Best Evidence

Journal scan

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Objective: To develop a guideline for the decision to continue or stop antibiotics at 48–72 hours after their initiation in children with suspected ventilator-associated infection.

Population: 281 invasively ventilated children (≥ 48 hours) who are less than 3 years, underwent clinical testing and were started on IV antibiotics with suspected ventilator-associated infection were included in the study.

Design: Prospective, multicenter (22 PICUs) observational data collection and subsequent development of an antibiotic guideline

Result: In this study, Phase 1 was a prospective data collection. The median age was 8 months (inter quartile range, 4–16 mo) and 75% had at least one comorbidity. Phase 2 was development of the guideline scoring system by an expert panel, which was then applied retrospectively to the phase 1 data. Higher scores correlated with duration of antibiotics (p < 0.001) and higher Pediatric Logistic Organ Dysfunction 2 scores (p < 0.001) but not mortality, PICU-free days or ventilator-free days. Considering safety and outcomes based on the phase 1 data and aiming for a 25% reduction in antibiotic use, the panel recommended stopping antibiotics at 48–72 hours for guideline scores less than or equal to 2, continuing antibiotics for scores greater than or equal to 6, and offered no recommendation for scores 3, 4, and 5.

Conclusion: We developed a scoring system with recommendations to guide the decision to stop or continue antibiotics at 48–72 hours in children with suspected ventilator-associated infection. The safety and efficacy of which will be prospectively tested in the planned phase 3 of the study.

Reviewers Comment: Antibiotic resistance is clearly a raising concern globally. One of the most common use of antibiotics in PICU is suspected VAP. It is difficult to discriminate between VAI and other noninfectious causes, increasing the use of unnecessary long duration of antibiotics. In Phase 1, they found that the recommendation to discontinue antibiotics would have applied to 46% of subjects, over half (57%) of whom had actually received a long course of antibiotics that had no clear association with clinical outcomes. Limitation of this study were first, undoubtedly some children with a low score may actually have bacterial infection. Secondly the population of study was < 3 years, which might limit the study for the extrapolation to the larger group. Phase 3 trail will give us information about the acceptance of guidelines, revised criteria if any, and the safety of the group with low scores where antibiotics were discontinued. The scoring system designed is self-explanatory and easy to use. The estimated use of the guideline could reduce antibiotic exposure in approximately one-quarter of children with suspected VAI.

2. Specific Viral Etiologies are associated with outcomes in Pediatric Acute Respiratory Distress Syndrome


Objective: This study was done to characterize the epidemiology of viral pneumonia in Pediatric Acute Respiratory Distress Syndrome (PARDS) and compare characteristics and outcomes between pneumonia
subjects with and without viruses. Secondarily, study examined the association between specific viruses and outcomes.

**Population:** 544 children with PARDS as per Berlin definition were enrolled out of which 282 were included as in them pneumonia was the inciting etiology. They underwent testing of respiratory secretions for viruses and culture for bacteria and fungi and were stratified according to presence or absence of a virus

**Design:** Single centre prospective observational study

**Results:** In 141 of 282 (50%) pneumonia PARDS cases, a virus was the sole pathogen identified. Virus-positive pneumonia had fewer organ failures but worse oxygenation, relative to virus-negative pneumonia, with no differences in antibiotic use, ventilator duration, or mortality. Subjects with respiratory syncytial virus (RSV) associated ARDS had lower mortality (0%), and subjects with influenza-associated acute respiratory distress syndrome had shorter ventilator duration, relative to other viral acute respiratory distress syndrome. Non-adeno herpesviruses, tested for exclusively in immunocompromised subjects, had greater than 80% mortality.

**Conclusion:** Pneumonia was the most common cause of PARDS, and viruses were commonly isolated as the sole pathogen. Respiratory syncytial virus and influenza were associated with better outcomes relative to other viral etiologies. Viral pneumonias in immunocompromised subjects, particularly non-adeno herpesviruses, drove the mortality rate for pneumonia acute respiratory distress syndrome. Specific viral etiologies are associated with differential outcomes in pediatric acute respiratory distress syndrome and should be accounted for in future studies.

**Reviewers Comment:** Children have a distinct viral epidemiology, with higher rates of RSV and rhinovirus when related to adults. The epidemiology and outcomes of PARDS secondary to viral pneumonia has been understudied. The mortality in both virus positive and virus negative group was 11% but in virus positive cases the mortality was driven by deaths in immunocompromised state. Rhino/enterovirus was the most common (43%), followed by RSV (24%). Virus-positive subjects had fewer organ failures, worse oxygenation and more corticosteroid use but no differences in ventilator duration or mortality between virus-negative and virus-positive patients. Multiple viruses were detected in 25% and this group experienced immunocompromised state more commonly, had higher peak pressures, worse oxygenation 24 hours after ARDS onset, greater use of nitric oxide and paralysis, and higher mortality. When specific etiology was considered, children with RSV were younger while children with influenza (p < 0.001) were older. RSV-positive children had significantly lower PRISM III, non-pulmonary organ failures and lower mortality. Influenza was more common among children with no comorbidities (p = 0.001) and had shorter duration of ventilator. The limitations of the study were, most of the samples were from Nasopharyngeal aspirate than BAL. Secondly, antibiotic use and the definitions of culture-positivity were not protocolized, which limits conclusions regarding bacterial coinfections and finally, this study did not differentiate between a detected virus being causal, or representing asymptomatic shedding or inadequate sampling. This study also used Berlin definition for Pediatric ARDS which might again hamper interpretation of the study. Quantification of viruses can overcome this limitation in future studies.

3. **The Nursing Activities Score per Nurse Ratio is associated with In-Hospital Mortality, Whereas the Patients Per Nurse Ratio is not.**


**Objective:** The study investigated the association of the Nursing activities score per Nurse ratio (NNR), and the patients per nurse ratio (PNR), with in-hospital mortality in ICUs.

**Population:** All admitted ICU patients (29,445) and registered ICU nurses working at 15 Dutch ICUs over 2 years, were included.

**Design:** Multicentre, Retrospective analysis of the National Intensive Care Evaluation (NICE) database.

**Results:** NNR > 41 for both mean NNR as well as NNR on day 1 were associated with a higher in-hospital mortality (odds ratios, 1.19 and 1.17, respectively).
After case-mix adjustment the association between a NNR >61 for both mean NNR as well as NNR on day 1 and in-hospital mortality remained significant (odds ratios, 1.29 and 1.26, respectively). Patients per nurse ratio was not associated with in-hospital mortality.

**Conclusions:** A higher NNR was associated with higher in-hospital mortality. In contrast, no association was found between patients per nurse ratios and in-hospital mortality in the Netherlands. Therefore, we conclude that it is more important to focus on the nursing workload that the patients generate rather than on the number of patients the nurse has to take care of in the ICU.

**Reviewers comment:** Nursing manpower in ICUs is frequently studied, but these studies have shown contradicting results on the association of nursing workload and mortality. Most of these studies expressed workload as PNR; however, some patients required more nursing time than others, which was not considered. This can be quantified by a tool like Nursing Activities Score. This study focussed on workload of the nurse than the number of nurses, which was associated with mortality. The limitations of this study is, it is retrospective in nature, due to which they could only study the association but not the causality. It is unclear that which NAS (Nursing Activity Score) per ICU nurse is optimal. Based on the study results, they suggest that one registered ICU nurse should not provide more than 61 NAS points per day. More research preferably prospective studies are needed in this regard to define the cut-offs of NAS for effective nursing care.


**Objective:** Evaluation of the pharmacokinetics of commonly administered antimicrobials in an ex vivo continuous renal replacement therapy (CRRT) mode

**Design:** An ex vivo CRRT circuit was used to evaluate drug-circuit interactions and determine the disposition of five commonly used antimicrobials (meropenem, piperacillin, liposomal amphotericin B, caspofungin, and voriconazole).

**Intervention:** Antimicrobials were administered into a reservoir containing whole human blood, which was connected to a pediatric CRRT circuit programmed for a 10 kg child. CRRT was performed in the hemodiafiltration mode with three different CRRT clearance rates: 1) no clearance (0 mL/kg/hr, to measure adsorption), 2) low clearance (20 mL/kg/hr), and 3) high clearance (40 mL/kg/hr). Blood flow was maintained at 50ml/min, Low dose CRRT clearance settings were dialysate 100 mL/hr, replacement fluid 100 mL/hr, patient fluid removal 0 mL/hr, effluent 200 mL/hr, and effluent dose 20 mL/kg/hr. For high dose, these variables were doubled. Blood samples were drawn directly from the reservoir at baseline and at 5, 20, 60, and 180 minutes during each phase. Five independent CRRT runs were performed to assess inter-run variability. Antimicrobial concentrations were measured using validated liquid chromatography-mass spectrometry assays. For ensuring drug stability during the CRRT, a control reservoir was created and samples were tested at baseline and at each run.

**Results:** Circuit adsorption of antimicrobials ranged between 13% and 27%. Meropenem, piperacillin, and voriconazole were cleared by the CRRT circuit and clearance increased with increasing CRRT clearance rates (7.66 mL/min, 4.97 mL/min, and 2.67 mL/min, respectively, for high CRRT clearance). Amphotericin B and caspofungin had minimal circuit clearance and did not change with increasing continuous renal replacement therapy clearance rates.

**Conclusions:** Careful consideration of drug-circuit interactions during CRRT is essential for appropriate drug dosing in critically ill children. Antimicrobials have unique adsorption and clearance profiles during continuous renal replacement therapy, and this knowledge is important to optimize antimicrobial therapy.

**Reviewers comment:** Sepsis is commonly associated with AKI requiring CRRT in critically ill pediatric patients. The mortality rate in such population is as high as 65%. Control of sepsis in such population is challenging as it is difficult to distinguish between drug-circuit, drug-patient, and patient-circuit interactions. This study was done to describe the drug circuit interaction independent of the many other variables (Residual renal function,
hepatic metabolism, circulatory function, fluid shifts, and protein loss). This study was also unique in describing the adsorption fractions of amphotericin, caspofungin, and voriconazole during CRRT, which have not been previously reported to the best of our knowledge. Limitations of the study were, firstly it did not measure the adsorption fraction as a function of time after the initial 3 hours, which would be important if we were to distinguish whether the fraction adsorbed is continuous or saturable in order to provide optimal dosing recommendations and secondly, this experiment was conducted for all five antimicrobials mixed in the reservoir together which may result in an underestimation of adsorption for individual compounds if the circuit is saturable although this scenario of multiple antimicrobial coverage is not uncommon in the clinical setting. It is important to increase the dose in those antimicrobials that are adsorbed and that exhibit CRRT clearance. For antimicrobials that exhibit minimal or no CRRT clearance, dose reduction may be required if there is concern for drug accumulation in traditionally renally-cleared medications or no adjustments may be required if the antimicrobial is predominately hepatically cleared.

5. Quantitative EEG predicts outcomes in children after cardiac arrest

Seungha Lee, MSE, Xuelong Zhao et al., (Neurology May 2019, 92 (20) e2329-e2338; DOI: 10.1212/WNL.0000000000007504)

Objective: To determine whether quantitative EEG (QEEG) features predict neurologic outcomes in children after cardiac arrest.

Population: 87 consecutive children who were resuscitated and admitted in Pediatric Intensive Care unit (PICU) after cardiac arrest were included, out of which 69 patients were analysed.

Design: Single Centre prospective study. 8 QEEG features were computed from 5-minute epochs every hour after return of circulation, following which predictive models utilizing random forest classifiers trained on patient age and 8 QEEG features to predict outcome were used. The features included SD of each EEG channel, normalized band power in alpha, beta, theta, delta, and gamma wave frequencies, line length, and regularity function scores. All QEEG features were then averaged across early (0–17 hours after return of circulation) and late (18 hours–end after return of circulation). Outcome was measured using Pediatric Cerebral Performance Category (PCPC) scores. If the area under the curve (AUROC) is close to 1.0, then its discrimination is excellent. If the area is near 0.5, then its ability to discriminate between binary outcomes is close to chance.

Results: The best performing model had a 5-fold cross-validation accuracy of 0.8 (0.88 area under the receiver operating characteristic curve). It had a positive predictive value of 0.79 and a sensitivity of 0.84 in predicting patients with favourable outcomes (PCPC score of 1–3). It had a negative predictive value of 0.8 and a specificity of 0.75 in predicting patients with unfavourable outcomes (PCPC score of 4–6). The model also identified the relative importance of each feature. Analyses using only frontal electrodes did not differ in prediction performance compared to analyses using all electrodes.

Conclusions: QEEG features can standardize EEG interpretation and predict neurologic outcomes in children after cardiac arrest.

Reviewers Comment: QEEG data is an objective method that can be obtained noninvasively at bedside and is used to delineate extent of brain injury in many adult studies, but the pediatric data is lacking. In this study, 54% patients had favourable outcomes (PCPC 1–3) and 46% patients had unfavourable outcomes (PCPC 4–6). Early EEGs showed better results (Accuracy of 0.8) than late EEGs (Accuracy of 0.7) across all performance metrics, but the differences were not statistically significant. To better understand the generalizability of the models, 1,000 bootstrapped samples were taken, which showed the similar results with mean accuracy of early and late EEG as 0.8 and 0.61. As the injury was diffuse, it was hypothesised that, frontal montage (Fp1, Fp2, Fz) will be sufficient than full array of electrodes. The results were again similar with accuracy of 0.71 for early EEG and 0.67 for late QEEG. They also found out the the most important features for early EEG, were gamma band power, delta band power, and beta band power and for the late EEG model, the most important features were age, alpha band power, and delta band power.
The limitations of the study were small sample size, use of MATLAB script for removing artifacts which is inferior to the clinically trained neurologists, only short term outcome was studied and as it was not a blinded trial, the clinical decision would have been influenced with QEEG results. This can be a promising avenue of investigation because early EEG features can be reliably used for neuro-prognostication during the acute stages when interventions may be most efficacious. Further studies are needed to assess the benefit of using QEEG features in the context of multimodal models including clinical context for clinical trials or neuroprognostication.

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