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- PEDICON 2016, Hyderabad
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Journal Scan
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Critical Thinking

PICU Quiz
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Clinical Review

Viscoelastic Hemostatic Assays
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A synopsis by ILCOR Pediatric Task Force
Pediatric Advanced Life Support (PALS) 2015 Update
Pediatric Basic Life Support, Pediatric Advanced Life Support and Neonatal Resuscitation 2015
Dear friends and Colleagues

Oct-Dec 2015 issue of the journal is now published and we sincerely hope Pubmed indexing will be a reality next year. Reviewers have been very prompt and efficient in critical review of all the manuscript making it an unbiased process. I would like to thank the entire editorial board for their tireless efforts.

Highlights of this issue are: Symposium “Infections in the PICU-a side view” edited by guest editor Dr Soonu Udani, PD Hinduja hospital, with a detailed discussion regarding ventilator associated events (newer terminology for VAP: ventilator associated pneumonias, CRBSI (central venous catheter related blood stream infections), Endothelial Glycocalyx and sepsis, vitamin D and sepsis, optimizing doses of Colistin and Vancomycin.

In addition to a multicenter original article from the USA on the use of mannitol and Diabetic ketoacidosis in children by Novotni; et al, three very interesting case reports on laryngotracheoesophageal cleft presenting with recurrent pneumonia, acute pediatric myocardial infarction with infective endocarditis, and primary hyperoxaluria as an unusual cause of renal failure in infancy.

In addition, Journal scan with latest publications and PICU Quiz remain regular features.

With on line submissions (www.journalofpediatriccriticalcare.com) articles continue to pour in from wide range of Pediatric intensivists from different parts of the world. Overall submissions continue to be rising in numbers as well as quality. In this issue, a summary of new PALS guidelines by AHA, ILCOR is also included for dissemination of information. For detailed publication please refer to the journal “Circulation” or AHA website.

Please visit Facebook page and feel free to give feed back and suggestions

Hope you continue to enjoy reading regarding the current developments in Pediatric critical care .

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Basic Pediatric Intensive Care Nursing Course (BPICNC)

One day training course has been initiated by the College of Pediatric Critical Care and IAP Intensive Care Chapter for the critical care providers especially nurses working in the PICU, Pediatric emergency and pediatric cardiac care units. This is a comprehensive course that includes lectures on basic intensive care and workstations with hand on sessions in the afternoon. A manual of pediatric critical care nursing has been prepared for the participating candidates.

For organizing this course, you may contact:

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Guest Editorial: Symposium “Infections in the PICU- A side view”

Soonu Udani
Head of the Section of Pediatric and Pediatric Intensive Care, PD Hinduja Hospital Mumbai

Although only 5–10% of all hospitalized patients are treated in ICUs, they account for approximately 25% of all nosocomial infections, and the incidence of nosocomial infections in ICUs is 5–10 times higher than that observed in general hospital wards. While we deal with many conditions and in one patient several problems will overlap and co-morbidities exist, one inescapable entity remains and that is the bogey of infection. This may be primary or secondarily acquired. The portals for entry are many and are well known and don’t need to be named here. Host defences are down and the environment is replete with bacteria of many hues and powers of resistance. In a study on respiratory pathogens in an Indian setting, of 2776 specimens, 1233 (44.41%) isolates were recovered, of which 1123 (91.07%) were Gram-negative bacilli and 110 (8.92%) were Gram-positive organisms. Multidrug resistance was observed in 83% of total isolates. Similarly, in a Delhi hospital, in 2010, the prevalence of MRSA & VRE has been documented to be 40% and 10%, respectively. Over all the prevalence of penicillin intermediate resistant Streptococcus pneumoniae was found to be 9.52%. ESBL, AmpC, and Carbapenemase producing organisms were found to be 40 to 60%, 70 to 80% & 2 to 80% respectively in various multi drug resistant organisms like E. coli, Klebsiella spp., Pseudomonas spp. and Acinetobacter spp. 8% Pseudomonas spp. were found to be resistant to colistin. This horror story goes on.

Rarely will a child escape an antibiotic prescription once in an ICU. With the documented emergence of these difficult to treat organisms and the lack of any new really useful antibiotic on the horizon, it is important that we learn to use what we have in hand judiciously and appropriately. Today it is not unusual to see drugs like Vancomycin and colistin on at least one patient in every PICU. Prescription of an antibiotic for which the micro-organism is supposed to be susceptible in vitro is not synonymous of efficacy. It is especially the case for the most severe patients (with increase in the volume of distribution of antimicrobials) and for the less susceptible bugs, for which available antimicrobials have MICs at the border of susceptibility breakpoints. Pharmacokinetic/pharmacodynamic (PK/PD) targets need to be achieved for decreasing the risk of treatment failure and selection of resistant pathogens. Hence we have included an update on the use of these drugs.

The guidelines for the best practice for catheter related infections have not changed very much as reviews from the early part of the decade to now indicate. A detailed review is included to cover aspects of diagnosis and management in one article. As a recent review article was available on antibiotics and anti-fungals in the April-June-issue, this topic has not been repeated here. To add a slightly different flavour to infections and sepsis in the critically ill child we have chosen to veer off course a little and add some information about two side players in the game. These being two articles on Vitamin D in sepsis and innate immunity and the role of the Glycocalyx in the entire sepsis cascade and how it may improve our understanding of endothelial injury. We also need to modify our old methods of
administering antibiotics and urge our microbiologists to give us quick and accurate MIC values in order to optimise delivery. Many drugs are best given over a sustained period and some are best given once a day. The pharmacokinetic properties of beta-lactam antibiotics require sustained blood levels above the Minimum Inhibitory Concentration (MIC) for optimal efficacy. Administering them as infusions or if that puts a strain on the IV systems, at least over prolonged periods, spread over several hours to maintain such levels. E.g Meropenem over 4 hours. Dulhunty et al., after several years of working on the same subject with mixed results recently showed some benefit with continuous infusions.

Terminology for the reporting for Ventilator associated pneumonias which slide of our tongues as VAPs, has changed in the last few years. There remains some confusion over the application of this new algorithm to neonates and Pediatrics and CDC guidelines are yet unclear on this. However, the algorithm put forth does afford some extra clarity in differentiating non-infectious events from infectious events and we have attempted to deconstruct this complex document for easier reading.

We hope this symposium will bring you some information that you may not have otherwise sought out in your general reading.

References
Ventilator Associated Events: Deconstructing a new algorithm

Soonu Udani*, Rekha Solomon**

*Head of the Section of Pediatrics and Pediatric Intensive Care, **Junior Consultant in PICU, PD Hinduja Hospital, Mumbai

Introduction

The problem of diagnosing and treating every fever, new lung shadow or ventilator deterioration with antibiotics, which would necessitate covering flora exhibiting greater resistance in a hospital setting, has always been challenging. Intensivists in adult and pediatric units have struggled with trying to establish the best possible algorithms and guidelines to most accurately diagnose the presence of a ventilator associated pneumonia (VAP) and institute early treatment, while at the same time preventing the overuse of antibiotics for events and complications which may occur in the ventilated patient but may not be due to a new infection in the lower respiratory tract. In 2011, the Centres for Disease Control (CDC) convened a Ventilator Associated Pneumonia (VAP) Surveillance Definition Working Group to form a surveillance definition algorithm, which is referred to as the ventilator-associated events or “VAE surveillance definition algorithm” as a start to define what constitutes a VAP. Here more objective measures of conditions and complications that commonly occur in patients receiving mechanical ventilation and are recognized as confounding the diagnosis of infection, is considered in a tiered approach. These were adopted in January 2013 by the CDCs National Healthcare Safety Network (NHSN) as more objective for reporting and comparing VAP rates across institutions for adult ICUs.

In recognition of problems of neonatal respiratory distress and changes in the lungs, ventilator settings and requirements being very variable, these criteria are recognized as being inappropriate for this group by a special working committee convened to validate this algorithm in the NICU. Criteria are still being formulated for PICU reporting but the current ones given in the adult guidelines are as yet, not accepted. National reporting in the US continues to be done on the basis of the old VAP guidelines and on the basis of the new VAE surveillance guidelines from adult ICUs till the working committee reviews and formulates acceptable PICU reporting guidelines.

The ventilator-associated event (VAE): consists of 3 tiers:

**Tier I:** ventilator associated condition (VAC), which may progress to the
**Tier II:** an infection related ventilator associated complication (IVAC) and then to the
**Tier III:** which would be a possible or probable VAP by the criteria of the algorithm.

The entire algorithm constitutes the VENTILATOR ASSOCIATED EVENT.

Definitions

Ventilator-associated pneumonia (VAP): A pneumonia (PNU) that develops after the patient is on mechanical ventilation for >2 calendar days on the date of event, with day of ventilator placement being Day 1, AND the ventilator was in place on the date of event or the day before.

If the patient is admitted or transferred into a facility on a ventilator, the day of admission is considered Day 1.

(Hospital acquired pneumonias (HAPs or health care acquired pneumonias (HCAP) may occur in the hospital or other health care facility without mechanical ventilation but may have the same implication)

Transfer Rule: If the date of event for a PNU/VAP is on the date of transfer or the next day, the infection is attributed to the transferring/discharging location.

Imaging criteria:

Two or more serial chest imaging test results with at least one of the following:

- New or progressive and persistent infiltrate
- Consolidation
- Cavitation
- Pneumatoceles, in infants ≤1 year old

Clinical + symptomatic -- at least one of the following:

- Fever (>38.0°C or >100.4°F)
• Leukopenia (12,000 WBC/mm3)
• New onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements
• New onset or worsening cough, or dyspnea, or tachypnea
• Rales or bronchial breath sounds
• Worsening gas exchange (e.g., O2 desaturations (e.g., PaO2/FiO2 <240, increased ventilator settings and increased oxygen demand.)

This corresponds with the first tier of the VAE algorithm: (THIS IS DESIGNATED AS PNU 1 IN THE CDC device associated module January 2015 modified from Centers for Disease Control and Prevention. After a period of stability or improvement on the ventilator, the patient has at least one of the following indicators of worsening oxygenation:

1. Minimum daily FIO2 values increase ≥ 0.20 (20 points) over the daily minimum FIO2 in the preceding 2 days (the baseline period), for ≥ 2 days.
2. Minimum daily PEEP values increase ≥ 3 cm H2O over the daily minimum PEEP in the preceding 2 calendar days (the baseline period), for ≥ 2 calendar days.

The pediatric-neonatal working group agreed with VAE Tier I on this aspect and added that an increase in mean airway pressure (MAP) in a range of 3-5 cm H2O besides the above criteria, could be used to trigger concerns of a Pediatric ventilator associated complication (PVAC) in a VAE. Making this a probable valid tier in the algorithms applicability to pediatrics.

**Time frame of 48 hrs:** Complications mimicking infection, usually resolve in <48 hours with appropriate therapy and will show an improvement in ventilator settings, blood gases as well as chest Xrays. Atelectasis, secretions, fluid overload, malpositioned endotracheal tubes; are all easily recognizable and correctable but if left alone can themselves lead to VAP.

**TIER II OR IVAC (infection related ventilator associated complication)**

If the problem remains unresolved and the fever persists with leucopenia/leucocytosis, a new antibiotic is started and continued for a minimum of 4 days. This is the next tier where it may not always be possible to differentiate a probable from a possible VAP and where laboratory support, specimen collection and correlation become important.

**Probable VAP**

The above clinical and Xray criteria along with at least one of the following:

• Positive growth in blood culture not related to another source of infection
• Positive growth in culture of pleural fluid
• Positive quantitative culture from minimally-contaminated lower respiratory tract (LRT) specimen (e.g., BAL or protected specimen brushing) (table 1)
• ≥5% BAL-obtained cells contain intracellular bacteria on direct microscopic exam (e.g., Gram’s stain)
• Positive quantitative culture of lung tissue (Atypical pneumonia serology, Influenza A, H1N1 PCR etc is also included in the positive testing criteria.)
• Histopathologic exam shows at least one of the following evidences of pneumonia: Abscess formation or foci of consolidation with intense PMN accumulation in bronchioles and alveoli or Evidence of lung parenchyma invasion by fungal hyphae or pseudohyphae.

**Table 1: Threshold values for cultured specimens used in the diagnosis of pneumonia**

<table>
<thead>
<tr>
<th>Specimen</th>
<th>threshold value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung tissue</td>
<td>&gt;10^4 CFU/g tissue</td>
</tr>
<tr>
<td>Bronchoalveolar lavage (B-BAL)</td>
<td>&gt;10^4 CFU/ml</td>
</tr>
<tr>
<td>Protected BAL (B-PBAL)</td>
<td>&gt;10^4 CFU/ml</td>
</tr>
<tr>
<td>Protected specimen brushing (B-PSB)</td>
<td>&gt;10^4 CFU/ml</td>
</tr>
<tr>
<td>Nonbronchoscopically (NB) obtained (blind) specimens</td>
<td>&gt;10^4 CFU/ml</td>
</tr>
<tr>
<td>NB-BAL</td>
<td>&gt;10^4 CFU/ml</td>
</tr>
<tr>
<td>NB-PSB</td>
<td>&gt;10^4 CFU/ml</td>
</tr>
</tbody>
</table>

In the immunocompromised patient, Any of the tests from PNU 2 + additional tests should be sent for to get positivity for least one of the following: The category is straight PNU3.
1. Matching positive blood and sputum or endotracheal aspirate cultures with Candida spp.  
2. Evidence of fungi from minimally contaminated LRT specimen (e.g., BAL or protected specimen brushing) from one of the following:
   - Direct microscopic exam
   - Positive culture of fungi
   - Non-culture diagnostic laboratory tests

**Possible VAP:** On or after calendar day 3 of mechanical ventilation with the above clinical and X-ray criteria along with at least one of the following:
1. Purulent respiratory secretions (from ≥1 specimen collection) Defined as secretions from the lungs, bronchi, or trachea that contain ≥25 neutrophils and ≤10 squamous epithelial cells per low-power field (x100) (or corresponding semiquantitative results).
2. Positive culture (qualitative, semiquantitative, or quantitative) of endotracheal aspirate, BAL, lung tissue, or protected specimen brushing

**Excluded organisms and culture results** that cannot be used to meet the PNEU/VAP definition are as follows:
1. “Normal respiratory flora,” “normal oral flora,” “mixed respiratory flora,” “mixed oral flora,” “altered oral flora” or other similar results indicating isolation of commensal flora of the oral cavity or upper respiratory tract. The following organisms unless isolated from cultures of lung tissue or pleural fluid Candida species or yeast not otherwise specified; coagulase-negative Staphylococcus species; Enterococcus species; Candida species isolated from sputum or endotracheal aspirate; specimen combined with a matching blood culture can be used to satisfy the PNU3 definition.

**Ventilator-Associated Events Surveillance Definition Algorithm** (modified From Magill et al)
Patient MUST BE STABLE OR IMPROVING on the ventilator, defined by ≥2 days of stable or decreasing daily minimum FIO2 or PEEP values.

**TIER I**
After a period of stability or improvement on the ventilator, the patient has at least 1 of the following indicators of worsening oxygenation:
1. Minimum daily FIO2 values increase ≥0.20 (20 points) over the daily minimum FIO2 in the preceding 2 calendar days for ≥2 days.
2. Minimum daily PEEP values increase ≥3 cm H2O over the daily minimum PEEP in the preceding 2 days for ≥2 calendar days.

**TIER II: Ventilator associated condition (VAC)**
>=3 days of mechanical ventilation and within 2 days before or after the onset of worsening oxygenation, the patient meets **both** of the following criteria:
1. Temperature >38°C or <36°C, OR white blood cell count ≥12 000 cells/mm3 or ≤4000 cells/mm3 AND
2. A new antimicrobial agent is started, and continued for ≥4 calendar days (If the patient is better by this time it is probably an event, which got better and not a VAP)

**Table 2:** Ventilator associated pneumonia (VAP) rates from tertiary PICU

<table>
<thead>
<tr>
<th>Year</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015 (Jan-July)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilator days</td>
<td>560</td>
<td>575</td>
<td>348</td>
<td>228</td>
</tr>
<tr>
<td>VAP</td>
<td>4</td>
<td>6</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>VAP/1000 Ventilator days</td>
<td>7</td>
<td>10</td>
<td>11.5</td>
<td>4</td>
</tr>
<tr>
<td>Organisms</td>
<td>Pseudomonas-3 MSSA-1</td>
<td>Gram Neg B-5 MSSA-1 (GNB: MDR Acinetobacter, Pseudomonas, EColi, Enterobacter)</td>
<td>MDR acinetobacter-2, H influenza-1, MSSA-1</td>
<td>Pseudomonas-1</td>
</tr>
<tr>
<td>VAE</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

(Jan 1 2012- Dec 31 2014: VAP rate 9.4 / 1000 Ventilator days  
Jan 1 2012- July 31 2015: VAP rate 8.7 /1000 Ventilator days)
Data Analyses: we present our data of VAP rates from a tertiary care PICU for the last three and half years 2102-July 2015. The positive cultures using the above definitions and guidelines were used to identify probable VAPs only. The VAP rate per 1000 ventilator days is calculated by dividing the number of VAPs by the number of ventilator days and multiplying the result by 1000.

The VAP rate in our PICU from 2012 to 2015 was 9.4/1000 ventilator days. The International Nosocomial Infection Control Consortium (INICC) surveillance study from January 2007-December 2012 in 503 intensive care units (ICUs) in Latin America, Asia, Africa, and Europe prospectively studied device associated- health care associated infection and found a VAP rate of 16.8/1000 ventilator days². A prospective study from 12 adult ICUs in India, from 2004 to 2007 found VAP rates ranging from 3.69 to 18.17 per 1000 MV-days, with an overall rate of 10.46⁶. A cohort study of 64 PICUs in the United states between 2007 and 2012 found a decrease in VAP rates from 1.9 to 0.7/1000 ventilator days during the study period⁹.

TIER III: Infection - Related Ventilator - Associated Complication (IVAC)

On or after day 3 of mechanical ventilation and within 2 days before or after the onset of worsening oxygenation, 1 of the following criteria is met:

1. Purulent respiratory secretions (from ≥1 specimen collection)
   - Defined as secretions from the lungs, bronchi, or trachea that contain ≥25 neutrophils and ≤10 squamous epithelial cells per low-power field (x100)(or corresponding semiquantitative results).
2. Positive culture (qualitative, semiquantitative, or quantitative) of sputum*, endotracheal aspirate*, bronchoalveolar lavage*, lung tissue, or protected specimen brushing*

*Excludes the following:
- Normal respiratory/oral flora, mixed respiratory/oral flora or equivalent
- Candida species or yeast not otherwise specified
- Coagulase-negative Staphylococcus species
- Enterococcus species

POSSIBLE VAP

within 2 days before or after the onset of worsening oxygenation, 1 of the following criteria is met:

1. Purulent respiratory secretions (from ≥1 specimen collection—and defined as for possible VAP) AND 1 of the following:
   - Positive culture of endotracheal aspirate*, ≥105 CFU/mL or equivalent semiquantitative result
   - Positive culture of bronchoalveolar lavage*, ≥104 CFU/mL or equivalent semiquantitative result
   - Positive culture of lung tissue, ≥104 CFU/g or equivalent semiquantitative result
   - Positive culture of protected specimen brush*, ≥103 CFU/mL or equivalent semiquantitative result

*Same organism exclusions as noted for possible VAP.
2. One of the following (without requirement for purulent respiratory secretions):
   - Positive pleural fluid culture (where specimen was obtained during thoracentesis or initial placement of chest tube and NOT from an indwelling chest tube)
   - Positive lung histopathology
   - Positive diagnostic test for atypical organisms

PROBABLE VAP

Positive diagnostic test on respiratory secretions for viruses

Figure 2: VAP rates in Hinduja Hospital (Adult and pediatric ICUs)

On reviewing the sensitivity of gram negative organisms in cases of VAP in our hospital (Adult and pediatric), there were 38 positive cultures of pseudomonas, of which 19 were sensitive to first line drugs and 19 were ESBL. There were 29 cases with Acinetobactor of which 25 were Carbepenem Resistant.

Worth mentioning here is also the clinical pulmonary infection score CPIS which is often used in the clinical diagnosis of VAP by predicting which patients will benefit from obtaining pulmonary cultures as it uses tracheal aspirates and can also prevent unnecessary antibiotic administration due to treatment of colonized patients.
The score assigns numerical values to clinical, physiological, microbiological and radiographic parameters to predict the presence or absence of infection\(^{10}\). (Table 3) Scores range between zero and 12 with a score of \(\geq 6\) showing good correlation with the presence of VAP\(^{11}\).

This has been a popular tool, especially as it used tracheal aspirates but recently came into disuse as studies have questioned its validity, mainly due to inter-observer variance. A meta-analysis by Shan et al of 13 studies for sensitivity and specificity for CPIS as 65 % (95 % CI 61-69 %) and 64 % (95 % CI 60-67 %), respectively\(^{12}\).

Table 3: The clinical pulmonary infection score (CPIS)\(^{13}\)

<table>
<thead>
<tr>
<th>Assessed Parameter</th>
<th>Result</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature (°Celsius)</td>
<td>36.5-38.4 °C</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>38.5-38.9 °C</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>≤ 36 or ≥ 39 °C</td>
<td>2</td>
</tr>
<tr>
<td>Leukocytes in blood (cells/ mm(^3))</td>
<td>4,000-11,000/mm(^3)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&lt;4,000 or &gt;11,000/mm(^3)</td>
<td>1</td>
</tr>
<tr>
<td>Tracheal secretions (subjective visual scale)</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Mild/non-purulent</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Purulent</td>
<td>2</td>
</tr>
<tr>
<td>Radiographic findings (on chest radiography, excluding CHF and ARDS)</td>
<td>No infiltrate</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Diffuse/patchy infiltrate</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Localized infiltrate</td>
<td>2</td>
</tr>
<tr>
<td>Culture results (endotracheal aspirate)</td>
<td>No or mild growth</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Moderate or florid growth</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Moderate or florid growth AND pathogen consistent with Gram stain</td>
<td>2</td>
</tr>
<tr>
<td>Oxygenation status (defined by PaO(_2):FiO(_2))</td>
<td>&gt;240 or ARDS</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>≤240 and absence of ARDS</td>
<td>2</td>
</tr>
</tbody>
</table>

In order to more accurately diagnose and treat VAPs with the minimum of antibiotics for the shortest possible period of time without endangering our patients, we seek criteria, scoring systems and laboratory methods that are quick, accurate, easily accessible to most PICU and cost effective. Prevention is the keystone to the entire problem and full attention to the implementation of the “VAP BUNDLE” that is appropriate to and easily implementable in the PICU must be employed.

The typical VAP bundle that is recommended by would include:
- Upright position unless contraindicated
- No circuit change unless soiled
- Use HME unless contraindicated
- H2 blocker instead of PPI as far as possible
- Early feeding with 4 hrly residue check
- Hold feed if aspirate >10% of feed volume
- Aseptic suctioning technique.
- Do not keep connector on or unsterile test lung
- Do not use sterile glove for unsterile handling
- Use in line suction whenever feasible
- Daily wake up
- Least muscular blockade possible
- Chest PT & position change
- Chlorhexadine mouthwash three times a day
- Low pressure Suction at the ET cuff to prevent aspiration of secretions

Last but not least, meticulous and obsessive attention to hand washing and use of bedside chlorhexadine + alcohol based hand rub solutions will go a long way in prevention. This is recommended for use in all hospitals even by the JCAHO\(^{14}\).

In summary

Data collection and surveillance of the incidence of infections in the unit and institution are very important for keeping rates down.

One method that is appropriate, reproducible, comparable among peer groups and effective must be used for surveillance and data collection.

Regular reporting of VAP rates among units within an institution should be part of regular audits and the time to report nationally may soon be near.

The modified algorithm for Ventilator Associated Events (VAEs) can be applied in the PICU if not in the NICU as parameters are quite similar and it has greater objectivity.
References

10. Klompas M, Clinician’s Corner: Does this patient have ventilator-associated pneumonia? JAMA 2013, 297:1583-1593
Introduction

Catheter related blood stream infections (CRBSI) refer to bacteremias or fungemias for whose origin there is no documented distal source. A “catheter” could include a peripheral IV, arterial or central line-tunneled or non tunneled.

Although not necessarily more lethal, these infections are somehow dreaded more than acquired pneumonias. If the host is recovering and the organism is sensitive to available antibiotics, recovery is usual. The problem of obtaining positive blood cultures on a patient already on antibiotics, along with the fear of deterioration of a patient often improving from the primary illness, forces the clinician to start and continue empirical treatment according to local sensitivity and organism patterns. This often leads to overtreatment and unnecessary and prolonged antibiotic use.

Extraluminal colonization with the source of infection from the skin usually occurs at the time of insertion and is more common in non-tunneled devices whereas infection of the hub leading to intraluminal colonization is more common in tunneled devices. Sometimes the source of infection can be hematogenous seeding of the catheter tip. Catheter related infections lead to increased cost of therapy, duration of hospitalization, morbidity and even mortality. A old meta-analysis of 2573 catheter related blood stream infections showed that the case fatality rate was 14% of which 19% were attributed directly to the catheter related infection (2.6%).

CRBSI should be considered when a patient with a central venous catheter (CVC) presents with bacteremia or fungaemia in the presence of signs and symptoms of systemic infection, such as fever, chills, and hypotension in the absence of hypovolaemia or a cardiac event. Hence, probable CRBSI can be diagnosed by one or more positive blood cultures obtained from a peripheral vein, when there is no apparent source for the bloodstream infection except the catheter. In addition to the above, the Infectious Diseases Society of America (IDSA) has suggested one of the following microbiological methods to confirm diagnosis of CRBSI: (1) Gold standard: positive semiquantitative or quantitative culture of the catheter; (2) simultaneous quantitative blood cultures drawn through the CVC and peripheral vein with a ratio of 5:1 or more (CVC versus peripheral); or (3) differential time to positivity.

The most important decision besides the institution of antibiotic therapy lies in the dilemma of catheter removal. In critically ill children this is a major lifeline, which can also be a hangman’s noose if inappropriately handled.

In any patient with bacteremia and a catheter it is important to determine whether the catheter is the source of infection.

Situations & Organisms Where the Catheter MUST be Removed: As early as possible

- Obvious redness and infection at insertion site
- fungal infection
- atypical mycobacteria,
- vancomycin resistant enterococci and
- acinetobacter,
- evidence of metastatic seeding: endocarditis, pulmonary embolism
- repeated positive cultures
- no response to antibiotics in 3-5 days
- the child deteriorates
- blocked catheter.

Often salvage therapy will fail with MRSA & Gram negative infection and even with early apparent success the infection will often recur.

Definitive Method: Quantitative catheter culture:

Quantitative and semi-quantitative methods: Growth of \( \geq 15 \text{ cfu} \) by a semi-quantitative method or \( \geq 10^2 \text{ cfu} \) by a quantitative method is diagnostic of the catheter being the cause of the blood stream infection. The Quantitative method is at least 20% more sensitive (80% sensitivity) than semi-quantitative method (60% sensitivity). It should be remembered that
culturing the catheter tip in the absence of suspicion of a CRBSI should be avoided colonized organisms will be picked up and the device will have been lost The habit of routinely sending the device for culture on removal should also be avoided for the same reason.

Catheter Sparing Techniques: To help decide if the catheter is the culprit
1. **Simultaneous Quantitative blood cultures** help better define the issue. When the colony count is $\geq$ 5-10 times in the catheter sample as compared to the peripheral sample or when the CVC yields $\geq$ 100 cfu/ml, it is diagnostic of the catheter as being the source of infection. Simultaneous quantitative blood culture was found to be the most accurate test for diagnosis of CRBSI in a meta-analysis of studies of diagnostic tests. This is time consuming, labour intensive, prone to contamination and expensive and requires 10 ml blood at the least from the patient but compares favourably with the gold standard which is the quantitative culture of the catheter described above.

2. **Time to positivity**: If quantitative cultures are not available one can use differential time to positivity for the CVC line versus peripheral samples. This is possible in the currently used radiometric culture methods where constant automated monitoring is done to check for growth. When the growth in the catheter sample is detected $\geq$ 2 hours before that in peripheral sample, it highly suggestive of the catheter as being the source of infection. This is currently the most commonly used method of diagnosis in hospitals across India.

If these tests come out showing that the catheter is not the source, it could be spared. Whenever the decision is taken to remove the catheter, the tip or the subcutaneous part of the removed catheter must be cultured using semi-quantitative or quantitative techniques.

3. **Catheter-drawn quantitative blood cultures**
A single quantitative blood culture drawn through the line without an accompanying peripheral culture can also be used. The threshold for a positive diagnosis is 100 CFU /mL. This may even come from a high bacteraemia, and does not mean a definitive CRBSI

4. **Acridine orange leucocyte cytospin**: This is an almost bedside test that appears attractive as it requires only 1 ml of blood directly drawn from the catheter and placed on a slide, stained with the dye Acridine orange and scanned for bacteria. The sensitivity reported by the few reports on it is good. The sensitivity and specificity of this test have been reported to be 87% and 94%, respectively. However it has no robust following and needs more study.

5. Another novel approach has been to do a mini brush sample of the endolumen. A thin wire and brush is inserted in the lumen of the catheter where bacteria adhere to the fibrin sheath on the inner surface and this fibrin becomes enmeshed in the brush’s bristles, and give a rich culture from the biofilm. One study reported a 95% and a specificity of 84%. This method may be considered fairly hazardous to the safety of the catheter.

Prevention of Infection: These are recommended by the CDC, Healthcare Infection Control Practices Advisory Committee (HICPAC) and some are expected to be traditionally and universally followed. Education of health-care workers, proper catheter insertion and maintenance, routine audits of rates of infection, hand hygiene, use of sterile semi-permeable dressings, avoiding femoral insertion, removing the catheter as soon as possible. Others like using dedicated teams and in line filters are also recommended and should be followed where possible.

There are other methods that are also used and come strongly recommended and backed by evidence.

1. **2% aqueous chlorhexidine** gluconate tended to decrease CRBSI compared with 10% povidone-iodine or 70% alcohol. This was shown to be superior to 0.5 % chlorhexidine which had no beneficial effect over 10% povidone-iodine. Even the use of 1% chlorhexidine with alcohol or as shown by Parienti and Maki showed that 10% povidone-iodine with 70% alcohol...
appeared to work as well too\textsuperscript{12}. Today, \textbf{2\% chlorhexadine is the recommended solution for skin preparation.}

2. \textbf{Operating room gowns:} The use of sterile gown, gloves, and cap, and using a large sterile drape during the insertion of the CVC, similar to that used in the operating room has shown to reduce the risk of CRBSI in an RCT with a \textit{p} value of 0.06\textsuperscript{13}. This is followed by several studies and is now standard practice in all major centres\textsuperscript{14}. The HICPAC guidelines currently strongly recommends the use of full barrier precautions for the insertion of the Pulmonary artery catheter and CVCs.

3. \textbf{Chlorhexidine-impregnated sponge:} This can be placed over the CVC insertion site and covered with a transparent semipermeable dressing. In one study by Maki, its use led to a three-fold reduction in infection \textsuperscript{15} However, two paediatric studies showed a pronounced decrease in CVC colonisation but not CRBSI\textsuperscript{16,17}.

4. \textbf{Antiseptic coated catheters:} “The HICPAC guidelines strongly recommend the use of antiseptic or antibiotic-coated CVCs in patients whose catheter is expected to remain in place for more than 5 days, combined with a comprehensive strategy that aims to reduce CRBSI through education, maximum sterile barrier, and 2\% chlorhexidine skin antisepsis during CVC insertion.”\textsuperscript{19} However, despite this strong recommendation, the evidence for these catheters being the panacea for prevention of infections is rather weak. Over a dozen trials, including RCTs on antibiotic coated catheters, Silver or Chlorhexadine impregnated catheters showed reduction in colonization but failed to show a reduction in true CRBSI rates\textsuperscript{19}. One showed an actual fall in CRBSI rates using Chlorhexadine and silver sulfadiazine\textsuperscript{18}.

4a. \textbf{Antibiotic coated catheters:} Minocycline / Rifampicin coated (on both sides)ones are manufactured but not easily available and very expensive. They have greater activity against staphylococci compared with first-generation chlorhexidine/sulfadiazine silver catheters.

The use of two drugs seems to reduce the risk of resistance developing. There is a significant risk reduction reported with the use of these catheters\textsuperscript{20}. These catheters have been manufactured since the 1990s. However they have not come into routine use as the risk reduction has proved to not be cost effective compared to the best clinical practices when properly followed as outlined below.

5. \textbf{Catheter locks:} Saline and heparin have both been found to have equal efficacy in preventing phlebitis and maintaining patency in peripheral veins. There has been some evidence to show that both these agents may actually enhance Staphylococcal biofilm formation. Hence the solution may lie in an antibiotic/heparin lock rather than a heparin lock alone\textsuperscript{21}. Antibiotic lock therapy works on the principle that the CVC device is usually colonized intraluminally. Systemic antibiotic therapy will act on the extra luminal infection but not on the organisms in the intraluminal bio-film for which the antibiotic needs to be in a 100-1000 times greater concentration. This is possible by antibiotic lock therapy where 2-5 ml (sufficient to fill the device lumen) of antibiotic solution with 15 mg/ml concentrations along with 50-100 units of heparin is pushed and “locked” in the lumen of the device and kept there for at least 12 hours between use. This along with the systemic antibiotics is able to salvage the tunneled CVC in more than 85\% of cases. The drugs commonly used include quinolones, vancomycin or aminoglycosides. Even port devices can be salvaged with this.

\textbf{Other locks:} Chelators like citrate and EDTA enhance the activity of antimicrobial drugs against organisms embedded in the biofilm. Ethanol at 25-40\% also makes a good locking solution \textsuperscript{22}. It is difficult to get this grade of pure ethanol and it has been suggested by those braver than the author that laboratory grade ethanol can as well be used for this purpose.

6. \textbf{Daily Care:} This varies with unit/hospital protocols. One such recommended bundle is outlined below:

- Daily review of line necessity with prompt removal
- Hand hygiene before manipulation of the IV system
• Catheter injection ports are covered by injection ports, sterile end-caps or needleless connectors.  
• “Scrub the Hub” protocols before and after each use with 2% chlorhexidine.  
• Caps are changed no more often than 72 hours.  
• Aseptic techniques are used for all access to the line.  
• Catheter site care is performed with chlorhexidine at dressing changes.  
• Set is replaced no more frequently than every 96 hours, and at least every 7 days.  
• Every 24 hrs when lipid emulsions are used.

**Management:** A Multipronged attack: ORGANISM DEPENDANT
1. Remove??  
2. Treat through with antibiotics with or without antibiotic lock  
3. Which Antibiotic and for how long

Coagulase negative Staphylococcus (CONS): usually come from the skin and sensitivity may vary widely. These must not be underestimated to be benign in their ability to cause serious infection from the catheter. The nasal mucosa or even other areas besides the catheter insertion site may be the source. In the Non-tunneled CVC, it is best to consider removing it if possible and treating with Kloxacillin/vancomycin according to sensitivity for 5–7 days. If it has to be retained (or is a tunneled / implanted device) treatment for 7 days with concomittent antibiotic (Vancomycin) lock for 10–14 days is recommended. The device should then be used only for this and IV fluids and other medications should preferentially be given by another site. *At no time should any nutritional product be administered through a suspect device.*

For MSSA/MRSA all Non-tunneled devices should be removed as far as possible unless very precious. Otherwise treatment for ≥14 days only if the echocardiogram is negative may be an option. Tunneled/implantable devices are very expensive and salvage is important. Here a trial with antibiotics as well as lock for ≥14 days as described may be acceptable.

For all situations: **If deterioration or no improvement, repeat cultures and if positive, look for seeding: look for bacterial endocarditis, other end organs and remove the catheter.**

Gram-negative bacilli: Bacteraemia is usually from endogenous sources like the urinary tract, nosocomial pneumonia or from gut translocation. Personnel hands ofcourse can never be exonerated. However, Gram-negative bacillary CRBSI caused by any organism and even carbepenem resistant enterobacteriaceae (CRE) are seen. reported on 149 episodes of bacteraemias caused by *S maltophilia* and other nonaeruginosa Pseudomonas species and it is emerging in epidemic forms in neonatal and pediatric ICUs in India too. The temptation to treat through the catheter needs to be resisted as failure to remove the catheter is associated with poor clearance as well as high relapse rates. If the catheter is removed, relapse rates are less than 1%. Removal of the device shortens the treatment period as well.

Candida species and fungal sepsis: **All devices must be removed within 72 of suspected or proven infection.** There is no proven antifungal lock with Fluconazole or Amphotericin. Fluconazole has similar efficacy to amphoterincin B in the treatment of candidaemia, although fluconazole has a better safety profile. Echinocandins (caspofungin and micafungin) have been shown to be equivalent to amphoterincin B or liposomal amphoterincin B in the treatment of candidaemia, with a superior safety profile. A recent multicentre study has shown that anidulafungin (another echinocandin) is equivalent and possibly superior to fluconazole in the treatment of invasive candidiasis.

Therefore, in patients with catheter related candidemia, fluconazole or an echinocandin should be considered as an equal and safer alternative to amphoterincin B, although in centres where there are higher rates of fluconazole-resistant *Candida glabrata* and *Candida krusei*, an echinocandin should be used. According to IDSA guidelines, the duration of therapy for uncomplicated catheter-related candidaemia should be 2 weeks from the last negative blood culture. In India for over a decade *Tropicalis* and *Glabrata* have overtaken albicans as the predominant isolates when Candida is detected. The central line is an extremely important and life saving device in the PICU. It needs to be treated with utmost respect and aseptic handling from the moment of insertion till the very end. Like all interventions in
the critically ill patient, it needs to be used judiciously and removed as soon as it’s use is deemed to be over.

**Key Messages**

1. Strict aseptic insertion techniques must be followed
2. The protocol for diagnosis and establishing the presence of a CRBSI should be rigorous if the catheter is to be salvaged at minimal risk to the patient.
3. The appropriate and prompt institution of antibiotics is important
4. If the catheter needs to be sacrificed then it should be
5. Novel antibiotic lock treatments may help salvage and prevent infections.
6. All devices should be removed as early as possible
7. Use a bundled approach for insertion and daily care

**References**

12. Maki DG, Knasinski V, Naranja LL, Gordon BJ. A randomized trial of a novel 1% chlorhexidine-75% alcohol tincture versus 10% povidoneiodine for cutaneous disinfection with vascular catheters. 11th Annual Society for Healthcare Epidemiology of America Meeting; Toronto, ON, Canada; April 1–3, 2001. Abstract 142
Every medical student is familiar with Starling’s model\(^1\) of the vascular barrier:

1. The higher hydrostatic pressure in the vascular compartment drives fluid out of the arterioles into the interstitium.
2. The much lower oncotic pressure in the interstitium limits the amount of fluid that crosses the endothelium.
3. Most of the fluid that escapes from the arteriolar end is reabsorbed at the venular end, lymphatics reabsorb the remainder.

Subsequent research revealed that there were a few flaws in Starling’s original hypothesis:\(^3\)

1. The albumin content & oncotic pressure of the interstitium is much higher than that predicted by Starling also changes in the albumin content of the interstitium do not seem to affect movement of fluid across the vasculature.
2. Almost no reabsorption of fluid takes place at the venular end, all fluid that is reabsorbed is via the lymphatics.
3. Even though the interstitial oncotic pressure is just marginally lower than that of the plasma, the actual amount of fluid that leaves the vasculature is much lower than that predicted by Starling’s Equation (which is why the lymphatic channels are not overwhelmed).

The discovery of and subsequent research on the Endothelial Glycocalyx Layer (EGL) has helped resolve these holes in Starling’s theory. The EGL is a negatively charged gel–like web of membrane-bound glycoproteins and proteoglycans present on the luminal side of the endothelial cells. It’s associated with various glycosaminoglycans (GAGs). It is the active interface between blood and the capillary wall and it is this layer that determines the competence of the vascular barrier.\(^4,5\)

The Endothelial Glycocalyx

There exists a protein free space below the glycocalyx (the sub glycocalyx space). It is the difference in the oncotic pressure between this space and the plasma that limits the amount of fluid that escapes into the interstitium.

**Revised Starling’s Hypothesis\(^3\)**

The glycocalyx does not exist only to explain the flaws in Starling’s model. It has several other important functions. (Protection of Endothelium from shear stress, Ischemia reperfusion Injury etc)
This article will dwell on the glycocalyx and sepsis:

In addition to its barrier function, the healthy EGL covers the endothelium and prevents circulating WBCs and platelets from coming into contact with their receptors located on the endothelium.\(^7\)

The chemokines released during sepsis & SIRS cause denudation of the EGL and the barrier function is undermined thus contributing to capillary leak and interstitial edema. The worsening interstitial edema affects the delivery of oxygen across the microvasculature. Degradation of the EGL in sepsis exposes the WBCs to their adhesion receptors on the endothelium thereby amplifying the inflammatory process and causing further disruption of the vascular barrier and worsening of the capillary leakage. Platelets also come into contact with their endothelial receptors causing a procoagulant and antithrombolytic state.\(^9\)

Inappropriate fluid therapy in sepsis may also contribute to degradation of the EGL. Fluids (especially colloids) exhibit a phenomenon known as context sensitivity. In hypovolemic or normovolemic patients almost all of the infused colloids remain within the vascular bed. In hypervolemic patients the volume effect is only 40%.\(^10\) This is because hypervolemia causes degradation of the EGL through release of ANP (Atrial Natriuretic Peptide). This could also possibly explain why Colloids performed better than crystalloids in studies done on hypovolemic patients but did not do so well in other studies.

**The Perturbed Glycocalyx** (downloaded from www.glycocalyx.nl)

The context sensitivity of colloids

In the management of Sepsis, measures that protect the EGL may help limit capillary leak, decrease interstitial edema improve oxygen delivery, limit inflammation and coagulopathy. This is the subject of much research.

Some of many potential therapies that may preserve the EGL are:\(^11\)

- Antioxidants
- Steroids
- TNF α receptor antagonists
- Antithrombin III
- Infusions of Hyaluron & Chondroitin Sulfate

Unfortunately, as of now proof of efficacy of any of these measures is lacking.

Until such proof is available a few simple measures might help protect the EGL:

- Avoidance of Hyperglycemia
- Avoidance of Hypervolemia
- Maintenance of adequate levels of Sr Albumin

**The Context Sensitivity of Colloids**

Taken from Jacob et al\(^3\)

In the management of Sepsis, measures that protect the EGL may help limit capillary leak, decrease interstitial edema improve oxygen delivery, limit inflammation and coagulopathy. This is the subject of much research.

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**References**

2. C. S. Alphonsus and R. N. Rodseth The endothelial glyocalyx: a review of the vascular barrier Anaesthesia 2014, 69, 777–784
3. Levick JR, Michel CC. Microvascular fluid exchange and the revised Starling principle. Cardiovascular Research 2010; 87: 198–210
Part 1: Colistin update
The intravenous use of polymyxins has been considered to be associated with considerable nephrotoxicity and neurotoxicity. For this reason, the systemic administration of polymyxins had been abandoned for about 20 years in most areas of the world. However, the problem of infections due to multidrug-resistant (MDR) gram-negative bacteria such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii* has led to a resurgence in the use of polymyxins. Multidrug resistant (MDR) gram-negative nosocomial infection in intensive care units is a global health problem\(^1\,^2\) (Table 1). Dissemination of enterobacteriaceae producing carbepenemases such as *Klebsiella pneumonia* carbepenemase (KPC), New Delhi Metallo-β lactamase (NDM1), Verona Integron-encoded Metallo beta-lactamases (VIMs) and active on Imipenem Metallo beta lactamases (IMPs) occurs rapidly via plasmids. The other mechanisms of antibiotic resistance in these organisms are porin mutations leading to altered outer membrane permeability, efflux pumps, restricted access of drug to target and enzymatic modification or elimination of the cellular target (Figure 1)\(^3\). Carbepenem Resistant Enterobacteriaceae (CRE) are usually also resistant to fluoroquinolones, aminoglycosides and trimethoprim-sulfamethoxazole. KPC infections which were originally reported with *Klebsiella pneumonia*, have been reported in *Escherichia*, *Acinetobacter* and *Pseudomonas* species, with an estimated mortality of 27-44%\(^4\). Polymyxins are increasingly being used to treat CRE.

Table 1. Acquired resistance category definitions. (Intrinsic resistance to any specific antimicrobial agent would automatically eliminate that agent from being included in defining resistance.)

<table>
<thead>
<tr>
<th>Multi Drug Resistant (MDR)</th>
<th>Resistant to more than 1 agent in 3 or more antimicrobial categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extremely Drug Resistant (XDR)</td>
<td>Resistant to more than 1 agent in all but 2 categories</td>
</tr>
<tr>
<td>Pan Drug Resistant (PDR)</td>
<td>Resistant to all categories</td>
</tr>
</tbody>
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Figure 1. a | Impermeable barriers. Some bacteria are intrinsically resistant to antibiotics. |b | Drug injection | d | Drug activation | e | Resistance mutation | H冯 | Nature Reviews/Microbiology

ABSTRACT
Multidrug resistant gram-negative nosocomial infection in intensive care units has resulted in an increased use of antibiotics like Colistin and Tigecycline that the end user may have little experience with. Mechanism of drug resistance, when understood, leads to the correct choice and combination of antibiotics. Understanding the pharmacokinetics of Colistin and proper dosing with a correct loading dose is vital to treatment success. Issues regarding renal toxicity may be important factors in critically ill children and much of the dosing is extrapolated from adult studies.

Key words: Colistin. Multidrug resistance. Gram negative bacteria.

Optimising the Dosing of Antibiotics: Colistin and vancomycin updates

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resistant to certain antibiotics (blue squares) simply because they have an impermeable membrane or lack the target of the antibiotic. b | Multidrug resistance efflux pumps. These pumps secrete antibiotics from the cell. Some transporters, such as those of the resistance–nodulation–cell division family (pink), can pump antibiotics directly outside the cell, whereas others, such as those of the major facilitator superfamily (red), secrete them into the periplasm. c | Resistance mutations. These mutations modify the target protein, for example by disabling the antibiotic-binding site but leaving the cellular functionality of the protein intact. Specific examples include mutations in the gyrase (green), which cause resistance to fluoroquinolones, in RNA polymerase subunit B (orange), which cause resistance to rifampicin, and in the 30S ribosomal subunit protein S12 (encoded by rpsL) (yellow), which cause resistance to streptomycin. d | Inactivation of the antibiotic. Inactivation can occur by covalent modification of the antibiotic, such as that catalysed by acetyltransferases (purple) acting on aminoglycoside antibiotics, or by degradation of the antibiotic, such as that catalysed by β-lactamases (brown) acting on β-lactam antibiotics. Ac, acetyl group.

Colistin (polymyxin E) and Polymyxin B are cationic polypeptide antibiotics which act by binding to lipopolysaccharide on the outer membrane, leading to altered membrane permeability and cell death. Colistin is active against most gram negative bacteria except for serrata, proteus and providencia species which have intrinsic resistance. The breakpoints for colistin susceptibility are defined differently by two main societies: as per US Clinical and Laboratory Standards Institution (CLSI), ≤2 mg/L as the susceptibility breakpoint and >2 mg/L as the resistance breakpoint, while as per British Society for Antimicrobial Chemotherapy (BSAC), ≤4 mg/L as susceptible and ≥8 mg/L as resistant.

Colistin is administered as its prodrug, colistin methanesulfonate (CMS), which then undergoes hydrolysis to form a mixture of partially sulfomethylated as well as active colistin. The half-life of CMS is 2.2 hours, and that of colistin is approximately 14-18.5 hours. Colistin exhibits rapid, concentration-dependent bacterial killing with negligible post-antibiotic effects. Recent studies have shown that use of a loading dose helps achieving desired therapeutic levels rapidly. Pharmacokinetic studies were done on 18 critically ill adult patients receiving Colistin 240 mg (3 million Units) 8 hourly for MDR GNB infection. The predicted maximum concentration of drug in plasma after the first dose was 0.60 mg/liter which is below the MICs of many organisms that require Colistin therapy. The maximum predicted concentration at steady state was 2.3 mg/liter and achieved after 2-3 days of therapy, Garonzik et al conducted an open label population pharmacokinetic study on 105 patients of whom 16 were on renal replacement therapy. They then derived loading and maintenance dosing suggestions. (see Table 2). However, a recent study by Grégoire et al on 73 patients found a typical maximum concentration of drug in serum (Cmax) close to 2mg/l 3 hours after a dose of 2 MU CMS, with a colistin half life of 3.1 hours.

Table 2: Suggested loading and maintenance doses of Colistin (Modified from Ref. 7)

<table>
<thead>
<tr>
<th>IV loading dose (as Colistin Base Activity)</th>
<th>T (Target needed) X 2 X Ideal Body Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance Dose</td>
<td>Daily dose of CBA (mg)= T X (1.5 X Cr CI (ml/min/1.73m2)) X 30.</td>
</tr>
<tr>
<td>Recommended pediatric maintenance dose</td>
<td>3-5 mg/kg/day as BD</td>
</tr>
<tr>
<td>(As colistin base)</td>
<td>T= Targeted Therapeutic level (mg/l)</td>
</tr>
<tr>
<td></td>
<td>Depends on MIC, severity and site of infection. Usually = 2-4 mg/l = 25,000 - 100,000 units /l (for dosing)</td>
</tr>
<tr>
<td>Colistin activity equivalent</td>
<td>1 mg of CMS=0.375 mg of colistin base activity=12,500 IU</td>
</tr>
</tbody>
</table>

Combination therapy: In vitro studies have shown that monotherapy with Colistin may lead to bacterial regrowth and resistance while combination therapy increases antimicrobial activity reduces development of resistance. A retrospective cohort study from 5 ICUs in Italy looked at treatment and outcome in patients with infections with KPC-producing bacteria. It was found that combination therapy with at least two drugs displaying in vitro activity against the isolate was associated with lower mortality (OR, 0.52; 95% CI, 0.35-0.77), especially in patients with BSIs, lung infections or high APACHE III scores and/or septic shock at infection onset. Analyses of retrospective
studies have shown similar results. Various drugs such as Tigecycline, Rifampicin, Azithromycin and Dorapenem have been used in combination therapy. Carbapenem resistant KPC infections can still be used in combination therapy with the following caveats: MIC of the carbapenem should be <4mg/l, and the drug should be infused over a prolonged period at the maximum possible dose. The mechanisms of positive interaction between these agents are not known, with few exceptions. The combined action of polymyxins and imipenem appears to exist primarily against bacterial strains in which a permeability barrier, created by the loss of an effective outer membrane porin channel, is responsible for relatively low-level imipenem resistance. That polymyxin increases bacterial membrane permeability appears to explain its enhancement of imipenem’s activity. The effect of sulbactam alone or in combination with other agents appears to be due to its attachment to penicillin-binding proteins, specifically in A. baumannii. The enhancing action of rifampin and macrolides against multidrug-resistant gram-negative pathogens remains relatively unknown.

Pediatric data is limited to predominantly retrospective studies and shows that Colistin has a role in treating life threatening MDR infection with neprotoxicity of 2.8%. Colistin is poorly distributed to the bones, cerebrospinal fluid, lung parenchyma, and pleural cavity. In a study by Imberti et al, Colistin was undetectable in bronchoalveolar lavage fluid 2 hours after IV Colistin methanesulphate administration. Two recent meta-analyses found significant improvement in clinical response when aerolized Colistin was added to IV Colistin. However, there was no difference in mortality. Valachis et al included 8 studies (690 patients) and found a statistically significant improvement in clinical response as well as microbiological eradication, when AS colistin was added to the standard antimicrobial therapy in comparison with patients who received IV colistin (OR, 1.57; 95% CI, 1.14–2.15; p=0.006 and OR, 1.61; 95% CI, 1.11–2.35; p=0.01, respectively). Resistance to Polymyxins is currently around 10% worldwide with higher rates being reported from South East Asia and the Mediterranean. The first International Conference on Polymyxins at Prato identified the following issues:

1. Uniformity in expression of the amount of drug in a parenteral vial by different manufacturers should be expressed as mg of colistin base activity (CBA) or number of International Unit (IU).
2. Uncertainties regarding susceptibility testing and breakpoints (currently under review jointly by the Clinical and Laboratory Standards Institute, CLSI and the European Committee on Antimicrobial Susceptibility Testing, EUCAST).
3. Need of therapeutic drug monitoring in routine clinical practice
4. Suggested research areas are prospective studies using therapeutic drug monitoring, pharmacokinetic studies in special patient populations, randomized controlled trials on combination versus monotherapy, nebulized Colistin, polymyxin B versus Colistin,

**Aerosolised (AS) Colistin**

As only Colistin sensitive (COS) and XDR GNB become more common organisms for Ventilator associated events, the addition of AS colistin to the IV regimen may be a value addition. In an RCT of IV vs IV + AS dosing, a dosage regimen of IV-Colistin at 1,000,000 units/kg/day in 2-3 divided doses plus AS Colistin in the treatment group 1 million units 8 hrly. Clinical cure rates were significantly higher (69.2% vs 54.8%) in the IV+AS group. (p value 0.03) The median duration of post VAP ventilation was shorter in the IV+AS group (8 vs 12 days p value = 0.001). AKI onset during colistin therapy was associated with treatment failure. This could be an add on in the treatment of XDR VAP.

**Toxicity**

In 19 cases in a Greek study, over 4 weeks of Colistin treatment, the median creatinine value increased by 0.25 mg/dl during the treatment compared to the baseline (p < 0.001) but returned close to the baseline at the end of treatment (higher by 0.1 mg/dl, p = 0.67). No evidence of neuromuscular blockade was seen in any of these patients. In a study by Basso in Texas Children’s Hospital in 21 courses of colistin therapy in children with cystic fibrosis, with MDR *Pseudomonas* infection, there was one case of renal
toxicity with 6 cases of neurotoxicity31. Neurotoxicity was characterized by perioral paraesthesia with or without ataxia. All toxicities were reversed. Recent experience from all studies continue to show that the fear of renal failure appears to be largely exaggerated and the drug can be safely used in the higher dosages needed for MDR strains with good monitoring.

In critically ill patients with nosocomial infection, local epidemiology should be taken into account while starting empirical antibiotic therapy. In an ICU setting where MDR organisms may rule, the clinician often has no choice but to start a carbapenem on suspicion of a serious Gram negative infection. Once culture results are available, specific therapy can be started: Carbapenem for Carbapenem sensitive MDR organism and combination therapy for Carbapenem resistant MDR organism. However, as is often the case, empirical therapy may be needed if the child deteriorates especially in the setting of a febrile neutropenic immunocompromised child with invasive lines.

Caveats on Colistin
1. Use a loading dose
2. Slow infusions may help sustain levels
3. Use combination therapy always
4. Use Polymixin when there is a poor response to the colistin methanesulfonate salt

References


19. J. Rahal Novel Antibiotic Combinations against Infections with Almost Completely Resistant Pseudomonas aeruginosa and Acinetobacter Species • CID 2006:43 (Suppl 2) • S95


31. Falagas ME, Ioannis MR, Kostas AB, Sofia R, Kasiakou K, Michalopoulos A. Toxicity after prolonged (more than four weeks) administration of intravenous colistin. BMC Infectious Diseases 2005, 5:1


Part 2: Vancomycin: “Mississippi Mud” - An update

A 6 year old boy is admitted with septic shock and pyomyositis of the right thigh. He undergoes incision and drainage of the thigh abscess and drainage of septic arthritis of the left knee. Blood and pus culture grow Methicillin Resistant *Staphylococcus aureus* (MRSA) with Minimum Inhibitory Concentration (MIC) = 1. Five days later, he continues to be febrile and bacteremic Antibiotic coverage from admission includes Vancomycin, and Clindamycin. (Sensitive with D test negative) Multiple trough vancomycin levels remain <10 despite increasing Vancomycin doses to 70 mg/kg/day. The question arises- what is the optimum dosing and monitoring of Vancomycin. Vancomycin was isolated from *Streptomyces orientalis* in 1952. Its impure form also known as “Mississipi Mud” due to its brown colour was responsible for increased adverse effects and nephrotoxicity. Better purification methods have lowered the incidence of nephrotoxicity\(^1\). Vancomycin use has increased with the emergence of MRSA. Early recommendations were to aim for trough vancomycin levels of 5-10 mg/L and peak levels of 30-40 mg/L.

Table 1. Trough levels and Vancomycin dosing

<table>
<thead>
<tr>
<th>Author, year</th>
<th>No. of patients (samples)</th>
<th>Age</th>
<th>Dose</th>
<th>Target trough (µg/ml)</th>
<th>% achieving target trough</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim(^4), 2010</td>
<td>309</td>
<td>1-16 yrs</td>
<td>40 mg/kg/day</td>
<td>&gt;10</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>60 mg/kg/day</td>
<td>&gt;10</td>
<td>49%</td>
</tr>
<tr>
<td>Broome(^5), 2011</td>
<td>25</td>
<td>1 mth - 18 yrs</td>
<td>45 mg/kg/day</td>
<td>10-15, 15-20</td>
<td>0%</td>
</tr>
<tr>
<td>Frymover(^6), 2011</td>
<td>182</td>
<td>1mth - 12 yrs</td>
<td>45 mg/kg/day</td>
<td>15-20</td>
<td>7%</td>
</tr>
<tr>
<td>Eiland(^7), 2011</td>
<td>295 (435)</td>
<td>1 mth - 18 yrs</td>
<td>40-60 mg/kg/day</td>
<td>5-15, 10-20</td>
<td>78%</td>
</tr>
<tr>
<td>Geerl(^8), 2014</td>
<td>159</td>
<td>2 mths - 17 years</td>
<td>60 mg/kg/day</td>
<td>15-20</td>
<td>6.9%</td>
</tr>
<tr>
<td>Durham(^9), 2015</td>
<td>75</td>
<td>1 mth - 18 yrs</td>
<td>15 mg/kg 6 hourly</td>
<td>15-20</td>
<td>6.8%</td>
</tr>
</tbody>
</table>

For effective treatment with vancomycin, a serum concentration well above the minimum inhibitory concentration of the bacteria being treated is required. Recent studies have shown that exposure to trough concentrations <10 mg/l can produce strains with Vancomycin intermediate Sensitivity *Staphylococcus aureus* like characteristics\(^2\). Current guidelines recommend maintenance of trough levels greater than 10 mg/l to avoid development of resistance. For complicated infections such as bacteremia, endocarditis, osteomyelitis and meningitis due to MRSA, a trough level of 15-20 mg/l is recommended\(^3\).

Recent pediatric studies have shown that current pediatric dosing recommendations do not achieve the target levels, needing multiple dosage adjustments (Table 1).

This has been our observation as well (Unpublished data, Figure 1). Of 42 children studied, only 5% of children receiving 45 mg/kg/day of vancomycin achieved levels between 15 to 20 µg/ml, and 24% of children receiving 60 ml/kg/day achieved target levels. Eiland et al\(^7\) suggested a higher dose of 85 mg/kg/day, when the target trough is 15 mg/l. Other authors have suggested higher doses in children aged 2 to 12 years\(^10,11\).

There are concerns about toxicity with vancomycin with currently recommended trough levels. Van Hal et al performed a meta analysis of 15 studies to determine the nephrotoxicity associated with maintaining higher troughs (>15 mg/l)\(^12\). 14 studies involved adults and one study involved children\(^13\). Maintaining trough concentrations greater than 15 mg/L was associated with increased risk of a nephrotoxic event (OR 2.74; 95% CI 1.94–3.88, p...
b 0.01) compared to trough concentrations less than 15 mg/L\(^2\). The probability of a nephrotoxic event was also found to increase as a function of treatment duration, with most episodes occurring after seven days of therapy.

There is a lack of data to support a clear relationship between specific serum concentrations and patient outcome. To date, 7 studies have looked at the relationship between trough Vancomycin levels and clinical outcome; 6 studies found no correlation between trough levels and clinical outcome\(^14\). Only one study found that trough <15 mg/l and > 20 mg/l was associated with Vancomycin failure\(^15\).

Recent Literature suggests that 24-hour Area Under the Concentration-time Curve (AUC) of Vancomycin correlates better with drug efficacy and toxicity compared to trough values. AUC reflects the cumulative exposure for a defined time period while the trough is a single point exposure measurement at the end of the dosing interval. Data from animal models, in vitro studies, and limited human studies suggests that microbiologic success is optimized when the vancomycin AUC/MIC BMD (Minimum Inhibitory Concentration by Broth Micro Dilution) ratio exceeds 400\(^{16-20}\). A retrospective study by Moise-Broder\(^18\) et al looked at 108 patients with MRSA lower respiratory tract infection and found a significant association between clinical cure and an AUC/MIC more than 400. There was no correlation with time above MIC, which was 100% in all patients. AUC can be calculated by pharmacokinetic modeling, Bayesian approach\(^21\) or extrapolation from total Vancomycin dose and creatinine clearance\(^22,23\). Pharmacokinetic modeling needs post distributional peak and trough. The Bayesian approach is based on a single trough level (need not be at steady state) and patient data such as creatinine clearance; it can be done at the bedside and software programmes with Bayesian analysis are available\(^24\). Since vancomycin is primarily cleared by glomerular filtration, its clearance correlates well with creatinine clearance. The 24-hour vancomycin AUC is calculated using the formula\(^22,23,25\):

\[
AUC = \frac{\text{total vancomycin dose in mg over 24 h}}{[(\text{Cl Cr} \times 0.79) + 15.4] \times 0.06}
\]

and creatinine clearance (Cl Cr) is calculated using the Cockcroft-Gault equation\(^{26}\):

\[
\text{Cl Cr} = \frac{[(140 - \text{age in years}) \times \text{weight in kg}] \times 0.85 \text{ if female}}{\text{adjusted for BSA} 1.73 \text{ M}^2} \\
(\text{S. Creatinine in mg/dl} \times 72)
\]

Trough concentration at steady state has been suggested as a surrogate for achieving an AUC/MIC ratio ≥400\(^2\). However studies have not consistently shown correlation between the measured trough concentration and the actual AUC value. Pai et al studied the relationship between vancomycin area under the curve over 24 h (AUC24) and trough vancomycin concentration using an established adult population PK model of 5000 subjects and found poor correlation (R\(^2\)=0.409) and suggested that one cannot rely only on the vancomycin trough concentration range of 15-20 mg/l to achieve an AUC/MICBMD ratio ≥400 for S. aureus isolates with MIC values more than 1 mg/L\(^{21,27}\). Frymover\(^6\) et al found that a trough concentration of 7–10 lg/mL predicted achievement of an AUC/MIC = 400 in more than 90 % of MRSA-infected children with an MIC of 1 lg/mL\(^{28}\). Le et al studied 702 patients aged 3 months to 21 years, with 1660 Vancomycin trough levels and found that a minimum dosage of 60–70 mg/kg/day was necessary to achieve an AUC/MIC of 400 to a similar serum trough concentration of approximately 8–9 lg/mL.

Loading doses of Vancomycin have been suggested for rapid attainment of therapeutic levels. A recent systematic review looked at 6 adult studies and 2 studies in children. Only 4 adult studies found that loading dose of vancomycin led to significantly more patients achieving troughs of 15-20 mg/l\(^30\). A randomized controlled trial of loading dose in 46 children showed that loading dose of 30 mg/kg did not lead to earlier attainment of therapeutic trough levels\(^31\). Two of nineteen (11%) loading dose recipients had a trough 15-20 mg/L before the second dose, compared with 0 of 27 in the conventional dose group (P=0.17).

Continuous infusion Vancomycin has been studied in adults and neonates, but data is limited in children. A meta-analysis of adult studies by Waineo et al concluded that continuous infusion vancomycin produces clinical outcomes that are comparable to
intermittent infusion but may be associated with a lower relative risk of kidney injury than intermittent infusion therapy. Besides pharmacokinetics and pharmacodynamics, other issues may play a role in the response to Vancomycin. Vancomycin acts by inhibiting incorporation of monomers into the peptidoglycan chain which is the backbone of the cell wall; cell death occurs by osmotic cytolysis and may take as long as 24 hours. Studies have shown poor penetration of Vancomycin in many tissues- 0%-18% of serum concentrations in uninflamed meninges, 36%-48% in inflamed meninges, a maximum of 41%-51% in the lung, and 10%-30% in diabetic and normal skin and soft tissues. The bactericidal activity of vancomycin is weak in the presence of a high inoculum, known as the inoculum effect, and in the case of biofilm-associated infections, defined as biofilm resistance. Vancomycin resistance may occur due to alteration in peptides in the peptidoglycan chain or gradual clogging of the antibiotic into a thickened staphylococcal cell wall.

At present, there is no clarity on the optimal dosing regime for Vancomycin, or how to monitor therapy. It is important to restrict the use of Vancomycin to serious infections (complicated skin infections, bloodstream infections, endocarditis, bone and joint infections, and meningitis) caused by MRSA. Alternatives to Vancomycin like Daptomycin, should be considered in the following scenarios: Vancomycin MIC > 1 mg/ml, or vancomycin treatment failure (positive blood cultures after 48 hours of vancomycin therapy without a focus of infection and after good source control).

In our patient as he had continued to be febrile and bacteremic on day 5 of illness, we planned to maintain higher vancomycin trough levels. Hence the total daily dose of vancomycin required to achieve an AUC of 400 was calculated as follows:

\[ \text{AUC} = \frac{\text{total vancomycin dose in mg over 24 h}}{\left[ \left( \text{Cl Cr} \times 0.79 \right) + 15.4 \right] \times 0.06} \]

Total vancomycin dose in mg over 24 h = AUC \times \left[ \left( \text{Cl Cr} \times 0.79 \right) + 15.4 \right] \times 0.06

For our patient’s Dose, we used the AUC as 400 and then worked backwards to find the total daily dose. 400 = x / \left[ \left( \text{Cl Cr} \times 0.79 \right) + 15.4 \right] \times 0.06. This resulted in the total daily dose being 2 gms. If the MIC had been 2, the AUC of 400 would not have been reached with this dose and the calculated does would have been double.

Despite this high dose, the trough levels remained <15 mg/l with positive blood cultures and Daptomycin was added. He improved after that.

Another method of adjusting the dose is by using the trough levels. There are several calculators that one can plug into on the open web. Some require one trough level and some require two. These are not tested for weights below 20Kg, for patients on dialysis or with unstable renal function, and where MICs are >2. There has been shown to be good correlation between these two methods by Holmes et al.

Summary

In seriously ill children with MRSA infection Vancomycin loading doses need to be used. As far as possible trough levels need to be measured before the 4th dose and the ideal total dose calculation made for an AUC of 400. If the blood culture does not clear in 48-72 hours after all source control, alternative treatment must be considered

References

LY, Hersh AL. Impact of a hospitalwide increase in empiric pediatric vancomycin dosing on initial trough concentrations. Pharmacotherapy. 2011 Sep;31(9):871-6
**The Role of Vitamin D in Sepsis: A review**

**Soono Udani**

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**Introduction**

Sepsis in humans is a complex cascade involving a series of interactions set in motion triggered when an organism invades the host. While many mediators are implicated in greater or lesser degree, no single one has been held responsible as the one to modulate, replace or remove in order to halt the chain of events. Vitamin D is only one compound among many that has been found to have a role in the innate immune system in the human cell. Vitamin D is a compound humans can only obtain either through Ultra violet band (UVB) radiation from the sun or ingested food. While this vitamin is needed for bones, only in the last two decades, has this it been linked to the immune system. Vitamin D is not the primary cause of the sepsis or infection. However, it may play a role in modulating the outcome of the disease.

The Endocrine Society’s clinical practice guidelines define vitamin D deficiency as 25D levels <20 ng/mL (50 nmol/L) and vitamin D insufficiency as 25D levels of 21–29 ng/mL (52.5–72.5 nmol/L). The Society, in their vitamin D supplementation guidelines, agreed that the critical level for deficiency was 20 ng/mL (50 nmol/L) but did not define vitamin D insufficiency as a health problem. The guidelines are designed to achieve serum levels of 25D of 50 nmol/L, but not 70–75 nmol/L.

**History**

The story of infections and Vitamin D starts with Tuberculosis. Robert Koch isolated tubercle bacilli in 1882 but won the Nobel for it in 1905. In 1887, Edward Livingston Trudeau opened the first sanatorium in the United States (Saranac Lake, NY) after observing that rabbits infected with TB had a more severe course if kept indoors in the dark. In 1903, Niels Ryberg Finsen won the Nobel prize for demonstrating that UV light helped patients with lupus vulgaris. In 1946 Dowling et al treated patients of lupus vulgaris with streptomycin and Vit D and reported better results in the cohort treated with Vitamin D in the Lancet.

**Vitamin D in cellular homeostasis**

Vit D is a pleiotropic hormone that is being increasingly recognized as being necessary for cellular well being and the functioning of several organs. Deficiency has been linked to increased respiratory infections by McNally, Juvenile Diabetes, and asthma. In Vit D replete conditions, there is an upregulation of the Vit D- PTH axis and with 1α hydroxylase, 1,25(OH)2D is formed. Most of this exits the cell and is used for calcium homeostasis and bone mineralization. Extremely minute quantities are required for intracellular homeostasis and cellular “well being”. The postulation is that several cellular functions are dependant on adequate levels of Vit D within the cell- immunity, glucose homeostasis, calcium balance, integrity of the mucosal barrier, cardiac contractility, endocrine function are all dependant on adequate levels. During illness, if levels are low, this may lead to poor recovery and increased morbidity and possible mortality.

**How did it All Start?**

1986-1987 Ross and Crowle infected human monocytes and macrophages with *M. Tuberculosis* and added 1,25D, which triggered significant antimicrobial activity. These results identified 1,25D as an immunomodulator which can activate human monocytes to express immunity against tuberculosis-referred to by the authors as “tuberculoimmunity”. This created a widespread interest in this connection between the two and many clinical trials were done trying to show that patients with lower levels of Vit D had poorer outcome in tuberculosis and visa versa.

**Toll Like Receptors (TLRs) and Cathelecidins**

TLRs were actually recognized in the abstract a hundred years ago but definitive work was done only in the last fifteen years. These are transmembrane proteins that sit as signal guards and are an essential
part of the innate immune system of the mammalian cell. They are “Pattern Recognition Receptors”, which bring into activation the steps of the inflammatory pathway and immune responses that will fight the invading organism. The system is highly complex and specific. In the context of its connection to Vit D, a simplification of its action would be in its role in further induction of the expression of antimicrobial peptides or Cathelecidins – CAMPs.

These are found in macrophage lysosomes and polymorphonuclear leucocytes and serve a critical role in the mammalian innate immune defense against invasive bacterial, viral, fungal infections; including Mycobacteria. **Vitamin D serves to up-regulate the genetic expression of Cathelicidin.**

The steps by which Vit D gets involved in this are simplified below:

1. 125 di hydroxy Vit D in the cell is dependant on 25OH D levels. Most of it will exit out for bone metabolism
2. TLRs recognise the molecular patterns of pathogens and induce catalytic synthesis of dihydroxy Vit D
3. dihydroxy Vit D then Combines with Vit D receptor (VDR) which
4. Upregulates the cathelicidin antimicrobial protein
5. Resulting in autophagy of bacteria, mycobacteria, etc

Cathelicidin rapidly destroys the lipoprotein membranes of microbes after fusion with lysosomes in macrophages.

### Table 1: Summary of Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Vit D- Events</th>
<th>Vit D+ Events</th>
<th>Weight</th>
<th>Risk Ratio IV, Random, 95% CI</th>
<th>Risk Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amrein, 2014[25]</td>
<td>34</td>
<td>160</td>
<td>7</td>
<td>3.8%</td>
<td>1.00[0.49, 2.06]</td>
</tr>
<tr>
<td>Aygencel, 2013[24]</td>
<td>57</td>
<td>139</td>
<td>15</td>
<td>8.5%</td>
<td>1.69[1.05, 2.75]</td>
</tr>
<tr>
<td>Braun, 2012[5]</td>
<td>249</td>
<td>668</td>
<td>42</td>
<td>24.7%</td>
<td>1.64[1.24, 2.18]</td>
</tr>
<tr>
<td>Flynn, 2012[22]</td>
<td>18</td>
<td>49</td>
<td>4</td>
<td>2.3%</td>
<td>1.56[0.61, 3.97]</td>
</tr>
<tr>
<td>Higgins, 2012[23]</td>
<td>22</td>
<td>50</td>
<td>15</td>
<td>7.9%</td>
<td>1.09[0.66, 1.79]</td>
</tr>
<tr>
<td>Moromizato, 2014[26]</td>
<td>123</td>
<td>566</td>
<td>221</td>
<td>50.5%</td>
<td>1.49[1.22, 1.82]</td>
</tr>
<tr>
<td>Venkatram, 2011[4]</td>
<td>43</td>
<td>340</td>
<td>4</td>
<td>2.3%</td>
<td>0.73[0.29, 1.85]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1972</td>
<td>1872</td>
<td>100.0%</td>
<td>1.46[1.27, 1.68]</td>
<td></td>
</tr>
</tbody>
</table>

Total events 546

Heterogeneity: Tau² = 0.00; Chi² = 5.62, df = 6 (P=0.47); I² = 0%

Test for overall effect: Z = 5.26 (P < 0.001)
Impact of Vit D Deficiency in Critically Ill Children

The Canadian Critical Care Trials Group conducted a prospective cohort study in tertiary-care PICUs in Canada, studying 337 children in 7 centres. They showed that those with low Vit D levels had more interventions in the way of fluid boluses, vasopressors and ventilation but failed to show any survival benefit in the Vitamin D replete group.

A metaanalysis done by Haan et al, using fourteen observational reports published from January 2000 to March 2014, involving 9,715 cases showed that there was an increased rate of sepsis (7 studies), infection (5studies) as well as mortality (7 studies) with decreased levels of Vit D with the suggestion that its deficiency increases the susceptibility to serious infection and increases mortality.

A study from a medical ICU in Bhubhaneshwar also showed higher mortality and increased days on mechanical ventilation in Vit D deficient adults.

To throw the cat among the pigeons, there are studies that show that there are actually higher levels in children with sepsis and it may be an acute phase reactant. The postulation being that if you are Vit D replete, there will be a push by the cells to increase the intracellular 1,25 dihydroxy Vit D in order to enhance innate cell immunity and enhance phagocytic activity.

Currently there is no strong evidence that proves that the level of Vit D strongly impacts the outcome in sepsis.

Summary

1. that Vit D is an important player in the innate immune system within the cell
2. there is data suggesting that ill children and adults may be deficient in Vit D
3. there is some data linking Vit D deficiency with poor outcome
4. there is no data supporting Vit D deficiency as the cause of poor outcome
5. hence we conclude that although it isn’t the direct cause of mortality it is a player and not a mere bystander in the greater scheme of things
6. supplementation is easy and inexpensive and probably harmless

References

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Original Research Articles

The Impact of Mannitol Administration in Pediatric DKA:
A 22 Year Experience

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ABSTRACT

Objective: To describe circumstances and outcomes associated with mannitol administration in children being treated for diabetic ketoacidosis (DKA).

Design: Retrospective chart review of consecutively admitted pediatric patients over a 22 year period (1988-2010).

Setting: Data originate from three pediatric tertiary care centers where DKA was routinely treated during the study period with a physiologic approach to gradual rehydration, continuous IV insulin and intensive monitoring for symptomatic brain swelling. Mannitol was the drug of choice for suspected raised intracranial pressure (ICP).

Patients: 941 consecutive patient episodes of moderate to severe DKA were reviewed for mannitol administration.

Interventions: None

Measurements and Main Results: Mannitol was administered during 76 of 941 episodes of DKA. Mannitol was successful in improving or reversing signs/symptoms of raised ICP in 65% of mannitol recipients. No patient in this series suffered neurologic morbidity of mortality.

Conclusions: Mannitol treatment for suspected raised ICP during treatment for DKA appears to be safe and beneficial to outcome when combined with careful rehydration, continuous insulin therapy, and cerebrovascular and biochemical monitoring.

Key words: Diabetic ketoacidosis, Children, Mannitol, Fluid therapy, Mortality, Cerebral edema

Introduction

Diabetic ketoacidosis (DKA) is a potentially life-threatening metabolic disorder characterized by ketoacidemia, dehydration, hyperosmolality and electrolyte imbalance. DKA may also be accompanied by altered mental status caused by or associated with shock, marked hypocapnea, hyperosmolality, profound fatigue, and perhaps most importantly, cerebral edema (brain swelling). While subclinical brain swelling may occur frequently among pediatric...
patients with DKA\textsuperscript{1-4} signs and symptoms of raised intracranial pressure (ICP) have been recognized in only 0.2 to 1% of episodes. Among these recognized cases, the associated mortality is as high as 21 to 25%\textsuperscript{5-8} with an additional 10 to 26% survival with neurologic sequelae in retrospective reviews\textsuperscript{5,7,8}. The true incidence of clinically apparent cerebral edema is not known since it is possible that in some cases, clinical signs of raised ICP may be unrecognized and resolve coincidentally with the correction of metabolic aberrations. There are no standardized bedside criteria for the diagnosis of DKA-related cerebral edema. Proposed criteria were applied in a small test sample, but one of two children who did not meet diagnostic criteria died with diffuse cerebral edema identified on head CT\textsuperscript{9}. It is clear that poor outcome is likely in pediatric DKA when mannitol is given after respiratory arrest or after development of fixed and dilated pupils\textsuperscript{10}. However, the signs and symptoms of raised ICP are well known despite the often non-specific nature of its early manifestations. This report describes circumstances under which we have given intravenous hypertonic mannitol for suspected raised ICP during DKA and the clinical responses that followed its administration.

**Materials and Methods**

Chart reviews were conducted for 941 consecutive episodes of moderate and severe DKA (total CO\textsubscript{2}< 15 mEq/L) referred to one of three centers for management from January 1988 through December 2010. The protocol for the conduct for this study was reviewed and approved by the University and Medical Center Institutional Review Board, East Carolina University and Vidant Medical Center with a waiver of informed consent. All referred children were managed using a previously reported physiologic approach to rehydration and correction of ketoacidemia\textsuperscript{11,12}. This plan included rapid correction of circulatory shock, individualized assessment of the degree of dehydration and a planned replacement of the remaining deficit volume evenly over 48 hours using fluids containing approximately 125 mEq/L of sodium plus potassium. In all patients, fluid and electrolyte therapy were delivered to promote repair of dehydration, a gradual rise of the measured concentration of sodium as glucose declined (or stability of the predicted sodium value) and correction of acidemia by administration of continuous IV insulin\textsuperscript{11-13}. All patients received intensive care monitoring after referral. Patients who received mannitol were selected for more detailed descriptive review. Biochemical data were assessed for trends in the concentration of serum sodium both prior to and after the administration of mannitol. If the measured concentration of serum sodium decreased as the concentration of glucose declined during treatment, this was considered an inappropriate decrease in the serum sodium concentration. In contrast, an increase in the serum sodium concentration by approximately 1-2 mEq/L for each 100 mg/dL decrease in the glucose concentration was considered an appropriate sodium trend during therapy\textsuperscript{14}. If the concentrations of glucose and sodium remained stable as rehydration proceeded, this was also considered an appropriate sodium trend. The trend was considered indeterminate if insufficient data were available to establish a trend prior to administration of mannitol. Hypertension was considered to be present when blood pressure exceeded the 95\textsuperscript{th} percentile for age and gender. Relative “decrease in heart rate” was an indicator for possible raised ICP when heart rate was deemed by the clinician to be inappropriately low given the hyperadrenergic state characteristically present during DKA. Abnormalities in neurologic status were assessed at the bedside by nursing and the most senior medical staff available. Hypertonic mannitol infusions were generally completed within 15 to 20 minutes. Clinical outcomes following mannitol administration were divided into three categories: 1] rapid responders (clinical improvement identifiable <30 minutes after infusion of hypertonic mannitol was completed); 2] intermediate responders (clinical improvement identifiable 30-60 minutes post infusion of hypertonic mannitol); 3] “yes” responders (clinical improvement noted by provider but no time frame documented in the medical record); 4] non- responders (there was no apparent response to the drug); 5] Undocumented response (no comment regarding response was recorded in the medical record). Data were analyzed...
with respect to safety of mannitol and its utility in the prevention of brain herniation during treatment for DKA.

Serum creatinine at hospital discharge was used to reflect renal function after the administration of mannitol.

**Results**

No patient in this series of 941 consecutive episodes of moderate and severe DKA suffered neurologic morbidity or mortality. All patients survived and no neurologic deficits were noted after resolution of DKA. During 76 admissions for DKA, there were 73 unique patients. No patient with suspected raised ICP received hypertonic saline (NaCl 3%) alone as treatment for raised ICP. Sixty four of 76 admissions were referred from outlying emergency departments where therapy was initiated prior to referral. Ages of mannitol recipients were 12 +/- 4.4 years; fifty percent were female and 52.6% were black. One child was admitted three times and another child was admitted twice; both received mannitol on each of their admissions. Multiple doses of mannitol were administered during 16 of 76 admissions, resulting in 95 total doses given; mannitol was given three times during three episodes and twice during each of 13 episodes. The decision to administer mannitol was based on neurologic and/or hemodynamic triggers rather than biochemical data. Mannitol doses were sub-therapeutic (<0.25 gram/kg) in two of 76 episodes. The indicators for mannitol administration are described in Table 1; responses following treatment are listed in Table 2. An alteration in the level of consciousness was an indication for administration of mannitol in 59 of 76 (78%) episodes. Improvement or resolution of the indicators for mannitol treatment occurred in 50 of 76 episodes. This positive response occurred mostly in the categories of “yes” or rapid responders (Table 2). Coma improved over a < 30 minute period in five of eight children (62.5%) but lesser degrees of altered mental status (obtundation, lethargy, agitation) improved less frequently (44.4%, 28.1%, 18.8%, respectively).

In all instances where more than one indicator triggered mannitol administration, if improvement occurred, all indicators improved. In patients with no apparent or an undocumented response to mannitol, gradual improvement occurred in all cases, often concomitant with correction of acidosis and dehydration.

**Table 1:** Signs and symptoms prompting 94 mannitol administrations

<table>
<thead>
<tr>
<th>Sign/Symptom</th>
<th>Number with indicator</th>
<th>% with indicator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hallucinations</td>
<td>3</td>
<td>3.2</td>
</tr>
<tr>
<td>Headache</td>
<td>20</td>
<td>21.3</td>
</tr>
<tr>
<td>Agitation</td>
<td>16</td>
<td>17.0</td>
</tr>
<tr>
<td>Lethargy</td>
<td>32</td>
<td>34.0</td>
</tr>
<tr>
<td>Obtundation</td>
<td>18</td>
<td>19.1</td>
</tr>
<tr>
<td>Coma</td>
<td>8</td>
<td>8.5</td>
</tr>
<tr>
<td>Slurred speech</td>
<td>3</td>
<td>3.2</td>
</tr>
<tr>
<td>Fluctuating Mental status</td>
<td>1</td>
<td>1.1</td>
</tr>
<tr>
<td>Pupils sluggish</td>
<td>14</td>
<td>14.9</td>
</tr>
<tr>
<td>Pupils large</td>
<td>5</td>
<td>5.3</td>
</tr>
<tr>
<td>Pupils tiny</td>
<td>2</td>
<td>2.1</td>
</tr>
<tr>
<td>Anisocoria</td>
<td>1</td>
<td>1.1</td>
</tr>
<tr>
<td>Eye Deviation</td>
<td>3</td>
<td>3.2</td>
</tr>
<tr>
<td>Relative ↑BP</td>
<td>10</td>
<td>10.6</td>
</tr>
<tr>
<td>Relative ↓HR</td>
<td>8</td>
<td>8.5</td>
</tr>
<tr>
<td>Sedatives</td>
<td>6</td>
<td>6.4</td>
</tr>
</tbody>
</table>

*More than one indicator was simultaneously present in 35 of 94 instances (37.2%). BP, blood pressure; HR, heart rate; ↑, increased; ↓, decreased

Hypertension occurred in 10 of 76 (13%) patient-episodes. In 5 of 10 cases a concomitant relative decrease in heart rate was present; three patients demonstrated a relative decrease in heart rate without hypertension. One of the 13 patients manifested hypertension and decreased heart rate after being placed in Trendelenberg position; both changes resolved when the head was elevated. Among the five non-responders, three required treatment with nicardipine and one was discharged home on an antihypertensive agent.

Treatment with mannitol possibly contributed to two instances of hemodynamic instability. Both patients had received more than one dose of mannitol. In one mannitol recipient in whom DKA was complicated by suspected streptococcal toxic shock syndrome, two doses of 3% saline were given to improve intravascular volume and treat suspected brain
swelling; sustained support with epinephrine and dopamine was required. The second patient was successfully treated for obtundation with two doses (0.5 gm/kg per dose) of mannitol and subsequently received two doses of 3% saline for decreased pulses at 40 minutes and 127 minutes after mannitol. No child became hypotensive during infusion of mannitol.

Serum creatinine was normal for age in 71 of 76 (93%) episodes at the time of hospital discharge. In three cases, the creatinine at discharge was abnormal (97.24 micromol/liter in each instance). At the time of clinic follow-up for two of these three patients, the serum creatinine had returned to normal. No follow-up value was available for the third patient.

Approximately 60% of children whose data were sufficient to demonstrate a sodium trend before administration of mannitol had an appropriate sodium trend. Nearly 40% had not yet demonstrated a sodium trend at the time of mannitol treatment. Tracheal intubation was performed in four patients; two intubations were performed for reasons related to altered mental status and one for reasons related to septic shock. The fourth patient had no identifiable reason for intubation.

All head CT scans were obtained after mannitol administration at the discretion of the attending physician. A total of 20 CT studies were performed in 76 patient-episodes. Changes consistent with cerebral edema were described by the clinical neuroradiologist in three of 20 scans. The indications for mannitol administration in these three patients were bradycardia (one), sluggish pupils and obtundation (one), and obtundation (one).

Diminished mental status triggered mannitol administration in four patient-episodes in which IV medications with sedative effects had been given. Benzodiazepines were given on two occasions; promethazine and diphenhydramine on one occasion and promethazine alone on one occasion. Two children, one treated with promethazine/diphenhydramine and one treated with a benzodiazepine, responded to mannitol (both in the “yes” category). Six patient episodes in which mannitol was given involved patients with previously diagnosed neuro-atypical disorders including attention deficit hyperactivity disorder (5/6), bipolar disorder (2/6), oppositional defiance disorder (1/6) and learning disabilities (1/6). Three children were rapid responders, two were “yes” responders and one was a non-responder.

Table 2: Signs and symptoms triggering 94 mannitol administrations with row percentages categorizing timing of response after completion of hypertonic mannitol infusion.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Number</th>
<th>&lt;30 min</th>
<th>30 to 60 min</th>
<th>Yes*</th>
<th>&gt;60 min</th>
<th>Undocumented</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coma</td>
<td>8</td>
<td>5 (62.5%)</td>
<td>-</td>
<td>-</td>
<td>2 (25.9%)</td>
<td>1 (12.5%)</td>
</tr>
<tr>
<td>Obtundation</td>
<td>18</td>
<td>8 (44.4%)</td>
<td>1 (5.6%)</td>
<td>1 (5.6%)</td>
<td>6 (33.3%)</td>
<td>2 (11.1%)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>32</td>
<td>9 (28.1%)</td>
<td>1 (3.1%)</td>
<td>10 (31.3%)</td>
<td>9 (28.3%)</td>
<td>3 (9.4%)</td>
</tr>
<tr>
<td>Hallucination</td>
<td>3</td>
<td>2 (66.7%)</td>
<td>-</td>
<td>1 (33.3%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fluctuating mental status</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1 (100%)</td>
</tr>
<tr>
<td>Slurred speech</td>
<td>3</td>
<td>2 (66.7%)</td>
<td>-</td>
<td>1 (33.3%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Headache</td>
<td>20</td>
<td>14 (70.0%)</td>
<td>-</td>
<td>2 (10.0%)</td>
<td>3 (15.0%)</td>
<td>1 (5.0%)</td>
</tr>
<tr>
<td>Agitation</td>
<td>16</td>
<td>3 (18.8%)</td>
<td>-</td>
<td>6 (37.5%)</td>
<td>5 (31.3%)</td>
<td>2 (12.5%)</td>
</tr>
<tr>
<td>Pupils sluggish</td>
<td>14</td>
<td>7 (50.0%)</td>
<td>1 (7.1%)</td>
<td>2 (14.3%)</td>
<td>4 (28.6%)</td>
<td>-</td>
</tr>
<tr>
<td>Pupils large</td>
<td>5</td>
<td>1 (20.0%)</td>
<td>-</td>
<td>3 (60.0%)</td>
<td>1 (20.0%)</td>
<td>-</td>
</tr>
<tr>
<td>Pupils tiny</td>
<td>2</td>
<td>2 (100%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anisocoria</td>
<td>1</td>
<td>1 (100%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Eye devitation</td>
<td>3</td>
<td>3 (100%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Relative ↑BP</td>
<td>10</td>
<td>5 (50.0%)</td>
<td>-</td>
<td>-</td>
<td>3 (30.0%)</td>
<td>2 (20.0%)</td>
</tr>
<tr>
<td>Relative ↓HR</td>
<td>8</td>
<td>5 (62.5%)</td>
<td>-</td>
<td>1 (12.5%)</td>
<td>2 (25.0%)</td>
<td>-</td>
</tr>
<tr>
<td>Sedatives</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>2 (33.3%)</td>
<td>4 (66.7%)</td>
<td>-</td>
</tr>
</tbody>
</table>

*A clinical improvement was noted but the timeframe was not documented
Discussion
This report examines 941 episodes of pediatric DKA managed with continuous IV insulin and a physiologic approach to rehydration coupled with early recognition of signs and symptoms consistent with raised ICP. Mannitol was given relatively frequently (76 of 941 admissions [8%] for DKA). In 50 of these 76 (65.8%) episodes during which signs or symptoms worrisome for raised ICP occurred, improvement followed administration of mannitol in less than 60 minutes. No neurologic disability was identified at hospital discharge. By contrast, in a large retrospective review, 61 of 6977 (0.87%) pediatric DKA admissions were treated for “clinically apparent cerebral edema” but over 40% of the 61 symptomatic children either died or survived with significant neurological deficits. Our data suggest that mannitol is effective and safe in the aggressive treatment of a broad range of signs and symptoms consistent with cerebral edema associated with raised ICP in children with DKA.

Four mechanisms leading to raised ICP from brain parenchymal swelling are recognized: vasogenic, ionic, cytotoxic and water intoxication. Vasogenic edema results from the disruption of endothelial cells and the tight junctions by which the blood-brain barrier (BBB) is formed. When integrity of the BBB is damaged, proteins as well as sodium and water (an ultrafiltrate of blood) leak from the intravascular into the extracellular space. Ionic edema involves abnormal passage of ions from the intravascular space to the extracellular and intracellular spaces followed by water. This loss of ionic homeostasis is likely associated with injury to multiple brain cell membranes including brain endothelial cells, neurons and glia. Tight junctions remain intact and leakage of macromolecules (e.g. proteins) does not occur. Cytotoxic edema occurs when the brain cell membrane becomes unable to regulate the ionic gradient that normally defines its intracellular volume. There is no contribution from the intravascular space unless or until cytotoxic edema itself generates a driving force for ionic and vasogenic mechanisms for swelling.

Water intoxication differs from these aforementioned mechanisms in that water moves across normal endothelial and brain cell membranes driven by osmotic forces. This results from a too rapid decline in plasma osmolality, with or without pre-existing hyperosmolality. Under conditions of established hypertonicity (e.g. DKA), formation of intracellular osmolytes prevent brain cell water loss. This defense against brain cell shrinkage may increase the risk of water intoxication and brain herniation during treatment, particularly when rehydration exceeds patient need. Elevated apparent diffusion coefficient values and T2 relaximetry sequences on brain MRI suggest increased interstitial fluid plays a role in DKA-related brain edema. No mechanism has been singularly identified as the cause of fatal brain herniation during DKA. Further, the pathophysiology of brain herniation may not be identical to that of subclinical brain edema or clinically reversible raised ICP during treatment. Any one or all of the aforementioned mechanisms may be operative in DKA, during which the pathophysiology of dehydration, systemic and central nervous system acidosis and components of therapy interact.

Administration of mannitol is a primary therapy for the lowering of ICP and enhancement of cerebral perfusion. Mannitol is a recognized treatment for cerebral edema following traumatic brain injury and has been reported to be useful for treatment of cerebral edema in DKA. The use of mannitol in the setting of water intoxication has been proposed to reduce both extravascular and intracellular water and reduce associated cerebral edema. There is no evidence that mannitol administration is helpful for certain types of cytotoxic edema (e.g. hypoxic brain injury). However its usefulness in head trauma suggests it may favorably impact cytotoxic swelling in certain settings.

Mannitol has at least four potential effects on the cerebral circulation that may decrease elevated ICP and increase cerebral perfusion: 1] hemodilution with viscosity change; 2] improved red blood cell deformability with viscosity change and improved oxygen delivery to tissues; 3] volume expansion with improved arterial blood pressure; 4] increased cerebral perfusion coincident with an increased cardiac output. Other mechanisms that may contribute to the effect of
mannitol during pediatric DKA and increased ICP include mobilization of water from the intracellular and/or interstitial space into the intravascular space\textsuperscript{33, 34} and reduction in the rate of cerebral spinal fluid formation\textsuperscript{34}. In adult stroke patients, the greatest reflex decrease in vessel diameter occurs 45 minutes after mannitol infusion and abates approximately 75 minutes post-mannitol infusion\textsuperscript{35}. In adult patients with varied intracranial pathologies and cerebral perfusion pressure (CPP) < 9.33 kPa the ICP response was maximal by 15 to 30 minutes post-mannitol; if CPP was ≥9.33 kPa, the maximal response was less and did not occur until 45-60 minutes post-mannitol\textsuperscript{27}. These factors may explain clinical improvement within the first 60 minutes after mannitol infusion. Osmotic effects from hypertonic mannitol may persist up to four hours\textsuperscript{36} after administration; these effects may have been operative but difficult to discern over a period during which metabolic repair of DKA was simultaneous. Altered mental status, headache, sluggish pupils and hypertension and/or bradycardia were the most frequent indicators for mannitol administration. Coma, sluggish pupils, headache and hypertension/bradycardia each had at least a 50% response rate to mannitol within 60 minutes.

Two children, each of whom had received two doses of mannitol, were given infusions of hypertonic saline (1027 mOsm/liter) for poor peripheral perfusion post-mannitol administration. Intravenous hypertonic mannitol has an elimination half-life of 0.5-2.5 hours\textsuperscript{33}. These episodes of circulatory insufficiency could have represented complications related to mannitol-induced diuresis. Notably, one of these patients had septic shock and required vasoactive medications in addition to volume expansion. Decreased perfusion was more likely the consequence of mannitol-induced diuresis than mannitol-associated vasodilation since all mannitol infusions were accomplished over 15 to 20 minutes. Cardiovascular instability was rare following mannitol administration in children who were undoubtedly dehydrated at baseline. Hypertonic saline may be an attractive alternative for the treatment of suspected raised ICP in the presence of shock, although IV hypertonic mannitol has been well tolerated in the setting of hemorrhagic shock\textsuperscript{32}. Other theoretical risks of mannitol involve potential reduction of cerebral perfusion secondary to excessive diuresis or vasodilation during rapid (<5 minutes) mannitol infusions\textsuperscript{29, 37}. Mannitol administration is discouraged in head trauma patients if measured serum osmolality exceeds 320 mOsm/kg\textsuperscript{33}. Mannitol was given emergently in our patients; osmolality was not measured. No renal complications occurred; nonetheless, mannitol administration mandates careful monitoring of kidney function.

Sixteen of the 76 patient-episodes (21.3%) were treated with multiple doses of mannitol. Multiple dosing has been demonstrated to aggravate cerebral edema in adult head trauma patients\textsuperscript{38} and while repeated doses of mannitol in pediatric DKA may be warranted, caution is advisable. However, multiple doses may be indicated when progressive or recurrent cerebral edema is suspected.

Administration of sedative agents preceded mannitol administration in four instances; a response was documented in two, suggesting that depression of mental status in this setting should not necessarily be attributed to sedative drug effects. The use of antiemetics for the nausea and vomiting of DKA can be avoided if definitive treatment with insulin therapy is timely. Use of other sedative drugs should be discouraged during treatment of DKA since decreased mental status can be important in early diagnosis of raised ICP.

Tracheal intubation was required infrequently in this series. Aggressive use of mannitol may have obviated the necessity for intubation by moderating the progression of cerebral edema.

Table 3: Mental status changes in DKA: Differential Diagnosis

<table>
<thead>
<tr>
<th>Shock (hypoxemia/ischemia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral edema</td>
</tr>
<tr>
<td>Cerebral infarction</td>
</tr>
<tr>
<td>Fluid and electrolyte imbalance</td>
</tr>
<tr>
<td>Hypertonicity (eg, hyperglycemia or hypernatremia)</td>
</tr>
<tr>
<td>Hyponatremia</td>
</tr>
<tr>
<td>Calcium and magnesium imbalance</td>
</tr>
<tr>
<td>Toxins or poisons or medications</td>
</tr>
<tr>
<td>Infections</td>
</tr>
<tr>
<td>Seizures</td>
</tr>
<tr>
<td>Behavioral</td>
</tr>
<tr>
<td>Acute hydrocephalus</td>
</tr>
</tbody>
</table>
Head CTs were performed sparingly. Complete resolution of worrisome indicators in a relatively brief time frame often prompted clinicians to withhold imaging investigations. Importantly, conditions other than DKA-related cerebral edema may be present and may require specific intervention. For this reason, emergent CT or MRI imaging may be warranted (Table 3).

In each case, mannitol treatment was administered based on clinical findings prior to CT imaging. Prior treatment with mannitol may have minimized findings typically associated with cerebral edema on CT scan possibly accounting for the small number of head CT’s that revealed cerebral edema.

Eighty-four percent of mannitol recipients were referred from outlying facilities. Once contacted, our team provided treatment recommendations, monitoring guidelines and reminders regarding the occurrence of cerebral edema in this patient population. The physiologic approach thus implemented included a recommended rate of volume delivery, isotonic rehydration strategies, attention to the trend of serum sodium concentration, effective insulin delivery and intensive monitoring. Further, if raised ICP is suspected, routine supportive measures (such as proper head positioning) should be advised.

Aggressive use of mannitol for suspected raised ICP, despite the presence of dehydration, was safe and effective in preventing death and/or neurologic injury from cerebral edema in our patients. The data presented are limited to some degree due to the retrospective nature of the study. For example, it is possible that prior to referral, volumes of fluid in excess of those recommended in the physiologic management guidelines were given; this could have contributed to the relatively high rate of mannitol administration as well as to the apparently excellent risk-benefit ratio associated with its use in this series. Strategies to minimize ICP in any at-risk population are multifaceted. Further, the successful outcome of the patients described may not be reproducible outside the context of a physiologic approach to rehydration and correction of ketoacidemia.  

Conclusions

In pediatric patients with DKA, early and aggressive treatment with mannitol for suspected raised ICP appears to be safe and prevents severe neurologic injury or death when coupled with a physiologic approach to rehydration of the hypertonic state, aggressive treatment of ketoacidemia and intensive monitoring.

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Stress has been defined as “psychological and physical strain or tension generated by physical, emotional, social, economic or occupational circumstances, events and experiences that are difficult to manage or endure”. This definition highlights the different components of stress, including the psychological component which is the focus of this study. Stress has devastating effects on individual, interpersonal, and societal level.1

One potentially stressful life event for parents is the birth of their neonate. It is not surprising that the birth of a fragile neonate who requires immediate Neonatal intensive care unit (NICU) care can be very stressful for the parents. Similarly parents who have a critically ill child in the Pediatric Intensive Care Unit (PICU) often experience extreme levels of stress. The majority of pediatric critical care admissions are unplanned, caused by life threatening illnesses or accidents, and evoke feelings of fear and helplessness in parents. It is important to research the nature of stress to assist the development of interventions to mitigate its negative effects on individual, interpersonal, and societal levels. Similarly advances in medical science have increased the number of children surviving illnesses and injuries that would have otherwise been fatal. Further more, informed knowledge about adverse events of admission in intensive care setup can increase level of stress amongst parents.

Multiple studies have been published in the past which compared stress amongst parents of NICU graduates with parents of healthy newborn2 but we could not find any such study which compared stress amongst parents of these two groups namely neonates and older children requiring intensive care specially from rural setup.

Aim and Objectives
Primary objective of this study was to assess the stress amongst the parents of babies admitted in

<table>
<thead>
<tr>
<th>ABSTRACT</th>
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| **Objective:** To compare the stress amongst parents whose babies were admitted in NICU with that of the parents of children admitted in PICU

**Methods:** Prospective study conducted at a tertiary level hospital with well equipped NICU and PICU. Eligible parent’s (both mother and father) stress level was analyzed with the help of Parental Stress Scale (PSS).

**Results:** Total 120 participants (mother and father) with 60 from each group were subjected to PSS. Mean score of fathers and mothers whose children were admitted to PICU had more stress as compared to those in NICU (p-value <0.001). Similarly stress was more in less educated (p-value <0.005) and low income group (p-value <0.01) parents.

**Conclusion:** Our study concludes that guardians of children admitted to PICU have more Stress compared to that of neonates admitted in NICU and stress is negatively related with their educational qualification, income and number of children.

**Key words** - Parental stress scale, stress study, NICU, PICU, Mother’s stress, Father’s stress.
NICU and to compare it with the stress amongst the parents of children admitted in PICU

**Materials and Methods**

The study was performed in Dhiraj hospital a multi-specialty tertiary care center, caters to rural population. All parents whose children or neonates admitted to PICU or NICU from March 2014 to Sept 2014 were eligible for participation in the study. All parents whose babies and children admitted for at least 24hrs in NICU and PICU respectively and willing to participate in the study were included.

Parents of babies and children who had obvious lethal congenital anomaly, had any chronic disorder like depression or any psychological problem as per history, parents of children who was suffering from chronic and critical sickness, parents age <18 yr of age, patients referred to Dhiraj hospital PICU after chronic stay in other PICU (>10 days) and parents of terminally ill with chronic disease patients admitted to PICU e.g chronic renal failure were excluded. All the participants were provided Parental Stress Scale (PSS) in the local language as per comfort of parents and was helped by person other than investigator to avoid interviewer bias.

**Stress assessment scale:** All the participants subjected to prestructured questionnaire (in local language). Parental Stress Scale (PSS) was adapted from original Parental Stressor Scale3 Required modification was carried out on the basis of pilot study and validation was done before it’s use for study purpose. Satisfactory validity for the PSS had been demonstrated by factor analyses, inter- scale correlations, and measurements of construct validity. Reliability in the form of internal consistency has been shown to be acceptable (> .70) for the PSS:NICU.

PSS-The PSS contains 40 items, corresponding to four subscales and a general stress item. The four subscales and their numbers of items are as follows: Sights and Sounds, 5 items; Infant Appearance, 16 items; Parent-infant Relationship, 09 items; and Staff, 10 items.

Participants were asked to rate each item on a scale of 1 to 5, according to how stressful the situation described in each item was for them:

1 = not at all stressful,
2 = a little stressful,
3 = moderately stressful,
4 = very stressful,
5 = extremely stressful.

**Results**

Study was carried out on guardians of 30 children admitted in PICU and 30 in NICU. Among 60 guardians, 24 had one child and 36 had more than one child. Majority of the guardians were having primary or less education.

**Table 1:** Risk factors for stress amongst father (F-stress)

<table>
<thead>
<tr>
<th>Variable</th>
<th>F-Stress (%)</th>
<th>RR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>One child</td>
<td>20 (83.3)</td>
<td>1.875</td>
<td>1.248-2.816</td>
<td>0.003</td>
</tr>
<tr>
<td>More children</td>
<td>16 (44.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PICU</td>
<td>26 (86.7)</td>
<td>2.60</td>
<td>1.538-4.396</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NICU</td>
<td>10 (33.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean stress level amongst father’s having one child were (83.3%) which was higher as compare to father’s having more number of children (44.4%) with RR of 1.875 (95% CI-1.248-2.816). Incidence of F-Stress among guardians whose children were admitted in PICU was 86.7% and those admitted in NICU was 33.3% with RR of 2.6 (95% CI-1.538-4.396).

**Table 2:** Risk factors for stress amongst mothers (M-stress)

<table>
<thead>
<tr>
<th>Variable</th>
<th>M-Stress (%)</th>
<th>RR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>One child</td>
<td>24 (100)</td>
<td>1.333</td>
<td>1.104-1.610</td>
<td>0.008</td>
</tr>
<tr>
<td>More children</td>
<td>27 (75)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PICU</td>
<td>30 (100)</td>
<td>1.429</td>
<td>1.130-1.806</td>
<td>0.002</td>
</tr>
<tr>
<td>NICU</td>
<td>21 (70)</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Mean stress level amongst mother’s having one child were (100%) which was higher as compare to mother’s having more number of children (75%) with RR of 1.333 (95% CI-1.104-1.610). Incidence of M-Stress among guardians whose children were admitted in PICU was 100% and those admitted in NICU was 70% with RR of 1.429 and (95% CI-1.130-1.806).

Mean Stress of father and mother scores (162.4±15.02 and 193.65±7.94 respectively) whose children were admitted in PICU is significantly higher as compared to that of NICU admission (115.67±7.16 and
129.93±11.93 respectively), with significant p-value < 0.001.

Mean Stress amongst father (154.5±26.9 and 125.97±16.78 respectively) having one child is significantly higher as compared to those having more than one children (180.24±31.37 and 149.84±27.66 respectively), with significant p-value.

Table 3: Correlation between stress and demographic variables

<table>
<thead>
<tr>
<th></th>
<th>Education</th>
<th>Income</th>
<th>No. of children</th>
</tr>
</thead>
<tbody>
<tr>
<td>F_Stress</td>
<td>-0.396</td>
<td>-0.689</td>
<td>-0.465</td>
</tr>
<tr>
<td>M_Stress</td>
<td>-0.512</td>
<td>-0.783</td>
<td>-0.435</td>
</tr>
</tbody>
</table>

Stress in father and mother were negatively related with their educational qualification, income and no. of children i.e. guardians with lower education, less income and less no. of children had higher stress as compared to others (p-value <0.001).

Discussion

Alteration of parenting role has consistently been identified as the greatest sources of distress to parents. The purpose of this study was to examine stress amongst parents whose newborns and children in develop in a group of families experiencing hospitalization of their child in a PICU as well as NICU. Similar kind of study by Pooni PA et al.4 found significant stress among parents of children admitted in PICU due to procedures, lights and sounds of monitors. They also found that the stress level was more in maternal group and in younger parents but could not establish significant relation with socioeconomic status and age of children. Another similar study by Gaurav et al.5 found significant stress among parents of children admitted in PICU due to procedures, lights and sounds of monitors. They also found that the stress level was more in maternal group and in younger parents but could not establish significant relation with socioeconomic status and age of children. Another similar study by Gaurav et al.5 found that there is significant stress among parents of children admitted to PICU as compared to ward patients. But there was no significant difference in stress levels amongst parents based on education or socioeconomic status of parents or sex of child. One more study has shown that there is difference between the stress level amongst mother and father6. There was not much difference in stress level scores based on demographic profile of the parents like education of parents and family income.

The knowledge gained from this study adds to a limited body of knowledge regarding parental stressors experienced and associated risk factor’s during child’s critical illness. This study assists healthcare providers to have a better understanding of the stressors that parents experience during their child’s hospitalization in the ICU. The current study found that decreasing income and parents whose has single child had more stress. Nurses should consider that parents of lower socioeconomic status and parents of children whose hospitalizations were not planned to be at risk for greater stress.

Limitations of our studies were - small sample size and only rural population was part of study. Similar studies should be conducted at primary care level as well as in urban population and results can be compared. A recent study indicates that parents have stressful experiences in four categories: facing boundaries, attempting to understand, coping with uncertainty, and seeking reassurance from caregivers6. Future research should focus on factors affecting the stress level and improvement in stress level after modification of factors.

Conclusion

Our study found parents of children admitted in PICU had more stress as compared to those in NICU. As expected higher stress was seen among mothers as compared to the fathers. Stress level was significantly higher amongst parents with single child, less educated, lower socio-economic class parents.

References

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Case Reports

Congenital Laryngotracheoesophageal Cleft Masquerading As Recurrent Pneumonia

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ABSTRACT
Laryngotracheoesophageal cleft (LTEC) is an uncommon congenital malformation of the posterior part
of the larynx, creating an abnormal communication between the laryngo-tracheal axis and the pharyngo-
esophageal axis. This condition manifest with non-specific respiratory symptoms, posing diagnostic
challenge. Here we report a case of 75 days old infant with recurrent pneumonia and acute life threatening
event manifested as milk aspiration. On endoscopic evaluation type 1 LTEC (Laryngeo trachea esophageal
cleft) was diagnosed. Intervention/Outcome : Infant was managed conservatively and doing well on follow
up.

Key Message: LTEC has to be highly suspected in case of recurrent pneumonia and aspiration.

Key words: Laryngotracheoesophageal cleft, recurrent pneumonia, aspiration.

Introduction
Laryngotracheoesophageal cleft (LTEC) is a rare congenital malformation, first described in 1792
by Richter. The incidence is 1 in 10,000 to 20,000 births, which represents approximately 1.5% of the
laryngeal anomaly in children1. Here we describe a case of LTEC which is least suspected as differentials
for recurrent pneumonia.

Case Report
We report a case of 75 days old male infant with
complaints of cough since 8 days, fever and hurried
breathing since 1 day (II admission). On admission,
infant was febrile, irritable, in respiratory distress
with HR- 140 per min, RR- 88 per min with subcostal
and intercostal retraction. Cyanosis present, SpO2
86% on room air. Hemodyamically stable. On
respiratory system examination: bilateral air entry
equal, vesicular breath sounds present, crepitations
present. Other systems were normal. Previously
hospitalised for 11 days at 40 days of life in view
of pneumonia. Birth history was uneventful. Growth
was unaffected (weight-5kg, length-52cm). Attained
milestones appropriate for age. No feeding difficuty.
Complete blood count was normal, chest X-ray
showing bilateral perihilar streaky opacities (fig 1a)
possibility of bronchopneumonia was considered
and was initiated treatment accordingly. On day
2 of admission, respiratory distress worsened.
Inspite of 72 hrs of antibiotics therapy, there was no
improvement thus second line antibiotics were added.
Infant started responding to the treatment. On day 6
infant was allowed orally. On day 7 had an episode
of milk aspiration (acute life threatening event).
Possibility of laryngotracheoesophageal anomaly,
gastroesophageal reflux (GERD), congenital heart
disease were considered. Further investigated,
HRCT thorax revealed bronchopneumonia changes
(fig 1b), modified swallow study was normal (fig 1c),
echocardiography was normal. Infant was subjected
to fiberoptic bronchoscopy and esophagoscopy.
Findings: Small laryngotracheoesophageal cleft
(grade I) was present (fig 1d). Following procedure,
as per pediatric surgeon’s opinion infant was managed
conservatively.

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Nursing in propped up position, burping following every feed and anti-reflux measures were added. Infant was discharged (wt- 4.6kg) on day 10. Parents were counselled regarding the condition and conservative management was advised. On one month follow up, infant doing well with conservative management, with adequate weight gain (wt- 5.3kg).

**Discussion**

A laryngealtracheoesophageal cleft (LTEC) is a congenital malformation of the posterior part of the larynx, creating an abnormal communication between the laryngo-tracheal axis and the pharyngo-oesophageal axis. Thus, the physiological separation between the airway and the digestive tract is lost, leading to chronic cough, aspiration, respiratory distress, pneumonia. Depending on the extent of tracheal involvement, Benjamin and Inglis classification (fig 2) is commonly used for classification of laryngeal cleft. Type 1 clefts are supraglottic interarytenoid clefts, where the cleft is above the level of true vocal cords. Type 2 clefts extend below the level of the vocal cords but do not involve the posterior cricoid lamina completely. Type 3 clefts extend completely through the cricoid cartilage, with or without further extension into the cervical tracheoesophageal wall. Type 4 clefts extend through the majority of the tracheoesophageal wall. The airway abnormality reported in this case, represents type 1 LTEC. Laryngeal clefts can occur in families and are likely to be associated congenital abnormalities, including gastrointestinal, cardiac and genitourinary malformations and chromosomal.
CASE REPORT
Congenital Laryngotracheoesophageal Cleft Masquerading As Recurrent Pneumonia

aberrations\(^2\,^3\,^5\), however no such abnormalities were present in this case assuring better prognosis. Infant presenting with stridor, choking, cyanosis, feeding problems, repeated aspiration, respiratory distress should have a thorough evaluation. Differential diagnosis include tracheo-bronchial fistula, GERD and neurological swallowing disorders, as well as laryngomalacia and laryngeal palsy\(^3\,^5\). This case reports the presentation of laryngeal cleft as recurrent aspiration pneumonia with an episode of acute life threatening event (presented as milk aspiration here). Possibility of GERD, laryngotracheoesophageal anomaly were considered and were ruled out by subjecting the infant to appropriate investigation. Diagnosis of laryngeal cleft is based on high index of suspicion. Chest radiography might show pulmonary infiltrates secondary to aspiration, neither standard X-ray examinations nor CT-scans or MRI scan is useful except to diagnose associated anomalies\(^3\). Modified swallow studies (MBS) and functional endoscopic evaluations of swallowing (FEES), suspension laryngoscopy with bimanual interarytenoid palpation, are helpful in evaluation of laryngeal cleft\(^3\,^6\). This case was diagnosed by fiberoptic endoscopy. Medical treatment aims to: 1. Maintain satisfactory ventilation in children presenting an obstructive form of LTEC (mostly by prolapsing mucosa). 2. Prevent secondary pulmonary complications as a result of repeated aspiration and 3. Ensure adequate feeding of the child\(^1\) Type I laryngeal cleft can be challenging diagnostically. Functional diagnostic and management algorithm and a trial of conservative therapy, including proton pump inhibitor for gastroesophageal reflux, maintaining an upright position during feedings, thickened feeds, and maneuvers during feeding to prevent aspiration prior to considering surgical repair. If conservative therapy fails, then surgical intervention is indicated\(^6\). In the more extensive forms of LTEC, the condition may be fatal unless properly diagnosed and corrected surgically in a timely fashion\(^5\).

Key Message
As per this case possibility of laryngotracheoesophageal cleft (LTEC), an uncommon laryngeal anomaly, should be considered when an infant presents with recurrent pneumonia and aspiration, after ruling out common conditions. The prognosis depends on early diagnosis, grade of LTEC and appropriate intervention.

References

Figure 2: The Benjamin—Inglis classification system of laryngeal clefts. Type 1 clefts are supraglottic interarytenoid clefts, where the cleft is above the level of true vocal cords. Type 2 clefts extend below the level of the vocal cords but do not involve the posterior cricoid lamina completely. Type 3 clefts extend completely through the cricoid cartilage, with or without further extension into the cervical tracheoesophageal wall. Type 4 clefts extend through the majority of the tracheoesophageal wall\(^4\)
Acute Myocardial Infarction in A Patient of Infective Endocarditis
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ABSTRACT
Infective endocarditis (IE) is associated with a number of complications. Peripheral systemic embolism is a common and serious complication of infective endocarditis linked to migration of vegetation. Here we present a case of a 9 year old girl admitted with left hemiplegia due to right MCA thromboembolism due to naïve aortic valve IE and ultimately expired due to an acute coronary syndrome (ACS) due to possible coronary embolism.

Key words: Infective Endocarditis (IE), thromboembolism, myocardial infarction.

Introduction
Infective endocarditis (IE) is still associated with high morbidity and mortality, ranging from 16% to 25%, and a high incidence of embolic events, ranging from 13% to 49%, despite recent improvements in diagnostic and therapeutic strategies. IE is well known to cause many types of complications among which systemic embolization of septic thrombi is the commonest, most frequently involving the central nervous system, spleen, kidney, liver, and iliac or mesenteric arteries, whereas involvement of coronary arteries and ACS is infrequently encountered. Acute myocardial infarction (AMI) complicated by septic coronary embolism from IE is a rare and fatal condition can arise due to coronary embolism and external coronary compression. Coronary ischaemic can also be due to a large vegetation obstructing the coronary ostium or severe aortic regurgitation, we report a case of AMI complicated by septic coronary embolism caused by IE of the naïve aortic valve.

Case Report
A 9 year old girl admitted with a history of sudden onset weakness of left side of the body associated with slurring of speech and deviation of face towards right. She was conscious but a bit agitated. There was No history of seizure, fever or altered sensorium. There was no significant past history as well as any previous hospital admission or surgery. On admission, she was febrile, BP was 109/46 mm hg associated with a high volume collapsing pulse with a rate of 120/min. On examination of the cardiovascular system, a grade 3 diastolic murmur was audible in the left second and aortic region. Auscultatory findings in the chest were normal and there was no hepatosplenomegaly. There were small petechial spots over the trunk. A detailed CNS examination revealed a GCS of 12/15, planter response was extensor in both the sides and Pupil was bilaterally equal and reactive to light. Left hand and left leg power was 2/5 and right hand and right leg was 5/5. Tone was decreased in left side but normal in right. There were features suggestive of left sided UMN (upper motor neuron) facial nerve palsy. So keeping together the findings of sudden onset complete hemiplegia of left side of the body along with a cardiac findings of possible Aortic Regurgitation, a provisional diagnosis of acute embolic stroke with rheumatic or infective etiology was made and investigations were sent accordingly. Routine blood report revealed Hb-7.5gm/dl, TLC-9900/cmm, ESR-72 in 1st hour, CRP-48.9mg/L (Normal reference <9), LFT (liver function tests)-normal, RFT (Renal function test)-normal. Echocardiography revealed Bicuspid aortic valve with severe AR (Aortic regurgitation) along with vegetation in aortic valve and in main pulmonary artery. There was dilated LV (left ventricle) with normal function and mild MR (mitral regurgitation) and TR (tricuspid regurgitation). The girl was treated conservatively with IV fluids, Ceftriaxone, Vancomycin, Enalapril and Frusemide. MRI scan of brain revealed an acute infarct in the right MCA (Middle cerebral artery) territory with occlusion...
of right MCA with few collaterals adjacent to the occluded M1 segment. (See photographs 1 and 2).

![Figure 1: Acute infarct in right MCA territory](image1)

![Figure 2: Occlusion of right MCA (M1 segment)](image2)

Bolod cultures revealed the growth of *Streptococcus gallolyticus* that was sensitive to most of the common 1st line antibiotics and antibiotics changed to IV Ceftriaxone plus IV Amikacin according to the sensitivity pattern. The girl’s HIV status was negative and immunoglobulin and CD4/CD8 counts came out to be normal. NG (Nasogastric) tube feeding started as she was not able to swallow and Physiotherapy and Speech therapy continued. A PICC (Percutaneously inserted central catheter) line was done in the anticipation of prolong antibiotics for 6 to 8 weeks and she was shifted to general pediatric ward after 7 days of PICU stay to complete her antibiotic therapy.

But almost after a month of uneventful days, at day 33 of admission she developed vomiting, abdominal pain, decreased urine output and restlessness that were treated conservatively with iv fluids and analgesics. USG (Ultrasonography) of whole abdomen revealed Cholelithiasis with left sided renal calculi and bilateral small pleural effusion. But she gradually developed agitation and became a bit confused. She was immediately transferred back to PICU and an urgent CT brain done that revealed the same finding of right MCA infarct. She became tachypneic, tachycardic and became dehydrated and sensorium and peripheral perfusion deteriorated gradually and she started developing abnormal rhythm (wide complex tachycardia) followed by bradycardia with frequent ventricular ectopics. Due to gradually worsening cardiorespiratory status and worsening sensorium she was intubated and initiated on mechanical ventilation. Central venous access and arterial line placement was achieved and invasive hemodynamic monitoring started. Multiple fluid boluses and inotropes were given and ECHOcardigram revealed very poor myocardial function with a LVEF (left ventricular ejection fraction of only 25%. Chest xray revealed diffuse pulmonary edema and ECG showed ST depression in inferior and lateral leads with bundle branch block pattern suggestive of Acute Myocardial infarction of anterior and inferior wall. There was raised LDH, CPK MB, Troponin T. The girl went into severe, irreversible cardiogenic shock. Despite full ventilatory and inotropic support she succumbed to death around 2-30am.

**Discussion**

Systemic embolism occurs in 22—50% of patients with IE, the majority (up to 65%) in the central nervous system, but other major arterial beds may be involved, including the coronary arteries. Acute myocardial infarction (AMI) complicated by septic coronary embolism from IE is a rare and fatal condition. The incidence of coronary septic embolism in pediatric population is very difficult to estimate as most of the data are coming from the case series of adult population. Three series found that 11 (10.6%) of 104 Russian patients had AMI as a result of septic embolism, only 14 (2.9%) of 586 Spanish patients had acute coronary syndrome, and half were associated with prosthetic valves, and only 2 (0.52%) of 384 patients had coronary embolisms in a multicentre prospective European study. There is no such published case series of IE and AMI in pediatric population. De caro; et al. presented a case of a child with acute myocardial infarction and residual impairment of the coronary reserve, complicating a mitral endocarditis. Ocal; et al. reported a case of Acute Myocardial Infarction Secondary to Bacterial Endocarditis in a 14 year old Child with congenital Aortic Stenosis. Our proband initially presented with a thromboembolic stroke as a complication of IE and later on in the verge of discharge developed fatal...
AMI.
Most coronary embolisms occur in the left ascending coronary artery because of the downward course of the left ascending coronary artery compared with the right coronary artery or left circumflex artery, which originate at 90° to the aortic cusp. Septic emboli are more frequent with mitral valve infection (25%) than with aortic valve infection (10%)8. Acute coronary syndrome in the form of AMI may present later in the course of a disease as a complication like in our case but may also be an initial presenting feature of IE. Iwao Okai et al9 presented a case where a 53 years old man presented with AM and later diagnosed to be having mitral valve IE.
The definitive diagnosis of AMI due to septic emboli from IE is difficult. Coronary angiography can establish the diagnosis of septic emboli in the coronary artery. However, contact between the catheter and the valve surface with vegetation may release systemic emboli. Therefore coronary angiography in patients with IE was reported to be safe if no vegetation is observed on the aortic valve.10 So in our case we were not able to do an angiography, but had to rely upon the clinical scenario, ECG, ECHO features and cardiac biomarkers. It is almost certain that if any patients develops an acute coronary syndrome (ACS) the presence of vegetation in the valves, the cause of this ACS must be a thromboembolic obstruction of one or more coronary arteries unless proved otherwise.1,4,5 The mortality in these cases of AMI secondary to coronary artery thromboembolism in a case of IE is very high mainly due to late identification of the problem and diagnosis and lack of proper guidelines to treat these types of patients. Though there are few case reports of successful treatment with thrombolytic therapy11 there is serious concern that thrombolytic treatment for myocardial infarction in the setting of infective endocarditis may be associated with higher risk of cerebral haemorrhage and there is little documented evidence supporting the safety of primary percutaneous coronary intervention with these patients.12
This case report is exceptional because acute myocardial infarction is a very rare complication of infective endocarditis in pediatric population and also as it raises concerns regarding lack of data on proper management approach in such cases. The girl was doing well even 12 hours before her sudden demise and was planned to be discharged after few days and died all of a sudden due to a fatal AMI and refractory cardiogenic shock. We suggest that physicians must be aware about this nasty complication of IE and there is also a need to develop some strategy to treat patients who present with endocarditis and acute coronary syndrome.

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Introduction

The primary hyperoxalurias (PH) are inborn error of metabolism resulting in increased endogenous production of oxalate leading to excessive urinary oxalate excretion. Lepoutre described a postmortem case of an infant with multiple kidney stones for the first time in 1925. To date, three distinct hereditary enzymatic deficiencies have been linked to PH, namely, PH type 1 (PH1), type 2 (PH2), and type 3 (PH3). The disease has an estimated prevalence ranging from 1 to 3 per million population. PH accounts for <1% of pediatric ESRD population in registries from USA, UK, and Japan. In contrast, PH is more prevalent in countries where consanguineous marriages are common. Latta and Brodehl estimated that 1 in 5 to 15,000,000 between the ages of 0 and 15 years will have renal failure due to primary hyperoxaluria. The measurement of oxalate in a timed 24-hour urine collection corrected for body surface area is preferred for the diagnosis of PH. New insights into potential therapies including the use of chemical chaperones and hepatocyte cell transplantation, or recombinant gene therapy for enzyme replacement, provide hope for curative treatments of primary hyperoxalurias in the future.

Case Report

A 21/2 months old male infant born to a second degree consanguineous parent at 34 weeks of gestation came to our hospital with repeated generalized tonic clonic seizures since three days moderate grade fever, altered sensorium, generalized swelling and decreased urine output. At arrival to hospital he had bradycardia followed by cardio respiratory arrest, he was resuscitated as per PALS guidelines and was connected to mechanical ventilator. His initial laboratory parameters were Hb 6.5 gm/dl, total leukocyte 5500/cumm, platelets 6000/cumm. Serum Na: 133mEq/L, serum K 7.67 mEq/L, creatinine 15.2mg/dl, blood urea 200mg/dl. His initial blood gas analysis showed severe metabolic acidosis with Ph 6.9 HCO3 2 BE -30. CT Brain was suggestive of mild front temporal atrophic changes, V-EEG showed abnormal sleep and awake EEG pattern with epileptogenic focus from right fronto-temporal lobe. His CSF Analysis was performed which showed Cell count: 12/cumm with 90% polymorphs and 10% lymphocytes with normal glucose and protein levels. His Blood culture grew Klebsiella pneumoniae.

ABSTRACT

Background: Primary hyperoxaluria is a rare disease characterized by the excessive production and accumulation of oxalate in the body.

Methods: We described the case of an infant with primary hyperoxaluria type who had end-stage renal failure in the second month of life, family history of deaths due to renal disease, renal biopsy showing intense deposition of oxalate crystals in the lumen, tubular cells, and kidney interstitium, with secondary glomerular disorder.

Conclusions: primary hyperoxaluria type I should be regarded as one of the differential diagnoses of renal failure in the first months of life, especially when no suggestive history of other diseases is present

Key Words: primary hyperoxaluria, renal failure

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His ultrasound abdomen showed bilateral severe echogenic kidney shadows with loss of Cortico medulary differentiation suggestive of chronic renal parenchymal disease. He was continued on mechanical ventilation, IV anticonvulsants and was submitted to peritoneal dialysis and restored his serum levels of creatinine and urea, on other hand his urine output was not restored after ten days of peritoneal dialysis. We considered the diagnosis of sepsis with acute kidney injury secondary to acute tubular and/or cortical necrosis versus inborn error of metabolism. He was investigated further and his metabolic work up was sent which came normal.

During his hospitalization after probing, parents gave history of death of maternal uncle and 10 cousin due to renal failure. So in view of persistent oliguria and family history of renal disease renal biopsy was performed. The analysis of the collected material revealed a large amount of oxalate crystals in tubular cells, kidney interstitium and tubular lumen with foreign body granulomatous reaction around the crystals (Figure 1A). Glomeruli were secondarily affected by the obstructive process with glomerular collapse and dilation of the Bowman’s space (Figure 1B). A urinary level of oxalate was not sent in view of persistent oliguria. The patient was kept on continuous ambulatory peritoneal dialysis, vitamin B6, received supplementation of iron, calcitriol, erythropoietin, sodium bicarbonate, and a high-calorie diet.

**Discussion**

All three types of PH are autosomal recessive. The infantile form often presents as a life threatening condition because of rapid progression to ESRD due to both early oxalate load and immature GFR; one half of the patients experience ESRD at the time of diagnosis and 80% develop ESRD by the age of 3 years9. These patients may have a defect in the cellular distribution of the enzyme, which is found in the mitochondrion rather than in hepatocyte peroxisomes, resulting in inadequate metabolic function10. The diagnosis of this defect in the enzyme is made by liver tissue biopsy and analysis of the alanine: glyoxylate aminotransferase catalytic activity11 which was not carried out in this case because the patient had already developed renal failure. In the existence of catalytic activity of alanineglyoxylate aminotransferase (AGT), the use of pyridoxine may be properly recommended, since pyridoxine phosphate is the coenzyme for aminotransferase, including AGT12. Pyridoxine has been used in cases of hyperoxaluria type I with variable responses in children aged one to two months. Five to 10% of the patients show partial or total response with the administration of pharmacological doses of pyridoxine. In the present case, pyridoxine was introduced at doses of 10 mg/day as therapeutic test, with the aim of reducing the excess of oxalate. The administration of pyridoxine hydrochloride has been shown to be associated with a decrease in urinary oxalate in about 10–30% of patients with PH [13]. In the present case, we couldn’t collect the urine sample for urinary oxalate level because of persistent oliguria.

The removal of oxalate by hemodialysis exceeds that by peritoneal dialysis. Better results may be obtained by combining daily high-flux hemodialysis and peritoneal dialysis or by long daily hemodialysis sessions14. The ideal moment for renal or hepatic transplantation is before the development of advanced systemic oxalosis15. Since the liver is the only organ responsible for glyoxylate detoxification by AGT, the excessive production of oxalate will continue as long as the native liver is left in place. Therefore, PH1 can be cured only when the deficient host liver has been removed. Liver Transplantation is a form of gene therapy as well as enzyme replacement therapy.
as it will supply the missing enzyme in the correct organ (liver), cell (hepatocyte), and intracellular compartment (peroxisome).

The symptoms reported at the onset of primary hyperoxaluria type I are: failure to thrive (22%), urinary tract infection (21%) and uremia (14%). Our patient had failure to thrive and might have developed dehydration with hypovolemia and subsequent excessive oxalate deposition in renal tubules, causing irreversibility of the renal condition at the second month of life. Our conclusion is that primary hyperoxaluria type I should be regarded as one of the differential diagnoses of renal failure in the first months of life, especially when no suggestive history of other diseases is present.

References
1. **Combination of arterial lactate levels and venous-arterial CO₂ to arterial-venous O₂ content difference ratio as markers of resuscitation in patients with septic shock**


**Summary**

This study was aimed at evaluating the prognostic value of the Cv—aCO₂/Da—vO₂ ratio combined with lactate levels during the early phases of resuscitation in septic shock. It was a prospective observational study in a 60-bed mixed ICU. One hundred and thirty-five patients with septic shock were included. The resuscitation protocol targeted mean arterial pressure, pulse pressure variations, or central venous pressure, mixed venous oxygen saturation, and lactate levels as per surviving sepsis guidelines. Patients were classified into four groups according to lactate levels and Cv—aCO₂/Da—vO₂ ratio at 6 h of resuscitation (T6): group 1, lactate ≥2.0 mmol/L and Cv—aCO₂/Da—vO₂ >1.0; group 2, lactate ≥2.0 mmol/L and Cv—aCO₂/Da—vO₂ ≤1.0; group 3, lactate<2.0 mmol/L and Cv—aCO₂/Da—vO₂ >1.0; and group 4, lactate <2.0 mmol/L and Cv—aCO₂/Da—vO₂ ≤1.0. Results: Combination of hyperlactatemia and high Cv—aCO₂/Da—vO₂ ratio was associated with the worst SOFA scores and lower survival rates at day 28 [log rank (Mantel–Cox) = 31.39, p<0.0001]. Normalization of both variables was associated with the best outcomes. Patients with a high Cv—aCO₂/Da—vO₂ ratio and lactate<2.0 mmol/L had similar outcomes to hyperlactatemic patients with low Cv—aCO₂/Da—vO₂ ratio. The multivariate analysis revealed that Cv—aCO₂/Da—vO₂ ratio at both T0 (RR 3.85; 95% CI 1.60–9.27) and T6 (RR 3.97; 95% CI 1.54–10.24) was an independent predictor for mortality at day 28, as well as lactate levels at T6 (RR 1.58; 95% CI 1.13–2.22)

**Comment**

Complementing lactate assessment with CvaCO₂/ Da-vO₂ ratio during early stages of resuscitation of septic shock can better identify patients at high risk of adverse outcomes. The Cv—aCO₂/Da—vO₂ ratio may become a potential resuscitation goal in patients with septic shock.

**Recommendations**

In this study, venous oxygen content was calculated using blood sampling from pulmonary arterial catheter. However in children, it may be difficult to insert pulmonary arterial catheter. ScVO₂ can be taken as surrogate marker for mixed venous oxygenation to calculate venous oxygen content. Pediatric studies can be done to evaluate the usefulness of venous-arterial CO₂ to arterial-venous O₂ content difference ratio as one of the markers during resuscitation in children with septic shock.

2. **Doppler-based renal resistive index for prediction of renal dysfunction reversibility: A systematic review and meta-analysis**


**Summary**

Doppler-based renal resistive index (RI) might help in distinguishing transient from persistent acute kidney injury (AKI). The main objective of this systematic review and meta-analysis was to investigate the diagnostic performance of RI in predicting short-term reversibility of AKI. Relevant studies were identified in PubMed and Cochrane databases covering the years 1985 to 2013 and reviewed independently by 3 authors. Renal transplant recipients were excluded from this analysis. The summary estimates were computed using a random-effects model based on the DerSimonian and Lair meta-analytic method. Among the 154 unique articles identified, 9 studies were...
Of the 176 patients in these studies with elevated RI or pulsatility index (Resistive index = (peak systolic velocity – end diastolic velocity)/peak systolic velocity) 146 (83%) had a persistent AKI vs 44 (16%) of the 273 patients with normal values. Elevated RI or pulsatility index was associated with an increased risk of persistent AKI (odds ratio, 29.85; 95% confidence interval [CI], 8.73-102.16; P < 0.00001) with significant heterogeneity (I²=75.0%, P < 0.0001). The pooled sensitivity and specificity were 0.83 (95% CI, 0.77-0.88) and 0.84 (95% CI, 0.79-0.88). The summary positive and negative likelihood ratios were 4.9 (95% CI, 2.44-9.87) and 0.21 (95% CI, 0.11-0.41).

Comments
These results suggest that an elevated RI may be a predictor of persistent AKI in critically ill patients. This article did not clearly describe how the renal RI was measured in individual original studies and interobserver variability. Further studies are warranted, however, to clarify the exact test performance given the marked heterogeneity among the included studies.

Recommendations
The best option for measuring RI is arcuate arteries (at the cortico-medullary junction) or interlobar arteries (adjacent to medullary pyramids). Provided non-invasive method to predict renal dysfunction, resistive index seems an attractive option for intensivist concerned about renal perfusion. However, adequate training is required in renal Doppler.

3. Conservative versus liberal oxygenation targets for mechanically ventilated patients – a pilot multicenter randomized controlled trial
Panwar R, Hardie M, Bellom R, Barrot L et al. Amer J Respir Crit Care Med Articles in Press. Published on 03-September-2015 as 10.1164/rcm.201505-1019OC

Summary
There are no randomized controlled trials (RCTs) comparing different oxygenation targets for Intensive Care Unit (ICU) patients. This study was aimed to determine whether a conservative oxygenation strategy is a feasible alternative to a liberal oxygenation strategy among ICU patients requiring invasive mechanical ventilation (IMV). At four multidisciplinary ICUs, 103 adult patients deemed likely to require IMV for ≥24 hours were randomly allocated to either a conservative oxygenation strategy with target SpO₂ of 88-92% (n=52) or a liberal oxygenation strategy with target SpO₂ of ≥96% (n=51). The mean area-under-curve and 95% confidence interval (CI) for SpO₂ [93.4% (92.9-93.9%) versus 97% (96.5-97.5%)], SaO₂ [93.5% (93.1-94%) versus 96.8% (96.3-97.3%)], PaO₂ [70 (68-73) mmHg versus 92 (89-96) mmHg] and FiO₂ [0.26 (0.25-0.28) versus 0.36 (0.34-0.39)] in the conservative versus liberal oxygenation arm were significantly different (p<0.0001 for all). There were no significant between-group differences in any measures of new organ dysfunction, or ICU or 90-day mortality. The percentage time spent with SpO₂ <88% in conservative versus liberal arm was 1% versus 0.3% (p=0.03), and percentage time spent with SpO₂ >98% in conservative versus liberal arm was 4% versus 22% (p<0.001). The adjusted hazard ratio for 90-day mortality in the conservative arm was 0.77 (95%CI: 0.40-1.50; p=0.44) overall and 0.49 (95%CI: 0.20-1.17; p=0.10) in the pre-specified subgroup of patients with a baseline PaO₂/FiO₂ <300.

Comments
Recommendations and practices related to oxygenation targets for mechanically ventilated patients are based on weak evidence. Conventional practice follows a liberal approach to oxygen therapy, often resulting in hyperoxia that may adversely affect outcomes. However, evidence from randomized trials is lacking, conservative oxygenation strategy is a feasible alternative to the usual liberal oxygenation strategy employed in mechanically ventilated patients.

Recommendations
As there were no harmful effects observed with the use of a conservative approach to oxygen therapy it can significantly reduce exposure to hyperoxia compared to standard care. Larger randomized trials of this intervention appear justified in pediatric age group also.

Summary
The purpose of the study was to compare the clearance of procalcitonin (PCT-c) in the first 24 and 48 hours of treatment of severe sepsis and septic shock with another early prognostic marker represented by the 48-hour Δ Sequential Organ Failure Assessment (SOFA). It was a prospective, observational cohort study conducted in a general intensive care unit including patients with severe sepsis and septic shock. The PCT-c was determined at the diagnosis of sepsis and after 24 and 48 hours. The SOFA score was determined at the time of intensive care unit admission and after 48 hours. One hundred thirty adult patients with severe sepsis and septic shock were studied over an 18-month period. The 24- and 48-hour PCT-c scores were significantly higher in survivors (P <0 .0001). In non-survivors, the initial SOFA was significantly higher, and the 48-hour Δ SOFA was significantly smaller (P=.01). The area under the receiver operating characteristic curve was 0.68 for Δ SOFA and 0.76 for 24- and 48-hour PCT-c.

Comments
The 48-hour Δ SOFA score and the clearance of 24- and 48-hour PCT are useful markers of prognosis in patients with severe sepsis and septic shock. An increase in PCT-c in the first 24 hours of treatment should prompt the reassessment of the appropriateness and adequacy of treatment. However, this study has limitations. First, this is a single-centre study. Large and multi-centre studies are necessary to confirm results. Second, these results cannot be applied to patients who have sepsis without organ dysfunctions or septic shock. Third, information was not collected regarding the appropriateness of antibiotic for the pathogen causing infection.

Recommendations
As procalcitonin levels can be easily estimated and available in almost all major health centres in India, procalcitonin clearance can be used as predictor of survival. However, multicentric, pediatric trials are required.


Summary
Use of systemic corticosteroids in acute respiratory distress syndrome (ARDS) remains controversial, and studies in children are lacking. The authors performed an observational, single-centre study in a prospectively enrolled cohort of children meeting criteria for ARDS (both Berlin 2012 and AECC 1994 acute lung injury) and pediatric ARDS (PARDs, as defined by PALICC 2015). Detailed information was collected on corticosteroid use, timing, treatment duration, and cumulative dose while mechanically ventilated and assessment of association between corticosteroid exposure >24 h and outcomes was done. Patients were dichotomized to those receiving no or ≤24 h of corticosteroids and those receiving >24 h, with the purpose of grouping patients with brief exposures to “stress dose” hydrocortisone (which were rapidly discontinued) and peri-extubation doses of corticosteroids together with those receiving no corticosteroids. Significant corticosteroid exposure was defined as those receiving >24 h of any corticosteroid formulation, consistent with previous reports. Total 283 children with PARDs (37 deaths, 13 %), 169 (60 %) received corticosteroids for >24 h while ventilated: 51 % hydrocortisone, 41 % methylprednisolone, 5 % dexamethasone, 3 % combination of corticosteroids. Corticosteroid exposure >24 h was associated with increased mortality, fewer ventilator-free days at 28 days (VFD), and longer duration of ventilation in survivors in unadjusted analyses (all p < 0.05). Multivariate and propensity score adjusted analyses confirmed independent association of corticosteroid exposure with fewer VFD and longer duration of ventilation in survivors, but not with mortality. In planned analyses of high-risk subgroups, no benefit was seen with corticosteroids exposure.
with fewer VFD associated with corticosteroid exposure >24 h in patients with ≥3 organ failures and immunocompromised patients.

**Comments**
Exposure to corticosteroid exposure >24 h was independently associated with fewer VFD and longer duration of ventilation in survivors, even after adjustment for key potential confounders, including severity of illness, oxygenation index, immunocompromised status, and number of organ failures.

**Recommendations**
Paediatric ARDS patients are commonly exposed to corticosteroids, despite a lack of evidence for their efficacy. Keeping an eye on the adverse effects of corticosteroids in these children, routine recommendation of steroids is not advisable.

6. **Inhaled [beta]2-agonist therapy increases functional residual capacity in mechanically ventilated children with respiratory failure**

**Summary**
It was hypothesised that in mechanically ventilated children with respiratory failure, aerosolized albuterol modifies functional residual capacity, lung mechanics, oxygen consumption, and hemodynamics. This study was a prospective, self-control clinical trial done in a 24-bed PICU in a quaternary care, academic children’s hospital. 25 children (age range, 1–18 yr) undergoing mechanical ventilation to treat respiratory failure were included. Entry criteria included previously prescribed inhaled [beta]2 agonists. Physiologic measurements were performed prior to and 20 minutes after administration of aerosolized albuterol solution. Functional residual capacity, oxygen consumption, respiratory mechanics, and vital signs were measured prior to and 20 minutes after administration of aerosolized albuterol solution. Functional residual capacity was determined via nitrogen washout. At baseline, functional residual capacity is only 53% of predicted. After aerosolized albuterol, functional residual capacity increased by 18.3% (p = 0.008). Overall, aerosolized albuterol had no effect on airway resistance. However, in patients with an endotracheal tube size of more than or equal to 4.0 mm, resistance decreased from 33 ± 3 to 25 ± 3 (p < 0.02). Inhaled albuterol administration had no effect on oxygen consumption despite an increase in heart rate from 116 ± 2 to 128 ± 2 beats/min (p < 0.0001).

**Comments**
This study has shown that in pediatric patients with respiratory failure, aerosolized albuterol increases functional residual capacity without a decrease in resistance. However, noteworthy point is that, the entry criteria for this study included children with previously prescribed beta 2 agonists. Hence, the effect of albuterol on children who don’t receive beta2 agonists is to be studied separately.

**Recommendations**
This intervention can be used in those children who are on regular bete2 agonists. On the other hand, further studies are required to demonstrate benefit of albuterol to improve respiratory mechanics in children who are not on beta2 agonist therapy.
Critical Thinking

PICU Quiz

Praveen Khilnani
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1. A patient ingests antifreeze and needs to eliminate the ingested acid. Renal elimination of the protons in this excess acid is primarily accomplished by which of the following mechanisms.
   A. Increased urinary ammonium excretion
   B. Increased urinary excretion of phosphates
   C. Hyperventilation
   D. Increased urinary free hydrogen ion concentration
   E. Increased urinary sulfate excretion

2. Which one of the following statements is true about the proximal tubule.
   A. The Na+/K+ ATPase drives sodium into the cell from the urine side of the tubule
   B. Na+/H+ exchange is largely the mechanism by which hydrogen ion secretion occurs
   C. Bicarbonate reabsorption is independent of carbonic anhydrase activity
   D. The pH in the lumen of the proximal tubule can reach as low as about 5.0

3. A patient takes a drug overdose and becomes comatose. His blood pCO2 was 40 mmHg ten minutes ago, but you discover it is now 80 mmHg. Which one of the following statements about this patient is correct.
   A. The pH of his CSF is likely to fall more slowly than the pH of his blood
   B. The pH of his blood is likely to fall more slowly than the pH of his CSF
   C. The pH of the blood and CSF will not change because he will rapidly eliminate bicarbonate in the urine in response to the rise in pCO2
   D. The pH of the blood and CSF will change to a similar degree in this time period

4. Atrial natriuretic peptide
   A. Increases H2O reabsorption
   B. Decreases sodium reabsorption
   C. Increases serum chloride
   D. Increases sodium reabsorption

5. Intravenous administration of 2 fluid boluses (20ml/Kg) of isotonic Ringer’s solution to a healthy child can cause:
   A. Increased cardiac output and renal blood flow
   B. Increased GFR
   C. Increased atrial natriuretic peptide and decreased renin in plasma
   D. A and C are correct
   E. all are correct

6. Concerning arterial blood pressure regulation:
   A. Prostaglandins and dopamine and bradykinin are vasodilators
   B. Angiotensin II and norepinephrine are vasodilators
   C. Heart rate is a strong determinant of blood pressure
   D. All are correct
   E. None are correct

7. Within an hour following intravenous angiotensin II infusion, the following is(are) clinically evident:
   A. Increased sodium uptake in the proximal tubular epithelium
   B. Systemic vasoconstriction
   C. Increased plasma aldosterone
   D. A and C are correct
   E. All are correct

8. Concerning water reabsorption by the proximal tubule:
   A. Main driving forces for water reabsorption in the proximal tubule are solute uptake and oncotic pressure in peritubular capillaries
   B. A significant amount of water uptake in the proximal tubule is dependent on sodium uptake by the Na/H antiports present in their luminal membrane
C. Aquaporine-I (water channels) are abundantly present in the cellular membranes of proximal tubule cells
D. A and C are correct
E. all are correct

9. Choose one correct answer.
A. The resting membrane potential of most body cells is positive inside and negative outside.
B. If the resting membrane potential is made more negative it is called hypopolarization.
C. If membrane potential moves in the positive direction it is called depolarization.
D. If you put both the measuring electrode (e.g., microelectrode) and reference inside of a cell, you will measure a negative voltage.

10. Which of the following is INCORRECT concerning a patient with ventricular tachycardia?
A. It occurs when the heart rate drops to dangerously low levels.
B. Cardiac output can fall to dangerous levels.
C. Arterial blood pressure falls to dangerous levels.
D. It involves impaired ventricular filling.

11. Which of the following will NOT increase aortic systolic blood pressure?
A. Decrease in arterial compliance
B. Decrease in aortic distensibility.
C. Increase in stroke volume.
D. Decrease in ejection velocity.

12. Which of the following is NOT an effect of a positive inotropic agent on the heart?
A. It increases stroke volume.
B. It increases the initial velocity of muscle shortening at all loads.
C. It increases the rate of blood ejection from the heart.
D. It decreases the rate of rise in ventricular blood pressure during systole.

13. Which of the following is NOT affected by the preload in the heart muscle?
A. End systolic volume
B. End diastolic volume
C. Stroke Volume
D. Ejection fraction
E. Cardiac output

Answers
1. Correct Answer: A
2. Correct Answer: B
3. Correct Answer: B
4. Correct Answer: B
5. Correct Answer: E
6. Correct Answer: E
7. Correct Answer: E
8. Correct Answer: E
9. Correct Answer: C
10. Correct Answer: A
11. Correct Answer: D
12. Correct Answer: D
13. Correct Answer: A
Coagulopathy in critically ill patients is common and of multifactorial origin (Fig.1). Coagulopathy associated risk of bleeding and the use of allogenic blood products are independent risk factors for morbidity and mortality in such patients. Prompt and correct identification of the underlying causes of these coagulation abnormalities is required since each coagulation abnormality necessitates a different therapeutic approach.

Hemostasis is a joint function of platelet activation to form a platelet plug and coagulation cascade leading to clot formation. Traditionally, this function is measured using conventional tests, such as platelet number and function, activated partial thromboplastin time (aPTT), prothrombin time (PT), thrombin time, fibrinogen levels and fibrin degradation products (FDP). These tests analyze different aspects of the coagulation cascade but do not provide information on the kinetics of clot formation and important coagulation defects e.g., reduced clot stability, platelet dysfunction, and hyperfibrinolysis. In the setting of rapidly changing coagulation-dynamics during management of critically ill patients, the delay in obtaining these test results from the laboratory is a limiting factor in guiding appropriate blood component transfusion.

Point-of-care (POC) coagulation monitoring devices assessing the viscoelastic properties of whole blood, i.e., thromboelastography (TEG®), rotation thromboelastometry (ROTEM®), and Sonoclot® analysis have the ability to overcome several limitations of routine coagulation tests (3, 4).

**Normal hemostatic mechanism**

A delicate balance of platelet aggregation, fibrin clot formation and fibrinolysis is crucial for the normal haemostasis. Endothelial cell damage stimulates platelet adhesion to the sub-endothelial matrix facilitated by von Willebrand Factor (vWF), and subsequently aggregation and platelet plug formation.

Endothelial injury exposes tissue factor which activates factor VII and thereafter the coagulation cascade leading to thrombin (FIIa) and fibrin clot formation. Endogenous activation of anticoagulants occurs simultaneously to prevent diffuse thrombosis. Thrombin-thrombomodulin complex activates protein C, which along with protein S, inhibits thrombin generation. Antithrombin III produced by liver inactivates factors IXa, Xa, XIa. Fibrinolysis acts in concert with the prothrombotic pathway. Plasminogen is activated by tissue plasminogen activator (tPA) to form plasmin which lyses fibrin to fibrin degradation products (FDPs). Plasminogen activator inhibitor (PAI) and α2-antiplasmin serve as regulatory agents to limit fibrinolysis. All pro- and antifibrinolytic proteins except tPA are synthesized by the liver.

**Thromboelastography and Other Viskoelastic Hemostatic Assays (VHA)**

The efficiency of blood coagulation is evaluated...
by conducting tests which utilize the viscoelastic principle and are as follows:-
(a) Thromboelastography (TEG®; Haemonetics Corporation, Braintree, MA, USA)
(b) Rotational thromboelastometry (ROTEM®; Tem International GmbH, Munich, Germany)
(c) Sonoclot analysis (Sienco Inc., Arvada, CO).

These tests utilize whole blood and therefore provide insight into both cellular and plasma-based components of coagulation pathway. TEG® and ROTEM® assess the viscoelastic properties of whole blood under low shear conditions and thus provide dynamic information about global haemostatic function from the beginning of clot formation through clot retraction and fibrinolysis.

**Methodology**

TEG® measures the physical properties of the clot using a cylindrical cup that oscillates in 10 second cycles at 4°45’ angle at 37° C temperature (Fig. 2). The sample of blood to be tested is placed in the cup. A pin is suspended in the blood by a torsion wire and is monitored for motion. The torque of the rotation cup is transmitted to the immersed pin only after fibrin strands develop between the pin and inner wall of the cup. As clot begins to lyse and retract the bonds between the pin and clot are broken resulting in decreased movement of the pin. The rotatory movement of the pin is converted to an electrical signal that is displayed as TEG® tracing. Thus, the electric output is directly related to the strength of fibrin platelet bonds.

ROTEM® differs slightly in technical aspects from TEG®. Signal from the pin is transmitted using an optical detector instead of torsion wire. It consists of 4 cylindrical cups and an optical detector system that detects the signal of a pin suspended in blood sample cup (Fig. 3). In ROTEM®, unlike TEG®, the cup is stationary and the pin oscillates. As the blood clots, the pin’s oscillations are reduced which is measured by the deflection angle of a light directed at the pin/wire transduction system. Four channels can be used simultaneously allowing multiple specimens to be sampled. Although TEG® and ROTEM® tracings look similar (Fig. 4); the nomenclature, interpretation and reference ranges are different (Table 1).

**Parameters of Measurement**

Variables measured by the viscoelastic assays are based on the test used and the tracings achieved. The parameters of measurement are utilized to assess the specific coagulation abnormality (Fig 4) (5).

(a) r-time: It represents period of time of latency from start of test to initial fibrin formation. This represents the standard clotting studies. Normal range: 15 to 23 minutes (native blood); 5 to 7 minutes (kaolin activated).

(b) k-time: Represents time taken to achieve a certain level of clot strength (where r-time = time zero) – equates to amplitude 20 mm. Normal range: 5 to 10 minutes (native blood); 1 to 3 minutes (kaolin activated).

c) α-angle: It measures the speed at which fibrin build-up and cross-linking takes place (clot strengthening), hence assesses the rate of clot formation. Normal range: 22° to 38° (native blood); 53° to 67° (kaolin activated).
(d) **Maximum amplitude (MA):** MA is a direct function of the maximum dynamic properties of fibrin and platelet bonding via GPIIb/IIIa and represents the ultimate strength of the fibrin clot, which correlates to platelet function and fibrinogen: 80% platelets; 20% fibrinogen. Normal range: 47 to 58 mm (native blood); 59 to 68 mm (kaolin activated).

(e) **Coagulation index (CI):** A mathematical formula determined by the manufacturer, which takes into account the relative contribution of each of these four values into one equation. It has a predefined value of 0 and ranging from -3 through +3 which represent normal, hypo- or hyper-coagulable state.

(f) **LY 30 & LY 60:** This is the percentage decrease in amplitude 30 minutes post-MA and gives measure of degree of fibrinolysis. Normal range < 7.5% (native blood); < 7.5% (celite-activated) and similarly LY 60 is the percentage decrease in amplitude 60 minutes post-MA.

(g) **A 30 & A 60:** Amplitude at 30 and 60 minutes post –MA.

Figure 4. Typical tracings of viscoelastic point-of-care coagulation devices.

**Table 1: TEG® and ROTEM® variables**

| Time until initial fibrin formation-period to 2 mm amplitude | TEG® (R 4-8 min) | ROTEM® (CT INTEM 137-246 s, EXTEM 42-74 s) | Clinical Relevance |
| Time period for amplitude of tracing to increase from 2 mm to 20 mm | K (1-4 min) | CFT (INTEM 40-100 s, EXTEM 46-148 s) | Measures kinetics of clot formation |
| Angle between tangent to a tracing at 2 mm amplitude and the horizontal line | α (47º–74º) | A (INTEM 71º-82º, EXTEM 46º-148º) | Relates to rapidity of fibrin cross-polymerization |
| Greatest vertical height of tracing-Maximal strength/amplitude (at set time in min) | MA (55-73mm, A30, A60) | MCF (INTEM 52-72mm, EXTEM 49-71mm, A5, A10, A15, A20, A30) | Ultimate strength and stability of fibrin clot, platelet number and function |
| Percent reduction in amplitude at time indicated – Maximal lysis | CL after 30 & 60 min CL30, CL60 | Ly 30, Ly 60 | Clot stability and lysis (Fibrinolysis) |

R: reaction time, CT: clotting time, CFT: clot formation time, MA: maximum amplitude, MCF: maximum clot firmness, CL: clot lysis, Ly: lysis

**Cell Based Model & Viscoelastic Hemostasis Assay’s**

According to the cell based model, hemostasis is described in three phases namely *Initiation, Amplification and Propagation*. During initiation, circulating activated coagulation factor (F) VII (FVIIa) forms a complex with exposed tissue factor (TF) on injured endothelium, which in the amplification stage generates a small amount of thrombin that mainly activates the platelets. In the propagation phase the coagulation factors assemble on the activated platelets generating large amounts of thrombin (“thrombin burst”). The rate and peak of thrombin generation influences the clot structure and stability, by activating FXIII to FXIIIa, which cross links fibrinogen and further stabilizes the clot. Furthermore, thrombin activates TAFI to TAFIa which prevents lysis of fibrin clot. The three different phases of cell based hemostasis resulting in clot formation are reflected by the VHA. Scanning electron microscopy demonstrated that the R (TEG)/CT (ROTEM) correspond to the initiation...
phase whereas K (TEG)/CFT (ROTEM) reflects amplification phase. The thrombin burst is reflected by the α-angle (TEG/ROTEM), and determines the clot strength and stability. The whole blood based VHA, therefore, reveals the contribution of all circulating plasmatic and cellular components, in their actual concentrations, to clot formation. The ability of VHA to reflect thrombin generation has profound clinical utility because coagulation factor deficiencies secondary to massive bleeding, dilution, consumption and thrombocytopenia/pathy among others result in impaired thrombin generation and impaired clot strength MA (TEG), MCF (ROTEM).

**Test Modifications of TEG® / ROTEM®**

The standard TEG® [KaoTEG] uses kaolin as a contact activator. For monitoring coagulopathy in presence of endogenous/exogenous heparinoids a modification with the use of heparinase called hepTEG is used. The heparinase neutralizes the effects of heparin all together. This is useful during long pump runs, deep hypothermia and use of ventricular assist devices or complicated major vascular cases such as thoraco-abdominal aneurysm. The test will also help in deciding if more protamine is required to fully reverse heparin effect. Rapid TEG is another modification which uses tissue factor in addition to kaolin activator for coagulation. It gives rapid results on clot strength but is lacking as regards kinetics of clot formation. The various modifications of ROTEM® with their characteristics are described in Table 2.

### Table 2: Modifications of ROTEM®

<table>
<thead>
<tr>
<th>Modification</th>
<th>Activator / Inhibitor</th>
<th>Parameter Measured</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXTEM</td>
<td>Uses tissue factor as an activator (comparable to PT)</td>
<td>MCF&lt;sub&gt;extem&lt;/sub&gt;</td>
<td>Maximum clot strength &amp; stability correlate with platelet count and fibrinogen level</td>
</tr>
<tr>
<td>INTEM</td>
<td>Ellagic acid contact activator (comparable to aPTT)</td>
<td>MCF&lt;sub&gt;inm&lt;/sub&gt;</td>
<td>General coagulation status</td>
</tr>
</tbody>
</table>

### Sonoclot® Analysis

The Sonoclot analyzer is a POC coagulation device introduced in 1975 by von Kaulla et al. (10). It uses different clotting activators/inhibitors (celite, kaolin, glass-beads, heparinase) contained in a cuvette into which the test sample is added (11). A hollow plastic probe mounted on a transducer is immersed into the sample. The change in impedance to the vertical oscillations of the probe following clot initiation is graphically displayed as the Sonoclot signature and also determines the activated clotting time (ACT), clot rate (CR) and the platelet function (PF) (Fig 4). The ACT is the time from addition of test sample till first upward deflection of the Sonoclot tracing, reflecting the initiation of clot formation. The CR denotes the maximum slope of the Sonoclot trace and reflects the kinetics of clot formation. It can be used to measure the fibrinogen levels. The PF analyses the platelet function in terms of clot retraction and amplitude of peak of the Sonoclot signature. The PF ranges from none (no retraction, flat peak) to 5 (faster clot retraction, sharp peak in the signature trace). Depending on the coagulation activator/inhibitor used, Sonoclot has been used for various applications, e.g. Son ACT (celite-based) and k-ACT (kaolin-based) for heparin management, gb-ACT+...
(glass beads) for overall coagulation and platelet function assessment and HgbACT+ (glass beads and heparinase) for overall coagulation assessment in the presence of heparin (Table 3).

Table 3. Sonoclot modifications

<table>
<thead>
<tr>
<th>Sonoclot® Assay</th>
<th>SonACT</th>
<th>kACT</th>
<th>gbACT+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activated Clotting Time (ACT)</td>
<td>85-145 s</td>
<td>94-178 s</td>
<td>119-195 s</td>
</tr>
<tr>
<td>Clot Rate (CR)</td>
<td>15-45 U/min</td>
<td>15-33 U/min</td>
<td>7-23 U/min</td>
</tr>
</tbody>
</table>

Viscoelastic Hemostatic Assays in Clinical Practice

While other conventional tests evaluate the coagulation pathway until the formation of the first fibrin strands, the VHA continuously evaluates clot formation, its strength, and platelet function until eventual clot lysis or retraction. Hence, it is dynamic and gives information on the entire coagulation process and not just an isolated part. Being a POC test with rapid results it facilitates timely intervention. Also being computerized, it is easy to use and results can be recorded and stored. It accurately pinpoints the cause of bleeding and helps in predicting how specific correction would work and minimize the need for blood transfusion. The coagulation status of patients is assessed in whole blood, allowing the plasmatic coagulation system to interact with platelets and red cells, and thereby providing useful additional information on platelet function. The VHA have been analyzed and are helpful in various clinical settings. Tracings obtained during TEG in different clinical conditions are depicted in figure 5, while an algorithm based on various test results has been suggested for management of patients with abnormal hemostasis (Fig. 6).

Cardiac Surgery

Coagulation management of patients undergoing cardiac surgery is complex because of a balance between anticoagulation for cardiopulmonary bypass (CPB) and hemostasis after CPB. The main reasons for bleeding in cardiac surgery patients can be classified under four broad headings of preoperative factors, CPB factors, post-CPB factors and surgical bleeding. Preoperative factors include antiplatelet drugs, patients on anticoagulants and pre-existing clotting or platelet abnormalities. Intraoperative factors might be decreased platelet count or heparin effect. Postoperatively factors could be reversal of heparin, nonfunctional platelets or fibrinolysis. TEG helps in pinpointing the specific problem and also predicting how treatment would work, thereby reducing blood transfusion in cardiac surgery. The institution of transfusion algorithms based on TEG/ROTEM parameters has been demonstrated to reduce transfusion requirements in adults and children undergoing cardiac surgery13,14.

Hepatic Surgery and Orthotopic Liver Transplant (OLT)

One of the first clinical applications of TEG® was in the hemostatic management of OLT15. The TEG® is a unique test of clot strength perfectly suited to the changes during liver transplantation. The use of TEG® in liver transplantation is focused on monitoring coagulation and management of blood products transfused rather than identification of patients at risk.

Hypercoagulability, Thrombosis, and Other Clinical situations

Major surgery has been shown to induce a hypercoagulable state in the post-operative period, and this hypercoagulability has been implicated in the pathogenesis of postoperative thrombotic complications. Identifying hypercoagulability with conventional tests is difficult unless the fibrinogen concentration or platelet count is markedly increased. However, hypercoagulability is readily diagnosed by VHA’s. Hypercoagulability is diagnosed if R/CT time is short and the MA/MCF is increased16.

Trauma

In major trauma patients, coagulopathy has been shown to be present in approximately 30% of admitted patients, accounting for up to 40% of all trauma-related deaths17. Coagulation factor deficiency (dilution) is the primary cause of coagulopathy in massive transfusion. The level of fibrinogen typically falls below the lower reference range after 150% blood volume loss,
followed by a decrease in other coagulation factors to 25% activity after 200% blood loss. The use of these POC viscoelastic devices has been shown to reduce blood product requirements in these patients.

Severe Sepsis
Because hemostatic alterations are a common early event in patients with severe sepsis, and commonly used sepsis biomarkers, such as procalcitonin and interleukin (IL)-6, may also increase in patients with trauma or surgery even without infection, thromboelastometry variables may have potential as early biomarkers of sepsis in critically ill patients. Adamzik and colleagues demonstrated that the thromboelastometry-derived lysis index was a more reliable biomarker of severe sepsis than were procalcitonin, IL-6, and C-reactive protein.

Antiplatelet Therapy and Platelet Function
Antiplatelet therapy is increasingly being prescribed for primary and secondary prevention of cardiovascular disease to decrease the incidence of acute cerebral and cardiovascular events. Because platelets play a key role in overall coagulation, the assessment of the PF (more than their number) is critical in the perioperative setting. The MA/MCF from TEG/ROTEM reflects overall PF and fibrinogen levels. The Sonoclot Analyzer has also been shown to reliably detect pharmacological GPIIb/IIIa inhibition. To obtain reliable results for PF, cuvettes containing glass beads for specific platelet activation (gbACT+) should be used.

Fig. 5: Examples of qualitative TEG traces for interpretation.
Normal: R, K, MA, Angle normal, Anticoagulants/Hemophilia: R & K prolonged, MA & Angle decreased, Platelet blockers: R normal; K prolonged; MA decreased, Fibrinolysis: R normal; MA continuous decrease; Ly 30> 7.5 %; LY 60 > 15 %, Hypercoagulation: R & K decreased, MA & Angle increased, DIC: Stage 1 – Hypercoagulation; Stage 2 – Antiocoagulation

Fig. 6: Suggested guidance for hemostasis management using a TEG-based protocol
Limitations of VHA
The main limitation of this technique is that it has never been formally validated or standardized by hematologists in comparison to the conventional tests. Delay in processing can alter the results. Hypercoagulability cannot be measured accurately by the instrument and even a modified thromboelastograph should not be used alone to express a hypercoagulable state. To ensure optimal accuracy and performance, standardized procedures for blood sampling and handling, strict quality controls and trained personnel are required. The Sonoclot analyzer has been criticized because its results were influenced by age, sex, and platelet count. Additionally, studies showed poor reproducibility of some of the measured variables, especially CR and PF. All these factors have to be considered when interpreting results in the literature and have to be known and standardized when running tests in a single center.

Conclusion
Viscoelastic POC coagulation analyzers are being used in certain clinical situations known for their inherent risk of coagulation disorders, especially in the management of patients undergoing cardiac and liver surgery. Furthermore, they provide useful information in a large variety of clinical scenarios, e.g., massive hemorrhage, assessment of hypo- and hypercoagulable states and monitoring of pharmacological treatment with anti- and procoagulant drugs. The advantage of these techniques is that they have the potential to measure the entire clotting process, starting with fibrin formation and continue through to clot retraction and lysis at the bedside, with minimal time delays. Improvements such as easier handling of blood samples, full automation, simultaneous testing with multiple activators, integrated analyzing software, and high robustness of the devices, would make viscoelastic POC coagulation analyzers highly desirable in future. Finally, prospective studies are urgently needed to analyze whether hemostatic therapy based on POC testing can provide significant benefits with respect to clinical outcomes for our critical care patients.

References
Prearrest Care

Effectiveness of medical emergency teams or rapid response teams to improve outcomes

Effectiveness of a pediatric early warning score (PEWS) to improve outcomes

Restrictive volume of isotonic crystalloid for resuscitation from septic shock

Use of atropine as a premedication in infants and children requiring emergency tracheal intubation

Treatment for infants and children with myocarditis or dilated cardiomyopathy and impending cardiac arrest

Intra-arrest Care

Effectiveness of extracorporeal membrane oxygenation (ECMO) resuscitation compared to standard resuscitation without ECMO

Targeting a specific end-tidal CO2 (ETCO2) threshold to improve chest compression technique

Reliability of intra-arrest prognostic factors to predict outcome

Use of invasive hemodynamic monitoring during CPR to titrate to a specific systolic/diastolic blood pressure to improve outcomes.

Effectiveness of NO vasopressor compared with ANY vasopressors for resuscitation from cardiac arrest

Use of amiodarone compared with lidocaine for shock-refractory VF or pVT

Optimal energy dose for defibrillation

Postarrest Care

Use of targeted temperature management to improve outcomes

Use of a targeted Pao2 strategy to improve outcomes

Use of a specific Paco2 target to improve outcomes

Use of parenteral fluids and inotropes and/or vasopressors to maintain targeted measures of perfusion such as blood pressure to improve outcomes

Use of electroencephalograms (EEGs) to accurately predict outcomes

Use of any specific post–cardiac arrest factors to accurately predict outcomes

Prearrest Care Updates

Medical Emergency Team/Rapid Response Team

Medical emergency team or rapid response team activation by caregivers or parents ideally occurs as a response to changes noted in a patient’s condition and may prevent cardiac or respiratory arrest. Several variables, including the composition of the team, the type of patient, the hospital setting, and the confounder of a wider “system benefit,” further complicate objective analyses. Observational data have been contradictory and have not consistently shown a decreased incidence of cardiac and/or respiratory arrest outside of the ICU setting.1-3 The data addressing effects on hospital mortality were inconclusive.1-8

2015 Recommendation—Updated

Pediatric medical emergency team/rapid response team systems may be considered in facilities where children with high-risk illnesses are cared for on general in-patient units (Class IIb, LOE C-LD).

Pediatric Early Warning Scores (PEWS)

In-hospital pediatric cardiac or respiratory arrest can potentially be averted by early recognition of and intervention for the deteriorating patient. The use of scoring systems might help to identify such patients sufficiently early so as to enable effective intervention. There is no evidence that the use of PEWS outside of the pediatric ICU setting reduces hospital mortality. In 1 observational study, PEWS use was associated with a reduction in cardiac arrest rate when used in a single hospital with an established medical emergency team system.9

2015 Recommendation—New

The use of PEWS may be considered, but its effectiveness in the in-hospital setting is not well

A synopsis by ILCOR Pediatric Task Force

Pediatric Advanced Life Support (PALS) 2015 Update

(Adapted from American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care)
established (Class IIb, LOE C-LD).

**Fluid Resuscitation in Septic Shock**

This update regarding intravenous fluid resuscitation in infants and children in septic shock in all settings addressed 2 specific therapeutic elements: (1) Withholding the use of bolus fluids was compared with the use of bolus fluids, and (2) noncrystalloid was compared with crystalloid fluids.

Early and rapid administration of intravenous fluid to reverse decompensated shock, and to prevent progression from compensated to decompensated shock, has been widely accepted based on limited observational studies. Mortality from pediatric sepsis has declined in recent years, during which guidelines and publications have emphasized the role of early rapid fluid administration (along with early antibiotic and vasopressor therapy, and careful cardiovascular monitoring) in treating septic shock. Since the 2010 Guidelines, a large randomized controlled trial of fluid resuscitation in pediatric severe febrile illness in a resource-limited setting found intravenous fluid boluses to be harmful. This new information, contradicting long-held beliefs and practices, prompted careful analysis of the effect of fluid resuscitation on many outcomes in specific infectious illnesses.

Specific infection-related shock states appear to behave differently with respect to fluid bolus therapy. Evidence was not considered to be specific to a particular setting, after determining that “resource-limited setting” is difficult to define and can vary greatly even within individual health systems and small geographic regions.

The evidence regarding the impact of restricting fluid boluses during resuscitation on outcomes in pediatric septic shock is summarized in Figure 1. There were no studies for many specific combinations of presenting illness and outcome. In the majority of scenarios, there was no benefit to restricting fluid boluses during resuscitation.

The most important exception is that in 1 large study, restriction of fluid boluses conveyed a benefit for survival to both 48 hours and 4 weeks after presentation. This study was conducted in sub-Saharan Africa, and inclusion criteria were severe febrile illness complicated by impaired consciousness (prostration or coma), respiratory distress (increased work of breathing), or both, and with impaired perfusion, as evidenced by 1 or more of the following: a capillary refill time of 3 or more seconds, lower limb temperature gradient, weak radial-pulse volume, or severe tachycardia. In this study, administration of 20

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Figure 1. Evidence for the use of restrictive volume of intravenous fluid resuscitation, compared with unrestricted volume, by presenting illness and outcome. Benefit indicates that studies show a benefit to restricting fluid volume, No Benefit indicates that there is no benefit to restricting fluid volume, and Harm indicates that there is harm associated with restricting fluid volume. No Studies Available indicates no studies are available for a particular illness/outcome combination.
mL/kg or 40 mL/kg in the first hour was associated with decreased survival compared with the use of maintenance fluids alone. Therefore, it appears that in this specific patient population, where critical care resources including inotropic and mechanical ventilator support were limited, bolus fluid therapy resulted in higher mortality.

The use of noncrystalloid fluid was compared with crystalloid fluid for the same diseases and outcomes listed in the preceding paragraph. Evidence is summarized in Figure 2. In most scenarios, there was no benefit to noncrystalloids over crystalloids. In patients with Dengue shock, a benefit was conferred in using noncrystalloid compared with crystalloid fluid for the outcome of time to resolution of shock.

2015 Recommendations—New

Administration of an initial fluid bolus of 20 mL/kg to infants and children with shock is reasonable, including those with conditions such as severe sepsis (Class IIa LOE C-LD), severe malaria and Dengue (Class IIb, LOE B-R). When caring for children with severe febrile illness (such as those included in the FEAST trial) in settings with limited access to critical care resources (ie, mechanical ventilation and inotropic support), administration of bolus intravenous fluids should be undertaken with extreme caution because it may be harmful (Class IIb, LOE B-R). Providers should reassess the patient after every fluid bolus (Class I, LOE C-EK).

Either isotonic crystalloids or colloids can be effective as the initial fluid choice for resuscitation (Class IIa, LOE B-R).

This recommendation takes into consideration the important work of Maitland et al, which found that fluid boluses as part of resuscitation are not safe for all patients in all settings. This study showed that the use of fluid boluses as part of resuscitation increased mortality in a specific population in a resource-
limited setting, without access to some critical care interventions such as mechanical ventilation and inotrope support.

The spirit of this recommendation is a continued emphasis on fluid resuscitation for both compensated (detected by physical examination) and decompensated (hypotensive) septic shock. Moreover, emphasis is also placed on the use of individualized patient evaluation before the administration of intravenous fluid boluses, including physical examination by a clinician and frequent reassessment to determine the appropriate volume of fluid resuscitation. The clinician should also integrate clinical signs with patient and locality-specific information about prevalent diseases, vulnerabilities (such as severe anemia and malnutrition), and available critical care resources.

**Atropine for Premedication During Emergency Intubation**

Bradycardia commonly occurs during emergency pediatric intubation, resulting from hypoxia/ischemia, as a vagal response to laryngoscopy, as a reflex response to positive pressure ventilation, or as a pharmacologic effect of some drugs (eg, succinylcholine or fentanyl). Practitioners have often tried to blunt this bradycardia with prophylactic premedication with atropine. The evidence regarding the use of atropine during emergency intubation has largely been observational, including extrapolation from experience with elective intubation in the operating suite. More recent in-hospital literature involves larger case series of critically ill neonates, infants, and children undergoing emergency intubation.²⁰-²²

There is no evidence that preintubation use of atropine improves survival or prevents cardiac arrest in infants and children. Observational data suggest that it increases the likelihood of survival to ICU discharge in children older than 28 days.²⁰ Evidence is conflicting as to whether preintubation atropine administration reduces the incidence of arrhythmias or postintubation shock.²¹,²²

In past Guidelines, a minimum atropine dose of 0.1 mg IV was recommended after a report of paradoxical bradycardia observed in very small infants who received very low atropine doses.³⁶ However, in 2 of the most recent case series cited above, preintubation doses of 0.02 mg/kg, with no minimum dose, were shown to be effective.²⁰,²¹

**2015 Recommendations—New**

The available evidence does not support the routine use of atropine preintubation of critically ill infants and children. It may be reasonable for practitioners to use atropine as a premedication in specific emergency intubations when there is higher risk of bradycardia (eg, when giving succinylcholine as a neuromuscular blocker to facilitate intubation) (Class IIb, LOE C-LD). A dose of 0.02 mg/kg of atropine with no minimum dose may be considered when atropine is used as a premedication for emergency intubation (Class IIb, LOE C-LD). This new recommendation applies only to the use of atropine as a premedication for infants and children during emergency intubation.

**Prearrest Care of Infants and Children With Dilated Cardiomyopathy or Myocarditis**

Optimal care of a critically ill infant or child with dilated cardiomyopathy or myocarditis should avert cardiac arrest. While significant global experience exists with the care of these patients, the evidence base is limited. The ILCOR systematic review ultimately restricted its analysis to patients with myocarditis and did not include the use of ventricular assist devices.

**2015 Recommendation—New**

Venoarterial ECMO use may be considered in patients with acute fulminant myocarditis who are at high risk of imminent cardiac arrest (Class IIb, LOE C-EO). Optimal outcomes from ECMO are achieved in settings with existing ECMO protocols, expertise, and equipment.

**Intra-arrest Care Updates**

**Extracorporeal CPR for In-Hospital Pediatric Cardiac Arrest**

The 2010 AHA PALS Guidelines suggested the use of ECMO when dealing with pediatric cardiac arrest refractory to conventional interventions and when managing a reversible underlying disease process. Pediatric OHCA was not considered for the
2015 ILCOR systematic review. Evidence from 4 observational studies of pediatric IHCA has shown no overall benefit to the use of CPR with ECMO (ECPR) compared to CPR without ECMO.23-26 Observational data from a registry of pediatric IHCA showed improved survival to hospital discharge with the use of ECPR in patients with surgical cardiac diagnoses.27 For children with underlying cardiac disease, when ECPR is initiated in a critical care setting, long-term survival has been reported even after more than 50 minutes of conventional CPR.28 When ECPR is used during cardiac arrest, the outcome for children with underlying cardiac disease is better than for those with noncardiac disease.29

2015 Recommendation—New
ECPR may be considered for pediatric patients with cardiac diagnoses who have IHCA in settings with existing ECMO protocols, expertise, and equipment (Class IIb, LOE C-LD).

End-Tidal CO2 Monitoring to Guide CPR Quality
High-quality CPR is associated with improved outcomes after cardiac arrest. Animal data support a direct association between ETCO2 and cardiac output. Capnography is used during pediatric cardiac arrest to monitor for ROSC as well as CPR quality. The 2010 Guidelines recommended that if the partial pressure of ETCO2 is consistently less than 15 mm Hg, efforts should focus on improving CPR quality, particularly improving chest compressions and ensuring that the victim does not receive excessive ventilation.

2015 Recommendation—New
ETCO2 monitoring may be considered to evaluate the quality of chest compressions, but specific values to guide therapy have not been established in children (Class IIb, LOE C-LD).

Intra-arrest Prognostic Factors for Cardiac Arrest
Accurate and reliable prognostication during pediatric cardiac arrest would allow termination of CPR in patients where CPR is futile, while encouraging continued CPR in patients with a potential for good recovery.

2015 Recommendation—New
Multiple variables should be used when attempting to prognosticate outcomes during cardiac arrest (Class I, LOE C-LD). Although there are factors associated with better or worse outcomes, no single factor studied predicts outcome with sufficient accuracy to recommend termination or continuation of CPR.

Invasive Hemodynamic Monitoring During CPR
Children often have cardiac arrests in settings where invasive hemodynamic monitoring already exists or is rapidly obtained. If a patient has an indwelling arterial catheter, the waveform can be used as feedback to evaluate chest compressions.

2015 Recommendation—New
For patients with invasive hemodynamic monitoring in place at the time of cardiac arrest, it may be reasonable for rescuers to use blood pressure to guide CPR quality (Class IIb, LOE C-EO). Specific target values for blood pressure during CPR have not been established in children.

Vasopressors During Cardiac Arrest
During cardiac arrest, vasopressors are used to restore spontaneous circulation by optimizing coronary perfusion and to help maintain cerebral perfusion. However, they also cause intense vasoconstriction and increase myocardial oxygen consumption, which might be detrimental. There are no pediatric studies that demonstrate the effectiveness of any vasopressors (epinephrine, or combination of vasopressors) in cardiac arrest. Two pediatric observational out-of-hospital studies30,31 had too many confounders to determine if vasopressors were beneficial. One adult OHCA randomized controlled trial32 showed epinephrine use was associated with increased ROSC and survival to hospital admission but no improvement in survival to hospital discharge.

2015 Recommendation—New
It is reasonable to administer epinephrine in pediatric cardiac arrest (Class IIa, LOE C-LD).

Amiodarone and Lidocaine for Shock-Refractory VF and pVT
The 2005 and 2010 Guidelines recommended administering amiodarone in preference to lidocaine for the management of VF or pVT. This recommendation was based predominantly on pediatric case series or extrapolation from adult
studies that used short-term outcomes.

2015 Recommendation—New
For shock-refractory VF or pVT, either amiodarone or lidocaine may be used (Class IIb, LOE C-LD). The Pediatric Cardiac Arrest Algorithm (Figure 3) reflects this change.

Energy Doses for Defibrillation
The 2015 ILCOR systematic review addressed the dose of energy for pediatric manual defibrillation during cardiac arrest. Neither the energy dose specifically related to automated external defibrillators, nor the energy dose for cardioversion was evaluated in this evidence review.

2015 Recommendations—Updated
It is reasonable to use an initial dose of 2 to 4 J/kg of monophasic or biphasic energy for defibrillation (Class IIa, LOE C-LD), but for ease of teaching, an initial dose of 2 J/kg may be considered (Class IIb, LOE C-EO). For refractory VF, it is reasonable to increase the dose to 4 J/kg (Class IIa, LOE C-LD). For subsequent energy levels, a dose of 4 J/kg may be reasonable and higher energy levels may be considered, though not to exceed 10 J/kg or the adult maximum dose (Class IIb, LOE C-LD).
Postarrest Care Updates

Post–Cardiac Arrest Temperature Management

Data suggest that fever after pediatric cardiac arrest is common and is associated with poor outcomes. The 2010 AHA PALS Guidelines suggested a role for targeted temperature management after pediatric cardiac arrest (fever control for all patients, therapeutic hypothermia for some patients), but the recommendations were based predominantly on extrapolation from adult and asphyxiated newborn data.

2015 Recommendations—New

For infants and children remaining comatose after OHCA, it is reasonable either to maintain 5 days of continuous normothermia (36°C to 37.5°C) or to maintain 2 days of initial continuous hypothermia (32°C to 34°C) followed by 3 days of continuous normothermia (Class IIa, LOE B-R). Continuous measurement of temperature during this time period is recommended (Class I, LOE B-NR).

For infants and children remaining comatose after IHCA, there is insufficient evidence to recommend cooling over normothermia. Fever (temperature 38°C or higher) should be aggressively treated after ROSC (Class I, LOE B-NR).

Post–Cardiac Arrest Oxygenation

Animal studies suggest that elevated levels of tissue Po2 after ROSC (hyperoxia) contribute to oxidative stress that may potentiate the postresuscitation syndrome, while some adult studies show associations between hyperoxemia and increased mortality. Three small observational studies of pediatric IHCA and OHCA survivors did not show an association between elevated Pao2 and outcome. In a larger observational study of 1427 pediatric IHCA and OHCA victims who survived to pediatric ICU admission, after adjustment of confounders, the presence of normoxemia (defined as a Pao2 60 mm Hg or greater and less than 300 mm Hg) when compared with hyperoxemia (Pao2 greater than 300 mm Hg) after ROSC was associated with improved survival to pediatric ICU discharge.

2015 Recommendations—New

It is reasonable for practitioners to target a Pao2 after ROSC that is appropriate to the specific patient condition, and limit exposure to severe hypercapnia or hypocapnia (Class IIb, LOE C-LD).

Post–Cardiac Arrest Paco2

Cerebral vascular autoregulation may be abnormal after ROSC. Adult data show an association between post-ROSC hypocapnia and worse patient outcomes. In other types of pediatric brain injury, hypocapnia is associated with worse clinical outcomes. There were no studies in children after cardiac arrest specifically comparing ventilation with a predetermined Paco2 target. One small observational study of both pediatric IHCA and OHCA demonstrated no association between hypercapnia (Paco2 greater than 50 mm Hg) or hypocapnia (Paco2 less than 30 mm Hg) and outcome. However, in an observational study of pediatric IHCA, hypercapnia (Paco2 50 mm Hg or greater) was associated with worse survival to hospital discharge.

2015 Recommendation—New

It is reasonable for practitioners to target a Paco2 after ROSC that is appropriate to the specific patient condition, and limit exposure to severe hypercapnia or hypocapnia (Class IIb, LOE C-LD).

Post–Cardiac Arrest Fluids and Inotropes

Myocardial dysfunction and vascular instability are common after resuscitation from cardiac arrest. Three small observational studies involving pediatric IHCA and OHCA demonstrated worse survival to hospital discharge when children were exposed to post-ROSC hypotension. One of these studies associated post-ROSC hypotension (defined as a systolic blood pressure less than fifth percentile for age) after IHCA with lower likelihood of survival to discharge with favorable neurologic outcome.
There are no studies evaluating the benefit of specific vasoactive agents after ROSC in infants and children.  

2015 Recommendations—New  
After ROSC, we recommend that parenteral fluids and/or inotropes or vasoactive drugs be used to maintain a systolic blood pressure greater than fifth percentile for age (Class I, LOE C-LD). When appropriate resources are available, continuous arterial pressure monitoring is recommended to identify and treat hypotension (Class I, LOE C-EO).

Postresuscitation Use of EEG for Prognosis  
Early and reliable prognostication of neurologic outcome in pediatric survivors of cardiac arrest is essential to enable effective planning and family support (whether it be to continue or discontinue life-sustaining therapy). Observational data from 2 small pediatric studies showed that a continuous and reactive tracing on an EEG performed in the first 7 days after cardiac arrest was associated with a significantly higher likelihood of good neurologic outcome at hospital discharge, while an EEG demonstrating a discontinuous or isoelectric tracing was associated with a poorer neurologic outcome at hospital discharge. There are no data correlating EEG findings with neurologic outcome after hospital discharge.  

2015 Recommendation—New  
EEGs performed within the first 7 days after pediatric cardiac arrest may be considered in prognosticating neurologic outcome at the time of hospital discharge (Class IIb, LOE C-LD) but should not be used as the sole criterion.

Predictive Factors After Cardiac Arrest  
Several post-ROSC factors have been studied as possible predictors of survival and neurologic outcome after pediatric cardiac arrest. These include pupillary responses, the presence of hypotension, serum neurologic biomarkers, and serum lactate. Four observational studies supported the use of pupillary reactivity at 12 to 24 hours after cardiac arrest in predicting survival to discharge, while 1 observational study found that reactive pupils 24 hours after cardiac arrest were associated with improved survival at 180 days with favorable neurologic outcome.  

Several serum biomarkers of neurologic injury have been considered for their prognostic value. Two small observational studies found that lower neuron-specific enolase and S100B serum levels after arrest were associated with improved survival to hospital discharge and with improved survival with favorable neurologic outcome.

One observational study found that children with lower lactate levels in the first 12 hours after arrest had an improved survival to hospital discharge.  

2015 Recommendation—New  
The reliability of any 1 variable for prognostication in children after cardiac arrest has not been established. Practitioners should consider multiple factors when predicting outcomes in infants and children who achieve ROSC after cardiac arrest (Class I, LOE C-LD).

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Pediatric Basic Life Support, Pediatric Advanced Life Support and Neonatal Resuscitation 2015

Pediatric Basic Life Support and Cardiopulmonary Resuscitation Quality

The 2015 Guidelines Update for pediatric BLS concentrated on modifications in the algorithms for lone- and 2-rescuer CPR, initial actions of rescuers, and CPR quality process measures. Algorithms for 1- and 2-person healthcare provider CPR have been separated to better guide rescuers through the initial stages of resuscitation. In an era where handheld cellular telephones with speakers are common, this technology can allow a single rescuer to activate the emergency response system while beginning CPR. Healthcare providers should perform an assessment of breathing and pulse check simultaneously, to minimize delays in starting CPR if the child is unresponsive with no breathing or only gasping.

Significant New and Updated Recommendations

The 3 major CPR process characteristics that were evaluated included C-A-B (Compressions, Airway, Breathing) versus A-B-C (Airway, Breathing, Compressions), compression-only CPR, and compression depth and rate. No major changes were made for the 2015 Guidelines Update; however, new concepts in CPR delivery were examined for children. Because of the limited amount and quality of the data, it may be reasonable to maintain the sequence from the 2010 Guidelines by initiating CPR with C-A-B over A-B-C (Class IIb, LOE C-EO). There are no pediatric human studies to evaluate C-A-B versus A-B-C, but manikin studies do demonstrate a shorter time to first chest compression. This recommendation was made to simplify training, provide consistency for teaching rescuers of adults and children, and hopefully increase the number of victims who receive bystander CPR.

Compression depth of at least one third of the anterior-posterior diameter, approximately 1.5 inches (4 cm) for infants and approximately 2 inches (5 cm) for children, was affirmed (Updated). The Class of Recommendation was downgraded from Class I to Class IIa, primarily based on the rigor of the evidence evaluation. There are limited clinical data on the effect of compression depth on resuscitation outcomes, but 2 clinical studies suggest that compression depth is also associated with survival.

Compression rate was not reviewed because of insufficient evidence, and we recommend that rescuers use the adult rate of 100 to 120/min (Updated). The asphyxial nature of the majority of pediatric cardiac arrests necessitates ventilation as part of effective CPR, and 2 large database studies documented worse 30-day outcomes with compression-only CPR compared with conventional CPR. For this reason, conventional CPR (chest compressions and rescue breaths) is a Class I recommendation (LOE B-NR) for children. However, because compression-only CPR is effective in patients with a primary cardiac event, if rescuers are unwilling or unable to deliver breaths, we recommend rescuers perform compression-only CPR for infants and children in cardiac arrest (Class I, LOE B-NR). Conventional CPR (chest compressions and rescue breaths) is a Class I recommendation (LOE B-NR).

Knowledge Gaps

Much of the data supporting pediatric BLS is primarily extrapolated from studies in adults. Multicenter pediatric studies from both in-hospital and out-of-hospital arrest are needed to optimize outcomes for children.

More knowledge is needed about the optimal sequence, feedback techniques and devices, and effect of different surfaces on CPR delivery in children.

Pediatric Advanced Life Support

Significant New and Updated Recommendations

The following are the most important changes and reinforcements to recommendations made in the 2010 Guidelines:
BLS Healthcare Provider

Pediatric Cardiac Arrest Algorithm for the Single Rescuer—2015 Update

Verify scene safety.

Victim is unresponsive. Shout for nearby help. Activate emergency response system via mobile device (if appropriate).

- Normal breathing, has pulse
- No normal breathing, has pulse

Look for no breathing or only gasping and check pulse (simultaneously). Is pulse definitely felt within 10 seconds?

- No breathing or only gasping, no pulse
- Normal breathing, has pulse

Provide rescue breathing: 1 breath every 3-5 seconds, or about 12-20 breaths/min. • Add compressions if pulse remains <50/min with signs of poor perfusion.
- Activate emergency response system (if not already done) after 2 minutes.
- Continue rescue breathing; check pulse about every 2 minutes. If no pulse, begin CPR (go to “CPR” box).

Witnessed sudden collapse?

Yes

Activate emergency response system (if not already done), and retrieve AED/defibrillator.

No

CPR

1 rescuer: Begin cycles of 30 compressions and 2 breaths. (Use 15:2 ratio if second rescuer arrives.) Use AED as soon as it is available.

After about 2 minutes, if still alone, activate emergency response system and retrieve AED (if not already done).

AED analyzes rhythm. Shockable rhythm?

- Yes, shockable
- No, nonshockable

Give 1 shock. Resume CPR immediately for about 2 minutes (until prompted by AED to allow rhythm check). Continue until ALS providers take over or victim starts to move.

Resume CPR immediately for about 2 minutes (until prompted by AED to allow rhythm check). Continue until ALS providers take over or victim starts to move.

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BLS Healthcare Provider
Pediatric Cardiac Arrest Algorithm for 2 or More Rescuers—2015 Update

Verify scene safety.

Victim is unresponsive. Shout for nearby help. First rescuer remains with victim. Second rescuer activates emergency response system and retrieves AED and emergency equipment.

Normal breathing, has pulse

Look for no breathing or only gasping and check pulse (simultaneously). Is pulse definitely felt within 10 seconds?

No breathing or only gasping, no pulse

Provide rescue breathing: 1 breath every 3-5 seconds, or about 12-20 breaths/min.
- Add compressions if pulse remains <60/min with signs of poor perfusion.
- Activate emergency response system (if not already done) after 2 minutes.
- Continue rescue breathing; check pulse about every 2 minutes. If no pulse, begin CPR (go to "CPR" box).

CPR
First rescuer begins CPR with 30:2 ratio (compressions to breaths). When second rescuer returns, use 15:2 ratio (compressions to breaths). Use AED as soon as it is available.

AED analyzes rhythm. Shockable rhythm?

Yes, shockable

Give 1 shock. Resume CPR immediately for about 2 minutes (until prompted by AED to allow rhythm check). Continue until ALS providers take over or victim starts to move.

No, nonshockable

Resume CPR immediately for about 2 minutes (until prompted by AED to allow rhythm check). Continue until ALS providers take over or victim starts to move.

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There is new evidence that when treating pediatric septic shock in specific settings, the use of restricted volume of isotonic crystalloid leads to improved survival, contrasting with the long-standing belief that all patients benefit from aggressive volume resuscitation. New guidelines suggest a cautious approach to fluid resuscitation, with frequent patient reassessment, to better tailor fluid therapy and supportive care to children with febrile illness.

New literature suggests limited survival benefit to the routine use of atropine as a premedication for emergency tracheal intubation of non-neonates, and that any benefit in preventing arrhythmias is controversial. Recent literature also provides new evidence suggesting there is no minimum dose required for atropine use.

Children in cardiac arrest may benefit from the titration of CPR to blood pressure targets, but this strategy is suggested only if they already have invasive blood pressure monitoring in place.

New evidence suggests that either amiodarone or lidocaine is acceptable for treatment of shock-refractory pediatric ventricular fibrillation and pulseless ventricular tachycardia.

Recent literature supports the need to avoid fever when caring for children remaining unconscious after OHCA (Out of hospital cardiac arrest).

The writing group reviewed a newly published multicenter clinical trial of targeted temperature management that demonstrated that a period of either 2 days of moderate therapeutic hypothermia (32° to 34° C) or the strict maintenance of normothermia (36° to 37.5° C) were equally beneficial. As a result, the writing group feels either of these approaches is appropriate for infants and children remaining comatose after OHCA.

Knowledge Gaps

What is the role of targeted temperature management in the care of children who remain unconscious after in-hospital cardiac arrest?

Does a postarrest bundle of care with specific targets for temperature, oxygenation and ventilation, and hemodynamic parameters improve outcomes after pediatric cardiac arrest?

Does a combination of intra-arrest factors reliably predict successful resuscitation in children with either OHCA or IHCA?

Neonatal Resuscitation

“Neonatal Resuscitation” presents new guidelines for resuscitation of primarily newly born infants transitioning from intrauterine to extratuterine life. The recommendations are also applicable to neonates who have completed newborn transition and require resuscitation during the first weeks after birth.

Much of the neonatal resuscitation guidelines remains unchanged from 2010, but there is increasing focus on umbilical cord management, maintaining a normal temperature after birth, accurate determination of heart rate, optimizing oxygen use during resuscitation, and de-emphasis of routine suctioning for meconium in nonvigorous newborns. The etiology of neonatal arrest is almost always asphyxia, and therefore, establishing effective ventilation remains the most critical step.

Significant New and Updated Recommendations

Umbilical cord management: The 2015 Guidelines Update includes for the first time recommendations regarding umbilical cord management. Until recently, it was common practice to clamp the umbilical cord immediately after birth to facilitate rapid transfer of the baby to the pediatric provider for stabilization. A significant issue with the available evidence is that the published studies enrolled very few babies who were considered to need resuscitation.

There is evidence, primarily in babies who do not require resuscitation, that delayed cord clamping is associated with less intraventricular hemorrhage, higher blood pressure and blood volume, less need for transfusion after birth, and less necrotizing enterocolitis. Delayed cord clamping conferred no benefit on mortality or severe intraventricular...
Neonatal Resuscitation Algorithm—2015 Update

1. Antenatal counseling
   Team briefing and equipment check

2. Birth
   Term gestation?
   Good tone?
   Breathing or crying?
   Yes → Warm and maintain normal temperature, position airway, clear secretions if needed, dry, stimulate
   No → Infant stays with mother for routine care: warm and maintain normal temperature, position airway, clear secretions if needed, dry.
   Ongoing evaluation

3. Apnea or gasping?
   HR below 100/min?
   Yes → PPV
   SpO₂ monitor
   Consider ECG monitor
   No → Labored breathing or persistent cyanosis?
   Yes → Position and clear airway
   SpO₂ monitor
   Supplementary O₂ as needed
   Consider CPAP
   No → Postresuscitation care
   Team debriefing

4. HR below 100/min?
   Yes → Check chest movement
   Ventilation corrective steps if needed
   ETT or laryngeal mask if needed
   No → HR below 60/min?
   Yes → Intubate if not already done
   Chest compressions
   Coordinate with PPV
   100% O₂
   ECG monitor
   Consider emergency UVC
   No → HR below 60/min?
   Yes → IV epinephrine
   If HR persistently below 60/min
   Consider hypovolemia
   Consider pneumothorax

Targeted Preductal SpO₂ After Birth

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<th>Time (min)</th>
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<tr>
<td>1</td>
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hemorrhage. The only negative consequence seems to be a slightly increased level of bilirubin, associated with more need for phototherapy.2,3

Delayed cord clamping for longer than 30 seconds is reasonable for both term and preterm infants who do not require resuscitation at birth (Class IIa, LOE C-LD). There is still insufficient evidence to recommend an approach to cord clamping or cord “milking” for babies who require resuscitation at birth.

Assessment of heart rate: Immediately after birth, assessment of the newborn’s heart rate is used to evaluate the effectiveness of spontaneous respiratory effort and determine the need for subsequent interventions. An increase in the newborn’s heart rate is considered the most sensitive indicator of a successful response to resuscitation interventions. Therefore, identifying a rapid, reliable, and accurate method to measure the newborn’s heart rate is critically important.

Available evidence comparing clinical assessment with ECG in the delivery room and simultaneous pulse oximetry and ECG heart rate determination found that clinical assessment was both unreliable and inaccurate.

ECG (3-lead) displayed a reliable heart rate faster than pulse oximetry. Pulse oximetry tended to underestimate the newborn’s heart rate and would have led to potentially unnecessary interventions.2,3

During resuscitation of term and preterm newborns, the use of 3-lead ECG for the rapid and accurate measurement of the newborn’s heart rate may be reasonable (Class IIb, LOE C-LD).

Maintaining normal temperature of the newborn after birth: It is recommended that the temperature of newly born non asphyxiated infants be maintained between 36.5°C and 37.5°C after birth through admission and stabilization (Class I, LOE C-LD).1 There is new evidence supporting a variety of interventions that may be used alone or in combination to reduce hypothermia. Temperature must be monitored to avoid hyperthermia as well.

Management of the meconium stained infant: For more than a decade, vigorous infants born through meconium stained amniotic fluid have been treated no differently than if they had been born through clear fluid. However, there remained a long standing practice to intubate and suction infants born through meconium stained amniotic fluid who have poor muscle tone and inadequate breathing efforts at birth. Routine intubation for tracheal suction in this setting is not suggested because there is insufficient evidence to continue recommending this practice (Class IIb, LOE C-LD).2,3

In making this suggested change, greater value has been placed on harm avoidance (delays in providing positive-pressure ventilation, potential harm of the procedure) over the unknown benefit of the intervention of routine trachea intubation and suctioning.

Oxygen use for preterm infants in the delivery room: Since the release of the 2010 Guidelines, additional randomized trials have been published that examine the use of oxygen during resuscitation and stabilization of preterm newborns. These additional publications have allowed an increase from Class IIb to a Class I recommendation.

Meta-analysis of the randomized trials that compared initiating resuscitation of preterm newborns (less than 35 weeks of gestation) with high oxygen (65% or greater) versus low oxygen (21%–30%) showed no improvement in survival or morbidity to hospital discharge with the use of high oxygen.2,3

Resuscitation of preterm newborns of less than 35 weeks of gestation should be initiated with low oxygen (21%–30%), and the oxygen concentration should be titrated to achieve preductal oxygen saturation approximating the interquartile range measured in healthy term infants after vaginal birth at sea level (Class I, LOE B-R). This recommendation reflects a preference for not exposing preterm newborns to additional oxygen without data demonstrating a proven benefit for important outcomes.

Oxygen use during neonatal cardiac compressions: The evidence for optimal oxygen use during neonatal cardiac compressions was not reviewed for the 2010 Guidelines. Unfortunately, there are no clinical studies to inform the neonatal guidelines, but the available animal evidence demonstrated no obvious advantage of 100% oxygen over air. However, by the time resuscitation of a newborn includes cardiac
compressions, the steps of trying to improve the heart rate via effective ventilation with low concentrations of oxygen should have already been tried. Thus, the 2015 Guidelines Task Force thought it was reasonable to increase the supplementary oxygen concentration during cardiac compressions and then subsequently wean the oxygen as soon as the heart rate recovers. Structure of educational programs to teach neonatal resuscitation: Currently, neonatal resuscitation training that includes simulation and debriefing is recommended at 2-year intervals. Studies that examined how frequently healthcare providers or healthcare students should train showed no differences in patient outcomes, but demonstrated some advantages in psychomotor performance, knowledge, and confidence when focused task training occurred every 6 months or more frequently. It is therefore suggested that neonatal resuscitation task training occur more frequently than the current 2-year interval (Class IIb, LOE B-R, LOE C-EO, LOE C-LD).

Knowledge Gaps
Umbilical cord management for newborns needing resuscitation: As noted previously, the risks and benefits of delayed cord clamping for newborns who need resuscitation after birth remains unknown because such infants have thus far been excluded from the majority of trials. Concern remains that delay in establishing ventilation may be harmful. Further study is strongly endorsed. Some studies have suggested that cord milking might accomplish goals similar to delayed cord clamping. Cord milking is rapid and can be accomplished within 15 seconds, before resuscitation might ordinarily be initiated. However, there is insufficient evidence of either the safety or utility of cord milking in babies requiring resuscitation. The effect of delayed cord clamping or cord milking on initial heart rate and oxygen saturations is also unknown. New normal ranges may need to be determined. The risks and benefits of inflating the lungs to establish breathing before clamping of the umbilical cord needs to be explored.

Utility of a sustained inflation during the initial breaths after birth: Several recent animal studies suggested that a longer sustained inflation may be beneficial for establishing functional residual capacity during transition from fluid-filled to air-filled lungs after birth. Some clinicians have suggested applying this technique for transition of human newborns. It was the consensus of the 2015 CoSTR and the 2015 Guidelines Task Force that there was inadequate study of the benefits and risks to recommend sustained inflation at this time. Further study using carefully designed protocols was endorsed (see “Part 13: Neonatal Resuscitation” in this 2015 Guidelines Update and Perlman et al2,3).

Determination of heart rate: Neonatal resuscitation success has classically been determined by detecting an increase in heart rate through auscultation. Heart rate also determines the need for changing interventions and escalating care. However, recent evidence demonstrates that auscultation of heart rate is inaccurate, and pulse oximetry takes several minutes to achieve a signal and also may be inaccurate during the early minutes after birth. Use of ECG in the delivery room has been suggested as a possible alternative. Although data suggest that the ECG provides a more accurate heart rate in the first 3 minutes of life, there are no available data to determine how outcomes would change by acting (or not acting) on the information. Some transient bradycardia may be normal and be reflective of timing of cord clamping. More studies are needed. The human factors issues associated with introducing ECG leads in the delivery room are unknown. In addition, improved technologies for rapid application of ECG are needed.

References

17th National Conference of IAP Intensive Care Chapter &
1st International Conference on Pediatric Rare Diseases

Workshops : 26th & 27th November, 2015
Main Conference : 28th & 29th November, 2015

Venue : B. M. Birla Science & Technology Centre, Statue Circle, Jaipur

Organized By
IAP – Intensive Care Chapter
IAP Rajasthan Chapter & Jaipur Branch
Department of Pediatrics, SMS Medical College, Jaipur

Topics to be covered...
- Setting the scene for hyponatremia
- Salt and water, death in disequilibrium
- So you think you know about sedation...?
- Solutions for confusions
- Who pays the ferryman? Rationing Critical Care
- Decision making in PICU
- Procedures - the art of PICU: Common Pitfalls
- Neurology cases
- Pediatric burns - do we have knowledge?
- Critical Care in disaster situation
- Cooling is good, cooling is bad Hypothermia for the pediatric patient
- Pediatric Sepsis: Recognition and ED Management
- Body fluids increase mortality in SEPSIS?
- Pain Management in PICU
- Nutrition and skin care in PICU
- Ventilator Associated events in Pediatrics
- ICU without ventilators
- Non-traumatic COMA
- Janitor for central lines
- Can simulation training improve emergency care?
- Why are we talking about EEMO, this is emergency department
- Pediatric Trauma - Initial Management and beyond
- Recruitment Maneuvers in Pediatrics - What does the evidence say?
- Oxygen Therapy in resuscitation, more is not better?
- Do we need strict PICU protocols?
- End of life - Medical issues in PICU
- Current Recommendation: Vaccines for Immuno-compromised Patient
- Brain Death Certification in Pediatrics

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NCPCC 2015

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Advanced CME - 27th November 2015

- Advance Pediatric Critical Care Directors: Dr. Dinesh Chirla, Dr. Arun Bansal

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- Structured abstracts to be submitted by 31st August, 2015.
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- The scientific committee will review the abstracts and decide the section of presentation.
- Registration is mandatory prior to any paper or poster presentation.

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Advanced CME: INR 2500  Workshop: INR 2500  Workshop (Nursing): INR 1500  BPICC: INR 3500

*PG students must provide certificate from the Head of the Department/Institution.


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