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Best Evidence

Journal Scan

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Articles Reviewed

1. **Early administration of azithromycin and prevention of severe lower respiratory tract illnesses in preschool children with a history of such illnesses---A randomized clinical trial**
   Bacharier LB, Guilbert TW, Mauger DT, Boehmer S, Beigelman A, Fitzpatrick AM; et al. *JAMA*. 2015;314 (19): 2034-2044

Objective

To evaluate if early administration of azithromycin, started prior to the onset of severe lower respiratory tract infection (LRTI) symptoms, in preschool children with recurrent severe LRTIs can prevent the progression of these episodes.

Study Design

A randomized, double-blind, placebo-controlled, parallel-group trial conducted across 9 academic US medical centers in the National Heart, Lung, and Blood Institute's Asthma Net network, with enrollment starting in April 2011 and follow-up complete by December 2014. Participants were 607 children aged 12 through 71 months with histories of recurrent, severe LRTIs and minimal day-to-day impairment. The primary outcome measure was the number of RTIs not progressing to a severe LRTI, measured at the level of the respiratory tract infections (RTI), that would in clinical practice trigger the prescription of oral corticosteroids. Presence of azithromycin resistant organisms in oropharyngeal samples, along with adverse events, were among the secondary outcome measures

Measurements and results

Participants were randomly assigned to receive azithromycin (12 mg/kg/d for 5 days; n=307) or matching placebo (n=300), started early during each predefined RTI (child's signs or symptoms prior to development of LRTI), based on individualized action plans, over a 12- through 18-month period.

A total of 937 treated RTIs (azithromycin group, 473; placebo group, 464) were experienced by 443 children (azithromycin group, 223; placebo group, 220), including 92 severe LRTIs (azithromycin group, 35; placebo group, 57). Azithromycin significantly reduced the risk of progressing to severe LRTI relative to placebo (hazard ratio, 0.64 [95% CI, 0.41-0.98], $P=.04$; absolute risk for first RTI: 0.05 for azithromycin, 0.08 for placebo; risk difference, 0.03 [95% CI, 0.00-0.06]). Induction of azithromycin-resistant organisms and adverse events were infrequently observed.

Conclusions

Among young children with histories of recurrent severe LRTIs, the use of azithromycin early during an apparent RTI compared with placebo reduced the likelihood of severe LRTI. More information is needed on the development of antibiotic-resistant pathogens with this strategy

Reviewer's comments

Recurrent severe wheezing episodes affect up to 15% to 20% of children prior to 6 years of age. Though viral etiologies are most common bacterial isolates have also been reported. In recent years, there is increasing evidence for using azithromycin in the management of various respiratory diseases such as acute bacterial bronchitis, mycoplasma pneumonia, bronchial asthma, RSV bronchiolitis and bronchiolitis obliterans syndrome. Longer durations of azithromycin therapy have been reported to decrease acute pulmonary exacerbations in cystic fibrosis, non-cystic fibrosis bronchiectasis, chronic suppurative lung disease, bronchial asthma, surfactant protein deficiency, and chronic obstructive pulmonary disease in adults. The therapeutic and prophylactic diversity suggests that the effects of azithromycin may not be mediated by antimicrobial action alone and point towards anti-inflammatory and/or immunomodulatory action.

The present study was done to evaluate if early administration of azithromycin in children with recurrent severe wheezing can prevent the progression to clinically significant LRTIs defined in the study as requiring systemic corticosteroids, unscheduled physician office visit, urgent or emergency department visit, or hospitalization. Prevention of severe LRTIs is a highly desirable outcome given recent evidence that oral corticosteroids, the typical rescue strategy for such episodes, may not be effective in reducing symptom burden in the preschool age group, in contrast to their efficacy in older children with established asthma. Children with significant symptomatic asthma, requiring frequent systemic corticosteroids were excluded in the trial. The study showed benefit in reducing the progression to severe LRTI and also reduced its symptoms irrespective of age group, sex, asthma predictive index (API) score, type of virus association, seasonal variations. The treatment group experienced a lower risk of developing a severe LRTI. For example, with the first RTI that was treated during the study period, 7% of children in the treatment group developed a severe LRTI compared with 10% of the placebo group. This difference became more magnified with each subsequent RTI, such that by the fourth RTI of the study, 4% of the treatment children vs 30% of the placebo children developed a severe LRTI. Over the entire study, this resulted in a treatment/placebo adjusted hazard ratio of 0.64. The results of this trial suggest that early treatment of RTI with azithromycin may decrease the development of severe LRTI by over 35%, an important result. Children may also benefit from repeating such therapy with subsequent illnesses

A recent study published by Stokholm et al titled 'Azithromycin for episodes with 'recurrent troublesome lung symptoms' (asthma-like symptoms) in young children aged 1-3 years (Lancet Respir Med. 2016;4:19-26) concluded that azithromycin caused a significant shortening these episodes by 63.3% (95% CI 56.0–69.3; $P<0.0001$). The effect size increased with early initiation of treatment, showing a reduction in episode duration of 83% if treatment was initiated before day 6 of the episode compared with 36% if initiated on or after day 6($P<0.0001$). The authors concluded that azithromycin reduced the duration of episodes of asthma-like symptoms in young children. But the authors themselves were weary of clinical application of these results knowing the fact antibiotic resistance could be a serious issue which was not studied in the study

The recent AZISAST (Azithromycin for prevention of exacerbations in severe asthma):a multicentre randomised double-blind placebo-controlled trial in adults (Thorax.2013 Apr;68(4):322) also showed a significant reduction in the LRTI rates in azithromycin-treated patients with non-eosinophilic severe asthma.

Despite the availability of several pieces of relatively high quality evidence highlighted above, it should be noted that azithromycin is still not included in management guidelines for most of these conditions as a standard of care. The current approach to RTI is to try to minimize the use of antibiotics unless an infection is clearly bacterial in origin, and to treat severe LRTI when it occurs. The concern for resistance is legitimate and this study had 16.7% resistance in azithromycin group vs 10.8% in the placebo group. Such concern needs to be balanced, however, with the potential for macrolides to improve the quality of life of children with recurrent, severe LRTI. Given the small sample size of the study, further studies are needed to assess the potential increased risk of antibiotic resistance vs the comparative effectiveness of azithromycin with respect to other asthma medications to prevent severe LRTI.

But whether this approach will cause a paradigm shift given that many clinicians will not remember the narrow criteria used for study inclusion and exclusion and will attempt to prescribe azithromycin treatment to other populations is a matter of speculation. This study examined the proactive administration of azithromycin at the early signs of RTIs which were not yet severe, and these findings cannot be extrapolated to azithromycin's potential role as a rescue therapy for patients already experiencing severe LRTI symptoms and who are on daily controllers. It is important to recognize that this study does not suggest treating all RTI with antibiotics, but rather that the use of a macrolide antibiotic may be considered, perhaps, in the select group of children similar to those studied with a history of recurrent wheezing with previous RTIs. Future studies comparing the relative benefits of early azithromycin therapy with either daily or

intermittent high-dose inhaled corticosteroids may help determine the relative efficacies of this treatment strategy.

2. Clinical ef cacy of high- ow nasal cannula compared to noninvasive ventilation in patients with post-extubation respiratory failure

Yoo JW, Synn A, Huh JW, Hong SB, Koh Y, Lim CM. Korean J Intern Med 2016;31:82-88

Objectives

The aim of this study was to evaluate the clinical outcomes of high flow nasal canula (HFNC) in patients with Post Extubation Respiratory Failure (PERF) compared to those of noninvasive ventilation (NIV).

Study design

Retrospective study was performed in 28-beded medical ICU in Seoul, South Korea. Two groups were established: the first group (NIV group) included patients who received treatment from April 2007 to March 2009, while the second group (HFNC group) included patients who underwent treatment from April 2009 to May 2011.

Measurements and results

Medical patients ≥ 18 years old who developed respiratory failure within 48 hours of Extubation, was regarded as PERF, and NIV or HFNC was performed.

Respiratory failure was defined as clinical signs of increased effort on breathing (such as active contraction of the accessory respiratory muscles) that developed within 48 hours of extubation, plus one of the following: (1) respiratory acidosis (defined as an arterial pH < 7.35 with a PCO2 > 45 mmHg);(2) Respiratory rate >than 25/min (3) hypoxemia defined as PaO2/FiO2 < 300 mmHg or SpO2 of < 90%.

The rate of avoidance of re-intubation was not different between the HFNC group (79.4%) and NIV group (66.7%, p = 0.22). All patients with HFNC tolerated the device, whereas five of those with NIV did not tolerate treatment (p = 0.057). The mean duration of ICU stay was significantly shorter in the HFNC group than in the NIV group (13.4 days vs. 20.6 days, p = 0.015). There was no difference in ICU or in-hospital mortality rate, incidence of ICU-acquired pneumonia associated with PERF, physiological parameters and Laboratory data.

Subgroup analysis done according to the level of PCO2. In the 50 patients with PaCO2 < 45 mmHg, patients with HFNC showed a lower ICU mortality rate (3.6% vs. 27.3%, p = 0.034) and in hospital mortality rate (14.3% vs. 40.9%, p = 0.033), as well as a lower incidence of re-intubation than those with NIV (85.7% vs. 63.6%, p = 0.07). In the 23 patients with a PaCO2 > 45 mmHg, there were no significant differences in the above outcome variables between the two groups.

Conclusion

HFNC may be at least equivalent to NIV in patients with PERF in terms of avoiding re-intubation. HFNC oxygen therapy is associated with shorter ICU stay and better tolerated in patients with PERF. In subjects without hypercapnic PERF, ICU and in-hospital survival rates were improved by HHFNC.

Reviewer's comments

This study showed that HHFNC exhibited a similar efficacy to NIV in terms of avoidance of re-intubation in patients with PERF. In addition, HFNC was better tolerated, and associated with a shorter ICU stay as well as lower ICU and in-hospital mortality rates than NIV in patients without hypercapnia. Re-intubation due to PERF is associated with poor outcomes and a mortality rate of up to 50%. Therefore, an effective intervention is required to prevent or reverse PERF to avoid re-intubation.

The early use of HFNC is effective and safe strategy to improve patient outcome in neonates, pediatric and adult population. By delivering a continuous high flow of oxygen, the pharyngeal dead space is washed out, nasopharyngeal resistance is reduced and some positive end expiratory pressure is generated, all of which contribute to a reduction in the work of breathing The heated humidification facilitates secretion clearance and expectoration of bronchial secretions. It also increases patient comfort because high-flow oxygen is delivered via a nasal canula, and does not interrupt eating, drinking or talking.

There are several limitations to this study. First, because of its retrospective design and the small number of

enrolled patients, the possibility of selection bias can not be excluded. Second, as a single-center cohort was analyzed, the results cannot be generalized. Third, the group of patients with hypercapnic PERF was small, and so the results of comparison of HFNC and NIV in such cases should be verified.

HFNC has become widely used in pediatric population not only for delivering oxygen therapy but also as a substitute for nasal CPAP. In Pediatrics at high flow of 2lit/kg/min, using appropriate nasal prongs, a positive end expiratory pressure of 4-8cm H2O is achieved. It is better tolerated in children especially small infants where using orofacial mask is cumbersome.

3. Ef cacy and toxicity of aerosolised colistin in ventilator-associated pneumonia: a prospective, randomised trial

Latif SA, Trifi A, Daly F, Mahjoub K, Nasri R and Lakhal SB . Ann. Intensive Care (2016) 6:26

Objective

To determine whether aerosolised (AS) colistin was beneficial and safe in therapy of gram-negative VAP (Ventilator associated pneumonia)

Study design

Single-center, prospective, randomised single-blind trial conducted in a medical ICU of a tertiary care university teaching hospital during 25 months, from April 2013 to April 2015 in all critically ill patients older than 18 years, with mechanical ventilation during more than 48 h, and who have presented a VAP. Primary outcome was cure of VAP assessed at day 14 of therapy and defined as resolution of clinical signs of VAP and bacteriological eradication. Secondary outcomes were incidence of acute renal failure (ARF), mechanical ventilation length, ICU length of stay and 28-day mortality.

Measurements and results

Total 149 patients of VAP were enrolled. An episode of VAP was defined as a Clinical Pulmonary Infection Score (CPIS) of more than six (features included were fever, leukocytosis, purulent secretions, hypoxemia or radiological infiltrate). In all cases where VAP was suspected tracheal aspirate was performed before starting on empirical therapy, including Imepenem and aerosolised (AS) colistin (intervention group; n = 73) or imepenem and intravenous (IV) colistin (control group; n = 76). Further 16 patients were excluded during the study period because of suspension of colistin (multisensitive strain imposing de-escalation, or a colistin-resistant strain), occurrence of a major side effect of inhaled route (severe bronchospasm or alveolar haemorrhage), decline in creatinine clearance below 10 ml/min in 48 h, occurrence of bacteraemia and/or septic shock, so finally 133 patients received allocated intervention. When anti-biogram was available, in a median time of 3.6 days (the same period of empirical anti-infective therapy), colistin was continued either in combination (AS group; n = 60 and IV group; n = 64) or as monotherapy (AS group; n = 13 and IV group; n = 12). AS colistin was given as 4 million units (MU) by nebulisation three times per 24 h. IV colistin was given as a loading dose of 9 MU followed by 4.5 MU two times per 24

The patient's baseline characteristics and distribution of pathogens VAP in both groups were similar. The clinical cure rate was 67.1 % in AS group and 72 % in IV group (p = 0.59). When administered in monotherapy or in combination,the AS regimen was as effective as IV regimen. Patients in AS group had significantly lower incidence of ARF (17.8 vs 39.4 %, p = 0.004), more favourable improvement of P/F ratio (349 vs 316 at day 14, p = 0.012), shortened time to bacterial eradication (TBE) (9.89 vs 11.26 days, p = 0.023) and earlier weaning from ventilator in ICU survivors with a mean gain in ventilator-free days of 5 days. No difference was shown in the length of stay and the 28-day mortality.

Conclusion

Aerosolised colistin seems to be beneficial. It provided a therapeutic effectiveness non-inferior to parenteral colistin in therapy of MDR bacilli VAP with a lower nephrotoxicity, a better improvement of P/F ratio, a shortened bacterial eradication time and earlier weaning from ventilator in ICU survivors.

Reviewer comments

This study evaluates the efficacy and safety of aerosolised colistin compared with parenteral colistin and not as adjunctive therapy to intravenous colistin in

patients with gram negative VAP. Both were equally efficacious and the other benefits of AS clistin was shown at several points: a significant lower incidence of nephrotoxicity (17.8 vs 39.4 %, p = 0.004), a greater improvement of P/F ratio, a faster time to pathogen eradication and an earlier weaning from ventilator in ICU survivors. The results were comparable to other majority of studies in the past where nebulised colistin has been used as an adjunctive therapy to intravenous colistin including a pediatric study by Polat et al. where they documented shorter median bacteriological eradication within 3 days when inhaled colistin was combined with IV colistin.

The rationale for inhaling antibiotics is to maximise drug delivery to the target site of infection (i.e. the airways) and limit the potential for systemic side effects. In the experimental study of Lu et al., colistin was found undetected in the lung tissue after intravenous infusion, while after nebulisation, peak lung tissue concentrations were significantly higher in the lung segments. Parentral therapy as compared with nebulised colistin also promotes acquisition of colistin resistance due to lower concentrations at the infection site. However, a study by Delissalde; et al showed that selection of resistant mutants is also facilitated with colistin nebulisations due to incomplete destruction of the bronchial epithelium and production of a biofilm that constitute a protective space for bacteria. Local side effects with Inhaled colistin has been reported like throat irritation,cough and bronchospasm, due to osmolality and preservatives within some of the solutions

The main limitation was the non-double-blind design of the trial protocol. Another pharmacologic limit was the absence of plasmatic dosages of colistin.

4. Hyperoxia Is Associated With Poor Outcomes in Pediatric Cardiac Patients Supported on Venoarterial Extracorporeal Membrane Oxygenation

Sznycer-Taub NR; Lowery R; Yu S; Owens ST; Hirsch-Romano JC; Owens GE.

Pediatr Crit Care Med April 2016;17(4):350-358

Objective

To examine the potential effect of hyperoxia on infants who were placed onto venoarterial Extracorporeal Membrane Oxygenation (VA-ECMO) after cardiac surgery.

Setting

A retrospective chart review of all infants was performed (< 1 yr old) who were placed onto VA-ECMO after surgery for congenital heart disease from July 1, 2007, to June 30, 2013, at the University of Michigan. The primary outcome was 30-day mortality after the initial surgery. Secondary outcomes included ICU length of stay, hospital length of stay, in-hospital mortality, need for dialysis, and neurologic injury during the hospitalization (defined as seizure, stroke, or intracranial hemorrhage).

Measurements and Main Results

A total of 93 patients were included in the study. The median age at the time of surgery was 7 days, and 75% were neonates. There was 38% mortality at 30 days after surgery and 49% in hospital mortality.

In univariate analysis, factors significantly associated with mortality 30 days after surgery included longer duration on ECMO ($p < 0.0001$) and a mean Pao2 in the first 48 hours of greater than 193 mm Hg ($p = 0.001$). With exclusion of the patients who had the sweep gas blended, a mean Pao2 greater than 193 mm Hg was still significantly associated with increased 30-day mortality ($p = 0.001$).

In terms of end-organ disease, the prevalence of renal dialysis ($p = 0.02$) but not neurologic injury ($p = 0.41$) was significantly higher in the patients with a mean Pao2 greater than 193 mm Hg.

Conclusions

In the postoperative period, a mean Pao2 greater than 193 mm Hg while on ECMO was an independent risk factor for mortality in infants with congenital heart disease. In addition, hyperoxia on ECMO may be used as a tool for clinicians to prognosticate potential ventricular recovery and the likelihood of survival after ECMO decannulation, which may influence decisions regarding further intervention or institution of long-term mechanical support (i.e., ventricular assist devices.

Reviewer's Comments

A review of the current literature indicates that across

a wide variety of clinical scenarios and situations, the effect of hyperoxia is unclear. In pediatric patients, the data are mixed as hyperoxia has been shown to be both associated and not associated with increased risk of mortality after cardiac arrests. In neonates with asphyxia, hyperoxia was associated with increased mortality and risk of brain injury.

In patients supported on VA-ECMO, there are various factors which determine the PaO2 values. one is the use of blender for the sweep gas to achieve more "physiologic" PaO2 levels. However, the practice is not universal. In addition, oxygen tension of blood ejected from the systemic ventricle and the ratio of mixing of blood from the systemic ventricle and the arterial ECMO cannula can affect the overall arterial (and hence end organ) oxygen tension. Another important factor is ECMO pump flow as higher flows would presumably decrease the amount of pulmonary venous return and therefore decrease preload to the systemic ventricle. Interestingly, when adjusting for ECMO pump flow and other factors, a mean PaO2 greater than 193 mm Hg was still associated with increased risk of 30-day mortality, suggesting that the association is not dependent on the requirement for increased ECMO support.

Thus, there is some suggestion from this study that elevated PaO2 levels may have a causative (due to reactive oxygen species or other mechanisms) effect on clinical outcome versus simply being associative due to improved clinical parameters.

Limitations of this study include the fact that it was a retrospective chart review performed at a single center and that there may have been other important clinical variables that could not be measured in a retrospective manner.

5. Limiting and withdrawing life support in the PICU: for whom are these options discussed?

Keele L; Meert KL; Berg RA; Dalton H; Newth CJL, Harrison R, Wessel DL, Shanley T,Carcillo J, Morrison W, Funai, Holubkov R, Dean JM, Pollack M; for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network et al. Pediatr Crit Care Med 2016;17(2):110-120

Objectives

The objective of this study was to describe the clinical characteristics and outcomes of children whose families discussed limitation or withdrawal of life support (LWLS) with clinicians during their child's PICU stay and to determine the factors associated with limitation or withdrawal of life support discussions.

Design

Secondary analysis of data prospectively collected from a random sample of children admitted to PICUs affiliated with the Collaborative Pediatric Critical Care Research Network between December 4, 2011, and April 7, 2013. Seven clinical sites affiliated with the Collaborative Pediatric Critical Care Research Network.

Measurements and Main Results

Ten thousand seventy-eight children less than 18 years old, admitted to a PICU, and not moribund at admission. Families of 248 children (2.5%) discussed limitation or withdrawal of life support with clinicians. By using a multivariate logistic model, we found that PICU admission age less than 14 days, reduced functional status prior to hospital admission, primary diagnosis of cancer, recent catastrophic event, emergent PICU admission, greater physiologic instability, and government insurance were independently associated with higher likelihood of discussing limitation or withdrawal of life support. Black race, primary diagnosis of neurologic illness, and postoperative status were independently associated with lower likelihood of discussing limitation or withdrawal of life support.

Out of 248 children whose families discussed limitation or withdrawal of life support, 173 children (69.8%) died during their hospitalization. Of these, 166 (96.0%) died in the PICU and 149 died after limitation or withdrawal of life support was performed and 10 (5.8%) after failed cardiopulmonary resuscitation (CPR). Hospital length of stay was shorter for children who died after a family discussion about LWLS with clinicians ($p < 0.01$). Among the 75 children who survived after a family discussion about LWLS, twenty-four survivors (32.0%)had moderate to severe functional abnormalities at baseline, 40

children (53.4%) were discharged with severe or very severe functional abnormalities, and 15 (20%) with coma/vegetative state.

Conclusions

Clinical factors reflecting type and severity of illness, sociodemographics, and institutional practices may influence whether limitation or withdrawal of life support is discussed with families of PICU patients. Most children whose families discuss limitation or withdrawal of life support die during their PICU stay; survivors often have substantial disabilities.

Reviewer's comments

High-quality communication is an important aspect of end-of-life care because of the gravity of the decisions being made for critically ill children. The basic obligation of a doctor should always be to act in the child's best interest, which may involve withdrawing care in the face of a poor outcome. There are medicolegal implications to it and issues debatable, whether a doctor can limit or withhold treatment from the patient in hospital premises even in corroboration with parents??. It may prove to be a herculean task to convince parents considering religious, socioeconomic reasons etc in our Indian setup.

The study found that younger age, poor functional status prior to hospital admission, primary diagnosis of cancer, greater physiologic instability, and government insurance were independently associated with higher likelihood of discussing withdrawal of life support. Primary diagnosis of neurologic illness, and postoperative status were associated with lower likelihood of discussing withdrawal of life support. As expected majority died, where families had discussed withdrawal of life support during their hospitalization in PICU. Of those who survived majority were discharged with severe or very severe functional abnormalities. Hence, a proper communication is very necessary. Parents have to be actively involved in the treatment making process and decide what's best for their child.

6. Double-Blind Prospective Randomized Controlled Trial of Dopamine Versus Epinephrine as First-Line Vasoactive Drugs in Pediatric Septic Shock

Ventura AMC, Shieh HH, Bouss A, Góes PF, Fernandes de Cássia, Souza DC, Paulo PRL, Chagas F, Gilio AE Crit Care Med. 2015 Nov; 43(11):2292-302

Objective

To study which first-line vasoactive drug is the best choice for children with fluid-refractory septic shock.

Study Design

This is the first prospective, controlled, randomized double blind trial conducted in a single centre from February 1, 2009, to July 31, 2013 in children with fluid-refractory septic shock. Children who were 1 month to 15 years old and met the clinical criteria for fluid-refractory septic shock which was defined as persistent clinical signs of hypoperfusion after fluid bolus of at least 40ml/kg were enrolled. Clinical signs of hypoperfusion included abnormal heart rate (HR) for age, altered/decreased mental status, altered capillary refill time (CRT) (> 2 s or flash), diminished or impalpable or bounding peripheral pulses, mottled cool extremities, and urine output (UO) below 1mL/kg/hr. The primary outcome was to compare the effects of dopamine or epinephrine in severe sepsis on 28-day mortality; secondary outcomes were the rate of healthcare-associated infection, the need for other vasoactive drugs, and the multiple organ dysfunction score.

Measurements and main results

Patients were randomly assigned to receive either dopamine (5 μg/kg/min) or epinephrine (0.1μg/kg/min) escalated every 20 minutes to reach a maximum dose of 10ug/kg/min for dopamine and 0.3 ug/kg/min in epinephine group through a peripheral or intraosseous line. Patients not reaching predefined stabilization criteria after the maximum dose were classified as treatment failure, at which point the attending physician started another drug and gradually stopped the study drug.

Baseline characteristics and therapeutic interventions for the 120 children enrolled (63, dopamine; 57, epinephrine) were similar. There were total 17 deaths (14.2%) out of which 13 (20.6%) in the dopamine group and four (7%) in the epinephrine group (p=0.033). On applying multiple logistic regression

analysis there were variables independently associated with outcome. Each unit increase in PELOD scoring resulted in an increased chance of death by 22% ($p< 0.001$). Patients on Dopamine had a 6.51-fold increased chance of death in comparison with patients who received epinephrine ($p = 0.037$). Renal replacement therapy increased the chance of dying in all patient ($p < 0.001$). Consequently, more patients had higher organ dysfunction scores (60% increase in PELOD) with higher percentage in dopamine group requiring renal replacement therapy as compared with the epinephrine group ($p = 0.001$)
Variables associated with the development of HAI were use of dopamine ($p = 0.001$), renal replacement therapy ($p = 0.004$), and length of ICU stay. HAI occurred in 18 of 63 patients in the dopamine group (28.5%) and four of 57 patients in the epinephrine group (2.3%).
Use of hydocortisone and increased duartion of resucsitation are independent predictors of the need of another vasoactive agent. None of the children in the dopamine group had received dopamine after being considered nonresponsive to study drug. On the other hand, epinephrine was chosen as the sole or one of the vasoactive drugs in 36.5% of patients in the dopamine group and in 33.3% of patients in epinephrine group who were considered nonresponsive to the study drug.
The epinephrine group had higher SBP and MAP/CVP at 6 hours after randomization and at the end of resuscitation. Groups did not differ in any laboratory test results (lactate, troponin, and d-dimer values).

Conclusions

Dopamine was associated with an increased risk of death and healthcare-associated infection. Early administration of peripheral or intraosseous epinephrine was associated with increased survival in this population.

Reviewer's comments

This rigorously conducted randomized controlled trial has important implications for the management of septic shock in pediatric patients. Surviving sepsis guidelines (2012) and more recently, a metaanalysis by Avni et al on "vasopressor of choice in adult septic shock "suggested norepinephrine instead of dopamine as the first line vasopressor in the treatment of septic shock. Dopamine has since fallen out of favour in the management of adult shock but is still used in the pediatric septic shock. The arrhythmogenic and immunosuppressive effects of dopamine are well known. The choice of vasopressor in pediatric shock is still unclear.
This is a high-quality study and the best available evidence on the topic to date in pediatrics. There are some inherent flaws with the study which needs to be considered. This study employed a large-fluid volume-resuscitation algorithm designed and initiated prior to the publication of the FEAST trial in 2011, which demonstrated that fluid boluses increased mortality in resource-poor areas of Africa and has raised questions about the proper fluid-management approach. Secondly, pharmacodynamics and pharmacokinetics are altered in sepsis so comparable doses of each vasoactive drug may be questionable. Thirdly, this study had cold shock as the sole criteria for initiation of vasopressor. A child may move from one hemodynamic state to another. Children with severe sepsis may present with low cardiac output and high systemic vascular resistance, high cardiac output and low systemic vascular resistance, or low cardiac output and low systemic vascular resistance Vasopressor or inotropic therapy should be used according to the hemodynamic state to achieve a minimal perfusion pressure and maintain adequate flow. Dopamine may not be a good agent in the setting of myocardial dysfunction with tachycardia and increased systemic vascular resistance. Fourthly, this study is a single center study the results of which will be difficult to extrapolate in different settings without analysing its external validity. The initial assessment of the patient and decision to start, stop, or increase the study drug were based solely on clinical variables, which are highly sensitive but lack specificity. Multiple other variables could have affected the outcome.
Although this is only a single study performed in a single hospital, the authors show a marked increase in mortality in children with septic shock who are given dopamine instead of epinephrine as the first-line vasoactive agent. These results should be reproduced

in other hospitals. It has a potential impact for a paradigm shift from dopamine to epinephrine as the vasoactive agent of choice in pediatric septic shock.

7. Early versus Late Parenteral Nutrition in Critically Ill Children

Five T, Kerklaan D, Mesotten D, Verbruggen S, Wouters PJ, Vanhorebeek I; et al. N Engl J Med March 2016; 374 (12) : 1111- 121

Objective

To investigate whether a strategy of withholding parenteral nutrition (PN) up to day 8 (late parenteral nutrition) in the pediatric ICU is clinically superior to providing early parenteral nutrition.

Study Design

A multicenter, randomized, controlled trial involving 1440 critically ill children were enrolled from June 18, 2012, through July 27, 2015, from term newborns to children 17 yearsvof age and if a stay of 24 hours or more in the ICU was expected. The two primary end points were new infection acquired during the ICU stay and the adjusted duration of ICU dependency, as assessed by the number of days in the ICU and as time to discharge alive from ICU.

Measurement and results

For the 723 patients receiving early parenteral nutrition, parenteral nutrition was initiated within 24 hours after ICU admission, whereas for the 717 patients receiving late parenteral nutrition, parenteral nutrition was not provided until the morning of the 8th day in the ICU. In both groups, enteral nutrition was attempted early and intravenous micronutrients were provided.

Although mortality was similar in the two groups, the percentage of patients with a new infection was 10.7% in the group receiving late parenteral nutrition, as compared with 18.5% in the group receiving early parenteral nutrition (adjusted odds ratio, 0.48; 95% confidence interval [CI], 0.35 to 0.66). The mean (±SE) duration of ICU stay was 6.5±0.4 days in the group receiving late parenteral nutrition, as compared with 9.2±0.8 days in the group receiving early parenteral nutrition; there was also a higher likelihood of an earlier live discharge from the ICU at any time in the late-parenteral-nutrition group (adjusted hazard ratio, 1.23; 95% CI, 1.11 to 1.37). Late parenteral nutrition was associated with a shorter duration of mechanical ventilatory support than was early parenteral nutrition (P=0.001), as well as a smaller proportion of patients receiving renal-replacement therapy (P=0.04) and a shorter duration of hospital stay (P=0.001). Late parenteral nutrition was also associated with lower plasma levels of γ-glutamyltransferase and alkaline phosphatase than was early parenteral nutrition (P=0.001 and P=0.04, respectively), as well as higher levels of bilirubin (P=0.004) and C-reactive protein (P=0.006).

Conclusions

In critically ill children, withholding parenteral nutrition for 1 week in the ICU was clinically superior to providing early parenteral nutrition

Reviewer's comment

Enteral nutrition is the preferred mode of nutrition in critically ill children. Current guidelines, which are based largely on small studies with surrogate end points and on expert opinion, advise care providers to initiate nutritional support soon after a child's admission to the pediatric intensive care unit (PICU) but enteral nutrition (EN) is often delayed or interrupted. Supplemental parenteral nutrition (PN) is often used to supplement EN in cases where caloric targets are not met.

Timing of initiating PN was a matter of debate in various studies. The current trial published in NEJM, 2016 is the first major RCT study addressing all the issues in children. The results, similar to the adult study (EPaNIC trial), reinforced the idea of delaying supplemental PN in critically ill children. The clinical superiority of Late PN was shown irrespective of diagnosis, severity of illness, age of the child. An unexpected result was critically ill children with the highest risk of malnutrition (STRONG Kids Score >2) were benefited with late PN. Indeed, immediate initiation of nutrition was currently advised for neonates because they are considered to have lower metabolic reserves. Though incidence of hypoglycemia was more in late PN group it did not affect the outcome.

Though this study was rigorously conducted it had

quite a few limitations. Firstly, more than 55% of the patients in the control group were discharged by day 4. They would not be considered candidates for PN within 24 hours after admission in most centers. Secondly, more than 77% of patients in the group receiving late PN were discharged by day 8 without having received any PN. Third, studies have shown, the equations used to determine energy requirements are unreliable in children. Indirect calorimetry is the most reliable method, which unfortunately is not available bed side. Fourth, the target caloric level beyond which to supply PN is also questionable. Fifth, the poor outcomes in the group receiving early PN may represent the risks associated with the parenteral route of delivery or the effects of caloric overfeeding. Sixth, the STRONGkids score is based on a simple questionnaire without anthropometric variables, which is a better marker of nutritional status in children. The use of STRONGkids has not been validated in critically ill children and may not be a reliable indicator of severe malnutrition. Seventh, the standard outcomes related to infection, such as VAP and CRBSI were not recorded and lastly patients, their parents, and the staff providing intensive care were aware of the treatment assignments.

This study supports the practice of delaying supplemental PN in an ill child. The recent SCCM/ ASPEN guidelines (Feb 2016) for exclusive and supplemental PN. Regarding supplemental PN states - in patients at either low or high nutrition risk, use of supplemental PN should be considered after 7–10 days if EN is unable to meet >60% of energy and protein requirements by the enteral route alone. Initiating supplemental PN prior to this period in critically ill patients on some EN does not improve outcomes and may be detrimental to the patient. For exclusive PN - in patients at low nutrition risk (eg, NRS 2002 ≤3 or NUTRIC score ≤5), exclusive PN may be withheld over the first 7 days following ICU admission if the patient cannot maintain volitional intake and if early EN is not feasible. Further, in the patient determined to be at high nutrition risk (eg NRS 2002 ≥5 or NUTRIC score ≥5) or severely malnourished, and when EN is not feasible, it suggested initiating exclusive PN as soon as possible following ICU admission.

Nutrition therapy should ideally be tailored to each individual child, delaying PN and advancing enteral nutrition in patients who are not severely malnourished seems to be a 'prudent step' in research into care of these children.

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