsis biomarkEr Risk modEl).

The candidate biomarkers for the derivation of PERSEVERE were first identified using a data set consisting of 98 children with septic shock within the first 24 hrs of admission to the pediatric intensive care unit that was able to correctly predict mortality outcome in 84 of the 98 patients. More specifically, the model correctly predicted 15 of the 17 nonsurvivors (88%) and 69 of the 81 survivors (85%) (3).

Despite the fact that robust illness severity scores are currently available for critically ill populations, these scores are not appropriate for the stratification of individual patients for the purposes of clinical trials or for making individual patient decisions. A combination biomarker such as PERSEVERE is intended to predict outcome and illness severity for individual patients with septic shock and function as a stratification tool for the care of individual children for the conduct of interventional clinical trials.

The biomarker industry is expanding. Successful candidates, performing efficiently and effectively in rapid "rule-out" or "rule-in" strategies and facilitating the early triage of patients into low-risk and high-risk treatment groups, will be quickly integrated into clinical decision-making protocols.

***See also p. 165.**

Key Words: biomarkers; sepsis

Dr. Nadel is supported in part by the Comprehensive Biomedical Research Centre of Imperial College Healthcare NHS Trust.

The author has not disclosed any potential conflicts of interest.

DOI: 10.1097/PCC.0b013e3181f4d5e5

However, biomarkers alone may not be the whole answer. Combining clinical and biological markers for the diagnosis and prediction of clinical outcomes has been of major value in many clinical disorders, including solid tumors, hematopoietic malignancies, and rheumatologic conditions. The largest studies integrating clinical and biological predictors have been done in patients at risk for and with existing cardiovascular disease. For example, current consensus recommendations for the diagnosis of acute myocardial infarction include clinical findings, such as electrocardiographic changes and circulating levels of cardiac troponins (4). Another study reported that adding cardiac troponin measurements to standard World Health Organization criteria for myocardial infarction classified an additional 26.1% of patients as having myocardial infarction as compared with World Health Organization criteria alone and produced an overall diagnostic alteration in 11.5% (5).

In the critical care field, a recent study of acute lung injury/acute respiratory distress syndrome in adults has concluded that a combination of biomarkers and clinical predictors is superior to clinical predictors or biomarkers alone for predicting mortality in acute lung injury/acute respiratory distress syndrome and may be useful for stratifying patients in clinical trials (6).

Will PERSEVERE be our holy grail—a marker or combination of markers that is easily measured, readily available, meaningful, and directly related to important clinical outcomes? It will take an enormous effort for such markers to be trusted by individual clinicians making therapeutic, research, or specific outcome predictions in individual patients. With careful attention to detail and appropriate understanding of their use and purpose, the full potential of such biomarkers in the treatment of patients with critical illness can be achieved.

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Red blood cell transfusions in children: Treat the child, not the number!*

The ability to safely transfuse red blood cells (RBC) has been shown to dramatically improve the survival of critically ill patients, who are suffering from severe anemia or hypovolemia. Although the benefit of RBC transfusion in the treatment of patients with massive blood loss due to trauma or surgical bleeding and in medical patients with severe anemia is clear, current practice in these areas continues to evolve toward less aggressive RBC support (1–4). However, the medical community may still be guilty of overutilizing transfusion therapy in the mildly-to-moderately anemic patient to the detriment of those patients. Recent literature tells us what we do know about transfusions; i.e., we know that a) the risk of infection transmitted by blood transfusion has been dramatically reduced over the past decade and that the general population has little to fear in this regard (5); b) a much lower hemoglobin (hematocrit) than generally allowed is well tolerated by the vast majority of patients (6, 7); c) restrictive transfusion regimens do not harm most patients (8–10); d) transfusions carry a risk for nonhemolytic reactions that may be more deleterious and common than previously realized (11–13); e) transfusions seem to affect our immune response in ways not fully understood but to such a degree that early and late mortality is increased in transfused patients (14–17); and f) transfusion practices vary widely across disciplines and geographic areas in spite of the recent increase in our knowledge regarding transfusion, and these differences do not seem to affect outcome (18–20). Although most of these data were generated on populations of adult patients, there are enough pediatric data to believe that the major conclusions are valid irrespective of the age of the patient.

In this issue of *Pediatric Critical Care Medicine*, Istaphanous et al (21) review the data for risks and benefits of RBC transfusion in critically ill children. They provide a great service to the medical community by producing a high-quality review of published literature on this topic in an easily readable and accessible form. The authors conclude that although ". . . blood transfusions are potentially life-saving in . . . hemorrhagic shock, transfusion has been linked with significant risks and complications [that] . . . likely outweigh the potential benefits in the majority of critically ill patients." As a hematologist, I could not agree more. For too long, we physicians have behaved like numerologists and not

***See also p. 174.**

Key Words: red blood cell transfusions; risks and benefits of transfusions; children; evidence-based approach

The author has not disclosed any potential conflict of interest.

DOI: 10.1097/PCC.0b013e3181e289db

physicians by treating a number rather than the patient, even when there were sufficient data to tell us that a more patient-directed response to anemia was physiologically and medically appropriate. The authors go on to state that ". . . RBC transfusion based upon objective evidence . . . rather than on a single arbitrary trigger value would appear to be justified." I take some exception to this statement as I believe that such an approach is justified by our current level of knowledge. Although one can argue with what objective measure(s) to use, I believe that the data clearly support such an evidence-based approach.

Recently, we have all been inundated with exhortations to use "evidence-based medicine" principles in our daily practice. Residents and medical students are being taught how to analyze medical literature using these principles, and faculty members are being trained how to teach evidence-based medicine. Excuse me for being a dinosaur, but I thought that's what we all were taught during medical school, residency, and fellowship when our teachers and mentors showed us (demanded of us) how to take information from the literature and apply it to our patients. I remember clearly having to defend on morning rounds why I chose which antibiotic or antihypertensive, or why I decided to (or not to) transfuse my pancytopenic patient. When did we, as a community of medical professionals, forget these principles and revert to a "we do it this way because this is the way we do it" approach? Has our fear of being criticized (or sued) for implementing a new treatment paradigm clouded our ability to recognize new approaches and to embrace them because they offer better care to our patients? Is the ease of giving an RBC transfusion causing us to not critically evaluate the need to transfuse a given patient? Would we be more likely to critically evaluate the need for a transfusion if it required more coordination of care and resources than currently required? Or, do we transfuse because we do not fully understand why patients are placed at risk with transfusions? I do not know the answers to each, or any, of these questions. However, I do believe that a lack of understanding of the mechanism of an adverse event causes many of us to question the causal nature of that event.

We understand the mechanism of acute hemolytic events with transfusion, the risk of transfusion-associated viral transmission, and now better understand (at some level) why transfusion-related acute lung injury occurs, and we have taken steps to minimize these events. However, the relationship between RBC transfusion and increased nosocomial infections or increased late mortality is not readily apparent. Why is it that patients with cancer who receive more RBC transfusions and those who receive an erythropoietin-stimulating agent have an increased cancer recurrence rate and late mortality (22)? The mechanism, the pathophysiology, escapes us. Consequently, we question whether this relationship is real or artifact. That response is not only normal, it is desired as it causes us to ask more questions and ultimately uncover more answers. However, what is not desirable is to discount the data and ignore the possible relationship to the detriment of our patients.

Fortunately, while we might not understand all of the "whys" presented by the data demonstrating a worse outcome in those patients who receive more RBC transfusions, there are enough studies showing that restricted transfusion regimens do not harm patients, and there are enough physiology studies explaining why most patients not only can, but do, tolerate lower hemoglobin levels than previously accepted. Istaphanous et al have done their job by presenting the published data in an easily digestible package. Now, we must do ours by taking that information and applying it to how we make decisions and provide care to our patients. Those who investigate the immunomodulatory effects of RBC transfusion will help by defining how and why this occurs. We should not wait for those data to implement change. Until then, I—for one—will continue to encourage my colleagues to not transfuse unless there is a clearly defined benefit that we can identify.

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It is what it was*

Severity and case-mix adjustment methodologies in pediatric critical care have not only spawned many quality assessments by comparing observed with predicted outcomes, but they have themselves become the focus on many evaluations. The two general pediatric severity of illness systems, the Pediatric Risk of Mortality and the Pediatric Index of Mortality (PIM), have published their validation data and have undergone intermittent adjustments and revalidations, which may or may not be in the public domain (1, 2).

What are our performance expectations of a severity of illness adjustment method? The answer, "It is what it was." The performance of a severity score in an independent sample, whether it is a pediatric intensive care unit (PICU), a group of PICUs, or a country, is not a "validation" of the method. Rather, it is a comparison of the relationship between the predictor variables (that is, physiological variables) and outcome in the two samples. If the relationship of predictor variables to outcome in the two samples is similar, the performance will be similar. If the relationship is not similar, the performance will be different. The most interesting question when the performance is different is, why does it perform different from expectation? Is it an issue with personnel? Are the diagnostic and therapeutic options equally available with equivalent use? Are there important issues in the healthcare delivery system? Is the score simply not appropriate for a different diagnostic population? Are there data collection issues? Remember, the future is "never" exactly the same as the past. With the ease of gathering large samples, there may be statistically detectable differences that are not clinically significant.

We should be able to assess the likelihood of good or poor performance of the scoring system based on the validation study and the new sample. Let us take the example of PIM-2 in the article by Czaja et al (3). PIM-2 was developed from data collected in 1997–1999. The study included a sample from 14 PICUs from Australia, New Zealand, and the United Kingdom contributing from 327 to 3276 patients (2). There were only 5301 cardiac patients and calibration was not specifically tested in this cardiac subsample. PIM-2 has only four physiological variables (systolic blood pressure, Pa_{O_2}, base excess, and pupillary reactivity) and only two specific cardiac diagnoses (hypoplastic left heart syndrome and cadiomyopathy/myocarditis). Importantly, PIM-2 has an inherent weakness in its potential for lead-time bias because its observation period is a variable time period starting when the first intensive care unit physician makes face-to-face contact with the patient (transport, emergency department, non-PICU care area, etc) through the first hour in the PICU. The study by Czaja et al describes a later time period (2005–2007) in a different healthcare system (United States) and in a larger sample of PICUs with greater diversity (44 PICUs with sample sizes ranging from one to 1057). Importantly, there are no data to assess if the data collection times were similar in the two samples. The pre-PICU care responsibilities for intensivists vary widely even in the United States, and the international comparison probably adds more variability.

Given these basic comparative facts between the validation data for PIM-2 and the current study, should we expect PIM-2 to perform well? Would it not be surprising if it did perform well? First, both cardiac surgery and intensive care for cardiac patients have evolved rapidly (4, 5); prediction algorithms developed more than 5 yrs ago are likely to be outdated. Second, although the different national healthcare systems may have superficial similarities, there may also be very important details that are different and affect outcome. This also may exaggerate the variable time period for data collection of PIM-2. The discussion by Czaja et al details many examples of differences in observed vs. predicted outcomes when scores are exported to different healthcare systems. Third, the PIM-2 score only has four physiological variables and two specific cardiac diagnoses. Intensive care unit outcome prediction for cardiac surgery patients is dependent on both anatomic and physiological data. Two existing coding systems with numerous anatomic diagnostic categories have insufficient predictive performance for reliable institutional assessments and are best termed "risk-stratification" methods (6, 7). The lack of physiological variables in PIM-2 is further disturbing because outcome is highly correlated with physiological variables and the vast majority of PICU "prediction power" comes from physiological not case mix variables when they are both available for model development (1). Fourth, a specific prediction model for cardiac patients was not developed in PIM-2. Could one reasonably expect excellence in PICU prediction performance for cardiac surgery patients with the PIM-2 score that is limited in both physiological and diagnostic information and never specifically modeled cardiac surgery patients?

***See also p. 184.**

Key Words: severity of illness; pediatric intensive care; pediatric intensive care unit; quality of care; outcomes; outcomes research; cardiac intensive care; congenital heart disease; severity scores; severity of illness

The author has not disclosed any potential conflicts of interest.

DOI: 10.1097/PCC.0b013e3181f2669f

Assuming reliable and accurate data collection and proper statistical methods, severity scores are what they were. If the prospective sample does not fit, the interesting question usually is, why? What has changed or is different? Unfortunately, Czaja et al may have missed an opportunity to help us determine what is lacking in PIM-2 so future model development efforts for cardiac patients will be more successful (8).

The most important use of severity and case-mix adjustment methods (whether they are Pediatric Risk of Mortality, PIM, or another method) is for internal benchmarking. Getting better is usually a slow process that we must continually work on (9, 10). Sequential assessments within a single unit (internal benchmarking) minimize the issues of sample differences, data integrity, and lead-time bias and enable us to track our progress going forward. The important goal is continued improvement based on reliable assessments of performance and severity scores help us accomplish this goal (11).

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Cortisol-binding globulin: More than just a carrier?*

Over the past few years there has been growing interest in the function of the hypothalamic-pituitary-adrenal (HPA) axis in children undergoing cardiac surgery. This interest was driven, among other factors, by the facts that hemodynamic instability in the postoperative period is associated with worsened clinical outcome and that HPA axis integrity is essential to maintain hemodynamic stability during homeostasis and in response to stress. So far, studies have focused on the diagnosis of adrenal insufficiency—the most studied form of HPA axis dysfunction—using criteria developed in noncritically ill children or in adults with sepsis. Most of these studies failed to establish a link between HPA dysfunction and worsened outcome of children undergoing cardiac surgery (1, 2). There are some particularities of the postoperative cardiac population that could explain these findings. Cardiac surgery is a major stressor and should activate the HPA axis response to stress. Therefore, patients undergoing cardiac surgery are expected to have "high cortisol levels." Since we do not know what the appropriate cortisol level in response to cardiac surgery is, we cannot use baseline (or random) cortisol to assess HPA activity. This problem is also found in other critical illnesses, such as sepsis. In sepsis, the HPA axis is also already activated, so the cortisol rise in response to adrenocorticotropic hormone (ACTH) stimulation has been used to identify adrenal insufficiency (3, 4). Use of this criterion in the early postoperative setting also has limitations. Cortisol levels are unexpectedly low in the early postoperative period following cardiopulmonary bypass (CPB) (5–7). This may be due to the use of corticosteroids before CPB that can theoretically inhibit the HPA response and artificially lower the cortisol level—although a recent study questioned this theory (1). It can also be related to hemodilution associated with CPB that could further decrease cortisol in the early postoperatory period (because priming solutions have little or no cortisol). Independent of cause, this "artificially" low baseline cortisol level makes it difficult to interpret the cortisol response to an ACTH stimulation test. Also, these studies used total cortisol, rather than free cortisol, levels to assess the HPA axis function in children. Although total cortisol has been widely used, most cortisol is carried in the circulation bound to a carrying protein—cortisol-binding globulin (CBG)—and the complex cortisol–CBG is thought not to have significant biological activity.

In this issue of *Pediatric Critical Care Medicine*, Dr. Wald and colleagues (7) went a step further on the assessment of the HPA axis function in critically ill children after cardiac surgery. The authors assessed the adrenal function of these patients using the ACTH stimulation test and found, not surprisingly, no association between total cortisol levels (baseline or post-ACTH stimulation) in the early postoperative period and clinical

***See also p. 190.**

KEY WORDS: adrenal function; pediatric intensive care; cardiac surgery; bypass; cortisol; synachten; cortisol-binding globulin; transcortin; adrenal insufficiency; hypothalamic-pituitary-adrenal axis

The authors have not disclosed any potential conflicts of interest.

DOI: 10.1097/PCC.0b013e318202f5ca

outcome. However, the authors also measured CBG and albumin levels, making it possible to estimate the free cortisol level—the biologically active form of this hormone. This analysis revealed that low CBG levels were associated with worsened clinical outcomes—a rational association since CBG levels decrease with stress and could be associated with severity of illness. However, the authors also reported that a higher free cortisol response to ACTH was associated with worsened clinical outcomes. This is a paradoxical finding because inadequate adrenal reserve (i.e., the inability to increase cortisol levels in response to ACTH stimulation) is associated with worsened outcome in other forms of critical illness (e.g., sepsis, acute respiratory distress syndrome) (3, 4). After cardiac surgery, children with the physiologic ability to increase free cortisol levels would be expected to build a better response to the stress of surgery and have a better recovery. Interestingly, children with a higher response to ACTH also tended to have lower free cortisol at baseline. It is reasonable to assume that the low baseline free cortisol may have played an important role in determining a patient's response to ACTH, and if the baseline cortisol was artificially lowered by one of the reasons described above, it could explain this paradoxical finding.

When CBG and free cortisol response to ACTH were included in a regression model, only CBG was associated with clinical outcomes (i.e., inotropic score and fluid requirement). This suggests that CBG is more important than free cortisol response to ACTH in this population, but how can a carrier protein have such an effect on the clinical outcome? There are several possible explanations. First, CBG plays an important role in controlling cortisol clearance. Free cortisol, but not CBG-bound cortisol, can be metabolized in target tissues and excreted by the kidneys (8, 9). High CBG levels, therefore, prevent metabolic and renal clearance of cortisol. If the low CBG levels described by Wald and colleagues (7) persist for prolonged periods, it could contribute to adrenal exhaustion by requiring a higher cortisol production rate to maintain hypercortisolemia expected in critical illness. Second, low CBG may impair site-specific activities of cortisol. Usually cortisol produced in the adrenal glands (insoluble in water) circulates bound to carrier proteins (mostly CBG, but also albumin or α1-acid glycoprotein) and is "delivered" into target tissues by conformational changes of CBG induced by environmental change (e.g., a change in pH or cleavage by neutrophil elastase) (8, 9). Low CBG levels after cardiac surgery may, therefore, impair this "delivery" mechanism, decreasing site-specific activity and increasing cortisol excretion/degradation. Third, recent studies suggest CBG itself may be biologically active. For example, *in vitro* studies showed that the CBG–cortisol complex can bind to cell membrane receptors and activate intracellular second-messenger systems, increasing cyclic adenosine monophosphate within the cell (10). Furthermore, mice genetically modified to be deficient in CBG have high free corticosterone levels (the cortisol equivalent in rodents) but do not exhibit features of enhanced glucocorticoid signaling. Instead, these animals showed increased activity of the pituitary axis of hormonal control (i.e., high ACTH levels), normal levels of gluconeogenetic enzymes, and fatigue, indicating an inability to appropriately respond to the excess free corticosterone in the absence of CBG. Finally, CBG-deficient mice also showed aggravated response to septic shock despite being able to appropriately increase circulating levels of free cortisol, therefore suggesting the aggravated response to septic shock is related to unknown biological activity of CBG (11). Last, the association between CBG and outcome could also represent the severity of illness and have no causation effect. Children with lower CBG levels had a longer bypass time, so they were likely to have higher elastase activity (12), with increased CBG cleavage yielding lower CBG levels. Since bypass time is associated with worsened clinical outcome (13), low CBG could only represent the severity of illness.

In summary, the study by Wald and colleagues (7) showed us that there is more to HPA axis activity than cortisol levels and adrenal responsiveness. This finding may have significant implications in the management of HPA axis dysfunction after cardiac surgery because corticosteroid replacement may not be the optimal therapeutic strategy for this population. However, before we can advocate for any therapeutic intervention, we need to understand the basics of the HPA axis response to cardiac surgery. A broader evaluation of the effects of bypass and preoperative steroids in the early postoperative HPA axis function may be an appropriate initial step. Further studies are needed to identify the role, if any, that HPA dysfunction plays in the outcome of children after cardiac surgery.

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Leaks cause problems not only in Washington politics! Has the time come for cuffed endotracheal tubes for newborn ventilation?*

Increasing awareness among clinicians of the dangers of hypocapnia and improved flow sensor technology available in modern infant ventilators has caused renewed interest in monitoring and controlling delivered tidal volume (VT). Volutrauma is now widely recognized as a key determinant of lung injury and a substantial body of evidence shows that volume-targeted ventilation can provide substantial benefits (1). However, as with any new technique, with increasing enthusiasm and wider use comes greater awareness of its limitations. This may be the case with volume-targeted ventilation in the presence of a large leak around an uncuffed endotracheal tube (ETT).

In this issue of the *Pediatric Critical Care Medicine*, Dr. Mahmoud, et al (2) retrospectively evaluated the magnitude of ETT leak in a large cohort of mechanically ventilated infants and report a high incidence and large variability of substantial leak, which is seen especially in the smallest infants. Although this is not a completely new observation, it does bring into focus an important aspect of mechanical ventilation that has important implications for clinical care, especially with volume-targeted ventilation. The authors clearly are aware of these issues and appropriately emphasize the importance of accurate monitoring of tidal volume in prevention of lung and brain injury. Unfortunately, many clinicians fail to recognize that tidal volume measurement and control become grossly inaccurate in the presence of a substantial ETT leak.

Although the key message is important, the specific findings of this retrospective study must be interpreted with some caution. There are several important limitations to the study design and execution that limit the strength of the conclusions. Reliance on VT values recorded in bedside flow sheets, rather than prospectively collected, inevitably results in increased random variability, because these values fluctuate from moment to moment in actively breathing infants. The interpretation of the relationship between ETT leak and underestimation of VT (as seen in Fig. 3 of the article) is questionable, given the wide scatter at any given magnitude of leak and especially given the fact that many of the data points indicate increased exhaled VT with leak rather than the expected decrease. The authors estimate that ≥40% leak will underestimate actual VT by 1.2 mL based on the slope of the regression line. However, even if one were to accept this estimate, it is important to recognize that this is a mean value and there is wide variation among individual subjects. Consequently, it would not be appropriate to apply this simple formula and assume that an accurate value for VT can be so easily derived.

The key finding of the study is that a majority of infants experienced substantial ETT leaks. Infants with significant leaks were smaller and less mature, a finding that does not come as a surprise. These extremely low-birth-weight infants typically remain mechanically ventilated for long periods. At a respiratory rate of 60 breaths/min, the immature tracheobronchial tree is stretched 86,000 times each day, leading to dilation of the airways and the larynx. This "acquired tracheomegaly" was described by Bhutani et al (3) less than 20 yrs ago and probably explains the frequency of leaks in the tiniest infants, because the larynx dilates along with the trachea. It is also partially responsible for the increasing VT requirement in infants with evolving chronic lung disease (4). By far, the largest leak was seen in infants intubated with a 2.0-mm tube, something that is generally not advisable because of the high resistance to flow through these tiny tubes and a high risk of occlusion with secretions. As the authors noted, the large leak is a reflection of their unit policy that dictates the use of smaller ETTs as an extra precaution in the belief that this will minimize the risk of airway injury. There are no data from the modern era of neonatology to validate this widely held assumption, which may, in fact, be counterproductive; the most immature infants are most susceptible to lung and brain injury and therefore are most likely to benefit from accurate control of VT and minute ventilation, which are rendered ineffective by small ETT with large leaks.

Ventilation with large ETT leaks poses other important hazards of potentially critical importance. The authors used a specialty neonatal ventilator that has an effective, continuously adjusted leak compensation algorithm lacking in the adult-type ventilators that extend their reach into the neonatal population but are not specifically designed for neonates. In the absence of such effective leak compensation, autotriggering and failure to breath-terminate in flow-cycled modes are likely to occur with substantial ETT leaks. Although some of the universal ventilators provide a fixed level of leak compensation, this is an imperfect solution, given the large fluctuation in the amount of leak over short periods of time. Autotriggering is a serious hazard of mechanical ventilation that can lead to inadvertent overventilation, air-trapping, and pulmonary airleak. Thus, awareness of the presence of ETT leaks and the limitations of each ventilator is important.

Finally, it is important to understand that the findings of this study are device-specific. The Draeger Babylog ventilator (Draeger Inc., Lubeck, Germany) uses exhaled VT measurement to regulate VT delivery. Most other devices use inspiratory VT to limit excessive VT delivery. Depending on which device is used, large ETT leak will lead to underestimation or

*See also p. 197.

Key Words: mechanical ventilation; endotracheal tube; tidal volume; complications; leak compensation

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DOI: 10.1097/PCC.0b013e31820ac50a

overestimation of actual VT that enters the infant's lungs.

Although the authors dismiss this option, this may be a good opportunity to reconsider the possibility of introducing cuffed ETT into neonatal care. Traditional cuffed tubes are not available in sizes smaller than 3.5 mm, for which the need appears greatest. However, an innovative design patented by Theodore Kolobow in 1995 not only provided a much lower resistance to flow, because of its thin wall and greater internal diameter, but also had a fringe of soft silicone rubber "gills" that effectively sealed the trachea without applying substantial pressure to the tracheal mucosa (5, 6). Regrettably, this simple device was never commercialized, depriving us of an important tool that might potentially improve the care of extremely low-birth-weight infants.

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Development of an accurate score to predict early-onset neonatal sepsis*

The World Health Organization estimates that >3 million newborns around the world die every year. The neonatal mortality rate (deaths per 1,000 live births) oscillates, according to the region: close to five in developed countries and reaching levels such as 17, 34, and 42 in Latin America, Asia, and Africa, respectively (1, 2). The vast majority of neonatal deaths in developing countries are a consequence of prematurity, infection, and birth asphyxia. Infection diseases, including sepsis, meningitis, respiratory infection, diarrhea, and tetanus, are responsible for >30% of all neonatal deaths (2, 3).

Early-onset neonatal sepsis (EONS) is defined as sepsis that occurs in the first 72 hrs after delivery (3–7). The relevance of this definition relies on the outcome, as well as the presumed infectious agent being acquired before, during, or immediately after delivery (2–4). Consequently, accurate diagnosis and appropriate antimicrobial therapy are key to the successful management of neonatal sepsis.

EONS has been defined on a clinical basis (association of several nonspecific signs and symptoms) and related to systemic inflammatory response syndrome. However, it has been demonstrated that these clinical manifestations have low sensitivity (30%–60%) and low specificity (60%–90%), depending on gestational age (6). A sepsis work-up is usually carried out with a series of laboratory tests, and if the newborn infant appears severely ill, antimicrobial therapy is started without confirmatory laboratory results (4). The gold standard for confirming EONS relies on a positive blood/cerebrospinal fluid culture, which has its positivity decreased depending on the laboratory facilities, previous use of antibiotics, and peculiar bacterial metabolism (2, 3, 5–8).

Because of the low specificity and sensitivity of the clinical parameters to define EONS, several laboratory examinations have been incorporated to increase the accuracy of this diagnosis. Despite worldwide use, the current biological parameters, such as the leukocyte indices and C-reactive protein (CRP) level, are defined as "late" markers and are not sensitive enough to define EONS (2, 3). CRP is synthesized within 6–8 hrs of exposure to an infective agent or tissue damage. As a result of this "late response," CRP presents a positive predictive value of <50% to define EONS (3). Therefore, early markers of EONS have been focused on various groups of chemokines, cytokines, adhesion molecules, and components of the immune pathway. Several previous studies (3, 9–14), including some conducted in nondeveloped regions, have evaluated different inflammatory mediators (interleukin [IL]-1β, IL-2, IL-6, IL-8, interferon-γ, tumor necrosis factor-α) as markers of EONS.

Currently, IL-6 and IL-8 are considered to be the earliest and most sensitive ILs associated with EONS. Newborn infants display a higher percentage of IL-6– and IL-8–positive cells than adults. IL-6 has the highest sensitivity (89%) and negative predictive value (92%) for EONS compared to other biochemical markers. There is a sharp increase of IL-6 blood levels after an exposure to bacterial products, which precedes the increase in CRP level. As a result, umbilical cord levels of IL-6 have been consistently shown to be a sensitive marker for diagnosing EONS (sensitivity of 87%–100% and specificity of 90%) (3, 9–11, 13).

In this issue of *Pediatric Critical Care Medicine*, Labenne et al (15), using an elegant study design, evaluated 213 newborns (gestational age, ≤32 wks) admitted to a French neonatal intensive care unit within 6 hrs of life with a presumptive diagnosis of EONS. The whole group

*See also p. 203.

Key Words: neonatal sepsis; sepsis score; neonatal mortality; cytokines

The authors have not disclosed any potential conflicts of interest.

DOI: 10.1097/PCC.0b013e3181e8b6f6

was submitted for a complete sepsis evaluation, including cytokines serum levels, and CRP level that were measured 12 hrs and 36 hrs after birth. In this sample, 31 (14.6%) newborns were classified as having a definitive or very possible diagnosis of EONS. There was a strong association between EONS and elevated serum levels of IL-6 (>300 pg/mL), IL-8 (>200 pg/mL), and IL-10 (>40 pg/mL). These IL-6 and IL-8 cutoff points presented high sensitivity (87% and 90%, respectively) with a modest specificity (82% and 62%, respectively) for identifying EONS.

After a multivariate analysis, a mathematical score model was developed on the basis of three clinical variables (presence of premature rupture of the membranes >12 hrs, mechanical ventilation, and positive maternal vaginal colonization or positive maternal urine culture) and three biological markers (levels of IL-6, IL-8, and CRP).

Using this score in the same source population, values of >6.5 had 100% sensitivity (95% confidence interval, 86%–100%) with a specificity of 80% (95% confidence interval, 73%–85%) to identify EONS. Even considering that this study could represent a good starting point toward the development of an accurate score for predicting EONS, these results should still be considered with caution. First, when a score is used in the same population from which it was derived, the results might be overestimated. Several scores when used (validated) in other comparable groups (although being similar to the original population) have decreased their accuracy (16). Validating the score developed by Labenne et al (15) in other groups of neonates with suspected EONS will define its real accuracy.

Another aspect is related to the sample size of the source population. Considering the high mortality risk with EONS, it is desirable that a score with extremely high sensitivity (no one possible EONS would be missed), despite its specificity, be <100%. However, depending on the sample in which this score was calculated, the "sensitivity of 100%" could be misleading or overestimated. Let us suppose that a score with 100% sensitivity (95% confidence interval) to detect EONS was obtained from a sample of 30 patients. In this case, it is assumed (on a statistical basis) that 9.5% of truly infected newborns would be missed. However, when using the same score to evaluate a sample of 300 newborns, the number of missed EONS would be <1% (3). Labenne et al (15) included in their study >200 newborns, but only 31 (14.6%) of them had proven or possible EONS. These few cases of true infections might have induced some bias and even overestimated the sensitivity and specificity in the derived score (3, 13).

Some ILs (IL-6, IL-8) and CRP increase their serum concentration in the presence of other neonatal stress such as hypoxic respiratory failure, perinatal asphyxia, meconium aspiration, persistent pulmonary hypertension, and histologic chorioamnionitis (3, 9, 11, 12). This is particularly relevant for this population (preterm infants); antenatal intrauterine infection and the fetal inflammatory response seem to be important pathogenic factors for preterm birth. Furthermore, the proinflammatory cytokines have a half-life of only a few hours. Subsequently, the precise time of blood examination collection is a decisive factor (12, 17). In this study, a moderate increment in the IL-6 and IL-8 levels was observed in noninfected newborns who had premature rupture of the membranes, were submitted to surgical procedures, required mechanical ventilation, and were born to mothers with chorioamnionitis. On the other hand, mechanical ventilation was provided to 94% (29 of 31) of the newborns with a diagnosis of EONS, which could represent a confounding factor for the increment of the IL levels in the EONS group. It could be one of the reasons to explain the high cutoff levels for IL-6 observed in EONS in this study, which are different from those observed in other studies (10, 13). Using this score in a similar group with different prevalence of mechanical ventilation would give us the exact impact of these variables in this mathematical model.

EONS is a critical clinical condition that must be identified rapidly. In addition, in this era of multidrug resistance, it is mandatory to avoid unnecessary use of antibiotics to treat noninfected infants. Thus, rapid tests that differentiate infected from noninfected newborns have the potential to decrease mortality, prevent unnecessary use of antibiotics, and reduce drug resistance (3). Several other biological markers have been proposed in this condition. In one study, the procalcitonin serum levels measured sequentially in 48 hrs intending to guide maintenance or withdraw antibiotic therapy in preterm babies admitted with suspected EONS could decrease in 27% the use of antibiotics compared with a control group (14).

We believe that Labenne et al provide an excellent contribution toward the development of an accurate score to predict EONS in the newborn population. In this regard, some complementary steps are lacking, such as a) validation of this score in similar and comparable populations and b) evaluation and possible incorporation of some other biological markers to increase the accuracy of this mathematical model score.

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Acute kidney injury treatment and the optimization of diuretics in newborns*

In this issue of *Pediatric Critical Care Medicine*, the article titled by Oliveros et al (1) suggests that in patients who are furosemide nonresponsive, bumetanide may be an alternative with improved dieresis when compared with furosemide. This retrospective study evaluated infants who had oliguric renal failure secondary to a myriad of diseases, but mostly related to hypoxic ischemia. These patients were treated with the usual therapy of volume reconstitution and/or volume restriction and were placed on furosemide as a way to enhance urine output. This increased urine output would subsequently allow for improvement in delivery of nutrition as necessary. The authors point out that in a subset of babies who did not respond adequately to furosemide, moving them to bumetanide as an alternative to furosemide seemed to result in improvement in their oliguria. The authors suggest that these patients have had no increased risk of complications, which would be ototoxicity and nephrotoxicity of bumetanide as opposed to the furosemide population.

Premature infants with acute kidney injury (AKI) comprise a difficult population. Mortality in those patients undergoing renal replacement therapy is in excess of 70% (2, 3). The prevalence of AKI may be as high as 26% in this very premature population according to recent work by Askenazi et al (4). Many programs are looking at ways to enhance recovery or even early prevention of renal function to avoid dialysis because of its associated high mortality rate. It needs to be suggested that the mortality rate is related to the severity of illness rather than to the dialysis.

Oliveros and associates (1) suggest that bumetanide would be a superior medication to furosemide. The difficulty with this article is that it is not a true head-to-head comparison of these medications. The dose comparison of roughly a 40 mg:1 concentration of furosemide to bumetanide makes it difficult to know whether the patient who took bumetanide received a proportionally higher loop diuretic dose. Furthermore, there is a compelling factor that these patients often had associated hyperbilirubinemia, which may affect the delivery of the loop diuretic at the level of the kidneys due to bilirubin binding of the medications.

Other maneuvers that have been done to minimize AKI include the use of aminophylline in the labor deck to improve oliguria as noted by Bhat et al (5). Recent work by Hobbs et al (6) would suggest that an impact on uric acid manipulation may improve AKI recovery. There is also a further shift away from the dopamine agents to other agents, such as epinephrine as well as norepinephrine, in the larger population and adults to improve renal function (7). These studies have not been conducted in the pediatric population or in the neonate population to date. It would, however, suggest that perhaps enhancing blood pressure by a tool to maximize good flow may have an impact on the recovery of urine function.

What is needed is a perspective-randomized study that compares dose equivalents of furosemide with bumetanide for the enhancement of oliguria; this work can be perceived, in this reviewer's opinion, as the next goal to achieve.

This reviewer would caution readers that this is not the next panacea for the treatment of AKI in the premature patient. Bumetanide, like furosemide, is associated with various toxicity, including ototoxicity and renal toxicity, with long-term consequences. Other regimens to enhance urine output, such as the use of thiazide-like diuretics before loop diuretics, may also improve urine output while

*See also p. 210.

Key Words: acute kidney injury; bumetanide vs. furosemide; oliguric renal failure; preterm infants; ototoxicity; renal toxicity

The author has not disclosed any potential conflict of interest.

DOI: 10.1097/PCC.0b013e3181e8b718

minimizing some of the exposure of a single agent (8).

In essence, a prospective randomized study is necessary to adequately compare dose equivalents of the benefit of one drug vs. the other. Without such a comparison, this work serves as an observational study that shows that in some infants bumetanide may be more effective; yet, one should not believe that it is the optimal therapy for all patients with AKI.

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Global versus local bioethics*

In this issue of *Pediatric Critical Care Medicine*, Dr. Pignotti takes up the Arielle's hypothetical and imaginary situation previously published by Dr. A. Janvier (1, 2). The scenario is similar (an extremely preterm baby admitted to the neonatal intensive care unit) but the actors are different. Janvier's drama is performed by Canadian doctors, nurses, parents, and baby. Pignotti's one is played by Italian actors. In both cases, futile treatments were started. In both cases, the epilogue was the same: Arielle died. However, in the first case, the parents more or less shared the decision with the neonatologist. Conversely, in the second case, they did not participate in the decision and "are silently waiting outside the door, eyes on everyone passing by, searching for a word, a message" (2). These imaginary scenarios lead to the fundamental question, "Why do physicians from different countries behave differently toward the same ethical dilemma?" A growing literature demonstrates the high degree of variability in end-of-life (EOL) care seen throughout the world (3, 4). As Dr Pignotti suggests, this variability can be justified on cultural, religious, and legal grounds. Historically, culture and religion have been the dominant forces shaping the nature of EOL care. For instance, in Italy, the Catholic church seems to have a huge influence in EOL decision and in legislation "there is an order: to resuscitate, every one, everywhere, irrespective of the cost" (2). Italian tradition considers the sanctity of all human life. Therefore, the Italian neonatologist had no choice. Conversely, the Canadian approach, under the North American influence, is more pragmatic: "the neonatologist shares his concerns with Arielle's parents. . . . He suggests 30 secs of chest compressions and one dose of epinephrine, if it does not work, he will stop. The parents agreed" (1). In the North American culture, Arielle's parents and the neonatologist share the decision, which is based on a contract-based relationship. Sanctity of life is also recognized, but the infant's best interest is also considered. If Arielle were born in France, the final decision would have been made by the doctors after exhaustive parents' information following strict procedure, which is written in the French law and published by the scientific societies. If Arielle were born in disadvantaged countries, these scenarios would appear surrealist and would have never happened: Arielle would have died at home; at the microlevel, all approaches are ethical and follow up the cultural and economic backgrounds of the respective countries. However, at a macrolevel, can we accept such variability in Arielle's care? The question is not to find universal bioethical norms. Such an approach would be a utopia because moral diversity and pluralism in medicine is a reality (5, 6). Global bioethics would never exist and we must accept different standards of EOL care. However, with Truog, we believe that some aspects of this issue are amenable to evidence-based analysis and recommendations (7). Too much variability in EOL care is too much. Across religious, cultural, and legal specificities, some standards of care are emerging from the literature (8). For instance, we know that families place a great importance on being able to communicate with clinicians about EOL care. We also know the importance of the use of sedation and analgesia, the importance of palliative care, of research, evaluation, quality improvement, spirituality, bereavement, and support services. The challenge for all of us who work in neonatal and pediatric intensive care units is not to judge who is right and who is wrong but to accept bioethical pluralism and to share our experience among countries. If we communicate among countries, we would be able to consider what aspect of this pluralism can be justified on cultural, religious, and legal grounds and what parts of our practices can be improved to conform with the best available evidence. Drs Janvier and Pignotti have provided us with Arielle's story a unique opportunity to work on this issue.

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***See also p. 215.**

Key Words: ethics; end-of-life; neonatology; pediatrics; culture

The authors have not disclosed any potential conflicts of interest.

DOI: 10.1097/PCC.0b013e3181f266af

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Let the pediatric intensive care unit's door open: But not to all winds!*

It's easy to say "let the door of the pediatric intensive care unit (PICU) open 24 hours a day." It's easier to say than to do. In this issue of *Pediatric Critical Care Medicine*, Giannini and Miccinesi (1) report that 88% of Italian PICUs have restrictive visiting policies and limit parents' presence during procedures and cardiopulmonary resuscitation. These data do not follow the wide consensus recognizing that the presence of parents during their child's hospitalization is of crucial importance (2, 3). They also disagree with recommendations from many scientific societies (2, 3). For instance, the American College of Critical Care Medicine recommends "Visitation in the PICU and NICU [neonatal intensive care unit] is open to parents and guardians 24 hrs a day (Grade of recommendation = C)," and "After participation in a previsit education process, visitation by siblings in the PICU and NICU is allowed with parental approval (Grade of recommendation = C)" (2). There is no scientific basis for limiting visitors' access to PICUs (4). Furthermore, there are many good reasons to open the PICU's door (4). Opening the PICU to the family may enhance communication with parents and help the child to endure the difficult period of intensive care. Furthermore, it has been shown that such a policy does not increase the risk of nosocomial infections (4).

For these reasons, we opened our PICU 24 hrs a day to families many years ago. This policy has required some psychological adaptation from both nurses and physicians. Our team is now accustomed to the presence of relatives during care, including invasive procedures and cardiopulmonary resuscitation. Parents, grandparents, and siblings are allowed to visit the child whenever they want. Parents can stay overnight at the child's bedside. Parents are also offered a comfortable room to rest and take a shower. A terrace planted with trees is accessible from the unit, where parents can relax and where they can have confidential conversations with nurses and physicians.

Despite this ideal surrounding, we remain dubious for several reasons. First, we have encountered dramatic and highly disturbing events related to open visitation, such as a mother attempting to murder her albino neonate, a brother disconnecting the hemofiltration catheters of his sister who had a life-threatening condition, and someone abducting a neonate. Obviously, these stories are anecdotal, but they do point out that the PICU cannot be open to all winds and that a regulation of visitations is mandatory.

Second, permanent availability of the medical and nursing teams to answer parents' questions may be detrimental. Bedside information might be superficial, repetitive, and contradictory among the caregivers. Providing information in PICUs requires a sort of ritual. Information should be given by the referring physician and nurse, in a place respecting confidentiality and privacy, with enough time to listen to parents' questions and with a compassionate approach.

Third, although family visits produce a significant positive effect on the patient, intensive care may be traumatic for the child's family. Parents, siblings, and relatives need to take a breather to better serve their role at the bedside, and they should be invited to pace themselves.

Unrestricted PICU visitation should not be dogma. Recommendations should not be universal or demagogic. Liberalizing visiting hours may not be good for every patient, every family, every PICU team. This crucial issue should be adapted on a patient-by-patient basis. We all should be grateful that this matter has been called to our attention by Giannini and Miccinesi. It is time to consider our relationship with our patients' families.

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***See also p. e46.**

Key Words: pediatric intensive care unit visitation, Italy; family presence during pediatric care; open door policy in pediatric intensive care unit; visitations regulation

The author has not disclosed any potential conflicts of interest.

DOI: 10.1097/PCC.0b013e3181dab1f0

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Imaging in severe malaria*

Acute life-threatening infection is still a leading cause of childhood morbidity and mortality in Africa. In malaria-endemic areas, *Plasmodium falciparum*, the lethal form of malaria, accounts for a substantial proportion of child mortality. Although current efforts to reduce mortality have rightly focused on prevention and early treatment, progress toward improved management and outcome has been slow. Management has been unchanged for decades, and case fatality remains high. Currently, the only specific treatments recommended for severe malaria are the time-honored quinine and, for children with severe anemia, blood transfusion (1).

At the clinical level, three major complications account for the majority of fatalities, but in reality there is substantial overlap in the clinical presentation: 1) cerebral malaria is defined as causing unarousable coma, in which parasite sequestration, perivascular inflammation, and intracranial hypertension have been implicated as etiological (2); 2) severe anemia is defined as a hemoglobin level of <50 g/L caused by increased red cell destruction (parasite-mediated, erythrophagocytosis) and reduced red cell production secondary to reduced erythropoietin activity and proinflammatory mediators (3); and 3) Respiratory distress, a clinical manifestation of metabolic acidosis, is the major independent risk factor for fatal outcome and to which hypovolemia (4), cytopathic hypoxia, and metabolic dysfunction contribute. Immunopathogenic processes are recognized as having a central role in severe malaria, with proinflammatory cytokine cascades leading to complex downstream metabolic changes that lead to multisystem involvement with similarities to sepsis (5, 6).

Globally, the use of sophisticated investigative technologies have transformed our understanding of pathophysiological derangements in critical illness and resulted in substantial improvements in acute management of children with life-threatening conditions. High-caliber, clinicopathophysiology studies of pediatric severe malaria are scarce but have the potential to provide vital information about disease in humans. However, in the context in which most cases of severe malaria are managed, even rudimentary, supportive, diagnostic information is rarely available; thus, advances have been slow.

In this issue of *Pediatric Critical Care Medicine*, Murphy et al (7) describe the use of bedside ultrasonography in helping to understand organ-specific complications. They used a relatively new tool, optic nerve sheath diameter and transcranial Doppler, as proxy measures of intracranial pressure and cerebral blood flow; they used echocardiography to examine myocardial function and ultrasound to examine spleen volume.

Using age-adjusted criteria for optic nerve sheath diameter, they found this measure to be increased or borderline in the five cases of cerebral malaria that they observed. The association between increased optic nerve sheath diameter and cerebral malaria was significant. In addition, they found either reduced cerebral flow in two cerebral malaria cases and increased pulsatility index (resistance to flow), indicating failure of autoregulation. Children with severe malarial anemia complicated by lactic acidosis also demonstrated an increased number with increased optic nerve sheath diameter measurement. Severe anemia has been previously noted to be a correlate with intracranial hypertension, and a diffuse pattern of damage suggests that reduced perfusion or hypoxia may play a role (8). In the current study, cerebral blood flow was increased in one-quarter of the children with severe anemia (3 of 12) but decreased in one child. Cerebral blood flow had no prognostic significance.

Beare et al (9) previously used this tool in children in Blantyre, Malawi, with nonmalarial causes of suspected raised intracranial pressure and used radiographic findings as the gold standard. They showed that, taking the normal upper limit as 4.2 mm, the sensitivity and specificity of this test to predict elevated intracranial pressure were 100% and 86%, respectively. Direct and indirect retinal ophthalmology linked to histopathological studies have provided valuable insights to clinical researchers. Retinal changes correlated well with histopathological findings in the brain and prognosis (10). Linking these two technologies in future research studies would provide valuable insight into cerebral blood flow, its autonomic regulation, and response to treatment. Although both of these represent minimally invasive tools with substantial utility to monitor novel interventions, optic nerve sheath diameter measurement requires specialist training to ensure quality images, because the changes are small (0.2–0.5 mm) and there are some safety concerns such as exposure of the eye to ultrasound, which might cause tissue damage by heating and cavitation but not if limited by time or intensity (<50 mW/cm^2 recommended) (11).

The authors report that, irrespective of the clinical phenotype and complications, cardiac function was well preserved with no evidence of myocardial dysfunction or, noted specifically, evidence of

***See also p. e58.**

Key Words: severe malaria; bedside ultrasonography; optic nerve sheath diameter; transcranial Doppler; echocardiography; ultrasound; myocardial function; spleen volume

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The author has not disclosed any potential conflict of interest.

DOI: 10.1097/PCC.0b013e3181e8b5f4

pulmonary hypertension. The hypothesis for the latter, although not advanced directly, implicates similarities in the consequences of intravascular hemolysis of acute severe malaria, leading to nitric oxide consumption and endothelial dysfunction, resulting in increased pulmonary arterial pressures, as seen with other causes of intravascular hemolysis (12). Traditionally, children with severe malaria complicated by symptomatic anemia were regarded as having biventricular heart failure and were treated with loop diuretics, digoxin, and gradual correction of anemia by slow blood transfusion (13). The results of clinical studies (4) have cast doubt on this approach, indicating that lactic acidosis was secondary to impaired oxygen delivery and impaired perfusion. Other studies have indicated that markers of myocardial damage and dysfunction complicate pediatric severe malaria correlating with severity of acidosis (14) and have shown evidence of mild-to-moderate myocardial dysfunction and evidence of reduced preload, which correlates with the severity of acidosis (15).

The rationale for measuring spleen size is not clear; thus, the findings and implications are more difficult to interpret. Chronic splenomegaly is usually present in children in malaria-endemic areas, with an increasing frequency in older children, and therefore are not necessarily part of the acute presentation. The authors of the current study found that splenomegaly was overdiagnosed by admitting clinicians when validated by using ultrasound. More work is required to examine spleen volume and function during the course of hospital admission, which may explain the discordance.

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What does it take to get some peace and quiet in the pediatric intensive care unit?*

Morning drags on in the pediatric intensive care unit (PICU) as you try to get through bedside rounds, a hungry baby who remains npo screams, and his alarms continue to blare; unfortunately, his nurse seems oblivious. One of the rounding physicians mutters, "Why doesn't someone intubate that baby?" and another nods in agreement. Can the stress of excessive noise cause this kind of attitude toward an event (the cry of a healthy baby) that should be "music to the ears" of the physicians who worked to get that baby back to health?

In this issue of *Pediatric Critical Care Medicine*, Jousselme et al (1) describe the efficacy and mode of action of a noise-sensor light alarm that decreased noise levels in their ICU. The authors tested an inexpensive, sound-activated, light device usually found in night clubs. The device flashed lights, which alerted nearby staff when sound levels exceeded 70 dB(A). The use of this device resulted in a 2-dB(A) noise reduction in both the central area and a nearby patient room of a 16-bed PICU/neonatal ICU. The presence of the large light device produced the 2-dB decrease in noise levels even when it was not activated to flash. Three months later, the authors returned with only the recording equipment (without the light device) and showed that the act of recording staff noise did not affect noise levels. This study replicates the finding from an neonatal ICU in Taiwan of a similar decrease in noise levels when using a homemade, sound-activated, light device triggered by sounds >65 dB(A) (2).

Levels of noise that patients and staff experience greatly exceed the recom-

***See also p. e69.**

Key Words: sound levels; noise; pediatric intensive care unit; stress; noise reduction

The author has not disclosed any potential conflict of interest.

DOI: 10.1097/PCC.0b013e3181e28a2c

mended guidelines for hospitals. A review of 32 hospital studies from 1960–2005 found that none complied with World Health Organization guidelines and that the trend over time is for increasing noise levels in hospitals (3). In 1999, World Health Organization guidelines for hospitals recommended a "maximal" level of sound not >40 dB(A) at night and for patient rooms an "average" level of sound of no >35 dB(A) during the day and 30 dB(A) during the night (4). Recently, PICUs throughout the world have reported their noise levels. Baltimore, USA reported in a 16-bed PICU an average daytime sound level of 61 dB(A), an average nighttime sound level of 59 dB(A), and the maximum sound level of 96 dB(A) (5). Sao Paulo, Brazil reported in a 10-bed PICU a basal noise level variation between 60–70 dB(A) with a maximum level of 120 dB(A) (6). Glasgow, United Kingdom reported in a 14-bed PICU an average daytime sound level of 61 dB(A), an average nighttime sound level of 59 dB(A), and the maximum sound level of 73 dB(A) during the day and 69 dB(A) at night, with the highest maximum recorded of 103 dB(A) (7). Nottingham, United Kingdom reported in a 7-bed PICU the mean noise level for all areas over the three shifts ranged from 46–61 dB(A) (8). In this issue of *Pediatric Critical Care Medicine*, the authors (1) from Marsielle, France report in a 16-bed neonatal ICU/PICU average sound levels of 61–64 dB(A) and maximum sound levels of 88–92 dB(A). These recent reports of noise levels in PICUs resemble the existing literature in that they significantly exceed noise guidelines suggested by the World Health Organization.

These continued reports (5, 8–10) of excessive noise levels in PICUs should raise concern and generate action because of the psychological and physiologic effects on patients and staff. The psychological effects of noise on patients include: annoyance, agitation, stress, confusion, irritability, reduced capacity to cope, disorientation, and intensive care "psychosis"/ICU syndrome. The physiologic effects on patients include: a) cardiovascular responses—hypertension, tachycardia, bradycardia, heart rhythm alterations, decline in oxygenation, increased metabolism, increased oxygen consumption, peripheral vasoconstriction, increased stress hormone levels, and increases in intracranial pressure; b) sleep disturbances—abnormal sleep patterns, sleep deprivation, reduction in the recuperative properties of sleep; c) increased sensitivity to pain and the need for increased dosages of pain medication; d) hearing loss and cochlear damage in neonates; and e) evidence for delayed/slowed wound healing in animals. Other detrimental effects of noise on patients include interference with speech privacy and both an increased length of hospital stay and an increased frequency of rehospitalization. The effects of noise on staff include: stress, irritability, anxiety, annoyance, fatigue, poor concentration, poor task performance, reduced sensitivity to others, job dissatisfaction, burnout, interference with staff communication, and increasing the likelihood of error. A study of staff stress in the PICU showed that, for every 10 dB(A) increase in the average sound level, the nurses' average heart rate increased by 6 beats/min (5). A study of patient sleep disturbance in the PICU found that, when maximum noise levels exceeded 75 dB(A) for ≥3 mins, wake states occurred in 57% of events (7).

There are many causes of noise in the PICU, and the typical sound levels of those events are reported (5, 6, 8, 9). Listed are groupings of the most common noise events and their levels in dB(A): a) staff conversations and activities: conversations up to 74, ward rounds and nurse handover up to 69, infants crying up to 78, coughing up to 71, closing a bin lid up to 70, closing a door up to 67, door slamming up to 78; b) medical equipment and alarms: mechanical ventilator 60–65, high-frequency ventilator up to 70, endotracheal aspiration system 50–60, nebulizer up to 65, monitor alarms 58–75, ventilator alarm 63–85, infusion pump alarm 55–75; c) communication systems: overhead pages 59–84, telephone ringing 71; d) other: cleaning crew/equipment up to 96, air conditioning up to 50. In one report, the communication between the PICU staff, anesthesiologists, and surgeons during an admission of a child for cardiac surgery postoperative care generated a basal noise level of 80 dB(A), with a maximum level of 120 dB(A) (6). Staff conversation is the main source of noise (approximately 50% of noise) within ICUs with sound levels ranging from 60–90 dB(A) (8). Environmental surfaces is another category that is an important contributor to noise levels in hospitals as walls, floor, and ceiling tend to be sound-reflecting. Reverberation is the persistence of sound in an enclosed space. Closing the doors to the patients' rooms, at least in the ICU, may actually increase the noise in the room as alarm and ventilator noise reverberates off the hard surfaces (5).

Multiple interventions to reduce hospital and ICU noise levels have been suggested. These interventions include both actions that can be taken by staff and those related to hospital design (6, 9, 11). The suggested staff actions include: staff education about noise and interventions, limiting conversations in patients' rooms, shift-change reports behind closed doors, keeping pagers on vibrate, reducing overhead pages, closing doors, using soft-soled shoes, changing intravenous bags before the alarm sounds, restocking supplies and cleaning during waking hours, abiding by policies regarding quiet times, checking medications in nonpatient areas, turning off equipment when not in use, and assessing alarm volumes and limits and reducing from the factory settings when appropriate. The ICU design suggestions include: acoustical ceiling tiles and other noise-reducing construction materials, noiseless paging systems, single-bed rooms, quieter alarms (including visual or vibratory), and the use of background noise (white noise or music).

Jousselme and colleagues (1) once again demonstrate that noise levels in PICUs greatly exceed the recommendations. They go further by showing that the use of a simple and inexpensive reminder of excessive noise lowers average sound levels. Whether a statistically significant 2 dB(A) decrease in average sound levels is clinically significant is not demonstrated (remember that the decibel scale is a logarithmic measure). Two dB(A) is the difference between daytime and nighttime PICU noise levels in several reports. Showing a clinical benefit to the use of this device on patient sleep pattern, staff stress level, or length of stay would be a worthwhile follow-up study.

The 70-dB(A) trigger for the activation of their device to remind staff is an interesting choice. Does setting the trigger at that high a level give the staff the impression that noise up to 70 dB(A) is permitted? Although the study by Jousselme et al (1) did not find a reduction in the number of the peak noise events, the study (2) with a similar device in Taiwan used a 65-dB(A) trigger level and found reductions in both average noise levels and number of peak events. The use of a trigger at a lower noise level to activate the light device may have a greater impact on noise reduction, and a study com-

paring trigger levels is needed. Additionally, this study raises the need for further investigation to determine if the reduction in average noise level due to the presence of a reminder device will persist for longer than a 6-day period.

The findings by Jousselme et al (1) show that using a reminder of excessive noise levels can have a positive effect on average noise levels in the PICU. This study scratches the surface of an area that should have great importance but remains largely ignored, as our patients and we continue to suffer. This is the beginning of much needed research into the elimination of noise, staff education, and technological advances that will lead to a quieter, less-stressful PICU environment in the future. Perhaps a future where bedside noise inside private rooms is limited by materials with low sound reflectivity and the reduction of alarm noise and bedside discussions through the use of safety glasses with heads-up, visual displays that show alarms, pages, and communications from colleagues. A future in which PICU noise levels are routinely monitored by individual dosimeters (for both staff and patients), with real-time feedback, and reviews of noise exposure occur at regular intervals (along with the usual quality improvement measures).

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Early exchange and pheresis therapies in critical pertussis*

This issue of *Pediatric Critical Care Medicine* includes a case report by Dr. Martinez and colleagues (1) on the use of exchange transfusion in a case of critical pertussis occurring in an 8-wk-old infant girl. To date, most reports of series of fatal *Bordetella pertussis* show a female prevalence in mortality (2, 3); although this may be confounded where immunization practices differ by gender. As well, the prevalence of pertussis critical illness in unimmunized, very young infants as compared with other age groups is well known (4, 5). Although the physiologic nature and etiology of these findings is beginning to emerge in ongoing studies as well as recent reports (6–8), it is encouraging to consider this report of the successful use of exchange transfusion to modify the course of this life-threatening and persistent problem. Critical pertussis illness is beginning to be described as "fulminant" and "malignant," as differentiated from the outpatient coughing illness (9, 10).

The prominent leukocytosis in this case (119,440 leukocytes per cubic millimeter) signified that organ failure and death were likely outcomes for this patient. Pulmonary hypertension (50 mm Hg calculated by tricuspid jet velocity) on the basis of occlusion of the pulmonary vascular tree via entrapment of abnormal leukocytes was severe. A recent report from France summarizes the pathophysiology of pulmonary arterial hypertension when pulmonary venous occlusion occurs in adults with diverse etiologies of the occlusive processes (11). Over time, diffuse intimal proliferation in the pulmonary vascular tree occurs, especially in the pulmonary venules and small veins. Such changes have presumably not taken place yet in the acute setting of critical pertussis with severe leukocytosis. We might expect that, in the acute setting, pulmonary veno-occlusive changes may be rapidly reversible in the young patient with critical pertussis illness, if the occluding white blood cells can be safely removed.

The cyclic adenosine monophosphate overdrive induced by pertussis toxin exposure reported in laboratory models may mediate fundamental disruption in cell stress responses and immune signaling (12). This could explain the organ system failure described in postmortem series (13). Such disruption may be induced to a greater or lesser extent by the amount of pertussis toxin elaborated by a given strain of *B. pertussis* and at least partially explain the persistent of pertussis critical illness in infants even wherein immunization coverage rates are high (14). The imposition of cyclic adenosine monophosphate overdrive on a relatively anergic host may contribute to the pathology described in recent reports (9) that suggest lymphocyte depletion may be prominent in infants dying of *B. pertussis* infection.

***See also p. e107.**

Key Words: Bordetella pertussis; leukapheresis; pediatric intensive care unit; exchange transfusion; pulmonary hypertension; leukostasis

Dr. Nicholson is an employee of NIH. The author has not disclosed any potential conflicts of interest.

DOI: 10.1097/PCC.0b013e3181fe293f

Evolution of *B. pertussis* in the post-vaccine era in a manner that enables the fulminant course and organ failure seen in the pediatric intensive care unit (PICU) is one explanation currently being actively explored in the Eunice Kennedy Shrive National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network (15, 16). This is a new model partnership between the Collaborative Pediatric Critical Care Research Network pediatric critical care investigators and an National Institute of General Medical Sciences-supported basic scientist seeking to understand the possibility of genomic variation, host microbe interaction, and strain ecology in *B. pertussis* critical illness pathogenesis (17).

Treatment of pertussis critical illness remains challenging, even in the most tertiary of PICUs. Reports of the use of advanced transfusion practice in the PICU have included apheresis, plasmapheresis, and partial-, single-, and double-volume exchange transfusion. Such practices are not evaluated in large trials, nor in descriptive cohorts, and are described in anecdotal studies to have varying degrees of efficacy in ameliorating the life threatening processes that they are used to treat. In addition, the removal of leukocytes via exchange transfusion by using leukocyte depleted blood or with pheresis techniques is occasionally described (18, 19).

One of the better-known uses for leukapheresis in the PICU is actually the severe leukocytosis that occurs at presentation (or relapse) of leukemia in the acute care setting. In adult acute myelogenous leukemia, hyperleukocytosis (defined in most reports as a white blood cell count of $>100{,}000/mm^3$), leukapheresis is used to reduce the risks for the early mortality that arise from leukostasis in pulmonary and cerebral vessels. One recent retrospective report of a series of twenty-five such patients found definite reduction in early mortality risk and no procedural side effects or complications (20). Experience with exchange transfusion in critical pertussis, as in this issue's case report is not reported extensively, however.

In pediatric critical illness, the use of exchange transfusion with leukodepleted blood, as well as the use of leukapheresis to treat the risks of leukostasis, are reported anecdotally (21, 22). This and many other critical care treatment strategies for critical pertussis illness await rigorous description, mechanistic understanding of therapeutic effect and risks, and hypothesis generation to inform studies of practices that are used in the PICU. An open and inquiring mind for the intensivist caring for a child with critical pertussis is the best way to move pediatric critical care medicine and treatment of critical pertussis forward.

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