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Chief Pediatric Intensivist and Head,
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Email ID: jpccjournal@gmail.com,
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Candidemia in pediatric intensive care unit: A new common and complicated comorbidity

Last decade has seen a rise in the use of advanced invasive and indwelling devices in pediatric intensive care units (PICUs) with the emergence of newer therapies for sick children. Unfortunately, it has led to the rising incidence of hospital-acquired infections and candidemia is one such condition. Candidemia has been demonstrated in PICU to be an individual risk factor contributing to higher mortality rate. This is possibly owing to the delayed diagnosis, increased incidence of nonalbicans candidemia (NAC), and rising resistance against the antifungals. Therefore, it is crucial to identify the risk factors, epidemiology, and adequate preventive and control measures.

It is estimated that 10%–20% of all nosocomial bloodstream infections in intensive care units (ICUs) are due to *Candida* species.[1,2] *Candida* is a part of normal flora, which in the presence of breached protective barriers due to invasive catheters and endotracheal tubes turns into a pathogen, particularly in vulnerable and immunocompromised hosts. Apart from this, cross contamination through the hands of health-care workers in PICU also plays a significant role in transmission.

Zaoutis *et al.* conducted a population-based case–control study in Children's Hospital of Philadelphia and identified an incidence of candidemia as 3.5/1000 PICU admissions. The presence of a central venous catheter (CVC), malignancy, and use of broad-spectrum antibiotics including antimicrobials with activity against anaerobic organisms were identified as risk factors. Vancomycin and hyperalimentation were identified as individual risk factors.[3,4] Singhi *et al.* in their retrospective cohort study found that the NAC accounted for 70% of Candidiasis in PICU. *Candida tropicalis* was identified as the most common and was associated with higher mortality and resistance to fluconazole. Although candiduria was identified commonly, they emphasized that it does not necessarily lead to Candidemia and hence need not be treated if not associated with clinical findings or suspicion of coexisting invasive disease. However, there is a need for high-risk surveillance and early antifungal therapy if the blood cultures are suggestive of fungal growth or there is presence of risk factor.[5] Mantadakis *et al.* reported few other risk factors such as prematurity, parenteral nutrition, neutropenia, steroid therapy, neurological disease, transplant recipients, and mechanical ventilation. The risk with the utilization of various invasive devices were different e.g., silastic percutaneous CVCs were related with a higher hazard than port-a-catheters.[6]

A shift from *Candida albicans* group to NAC group (*Candida parapsilosis*, *Candida glabrata*, *C. tropicalis,* and *Candida krusei*) has been noted since almost past two decades probably due to the increased use of azoles for both treatment and prophylaxis. *C. tropicalis* is associated with candidemia in neutropenic patients with hematologic malignancies[7] and is the most common NAC in Indian PICUs compared to the rest of the world.[8,9]

The prolonged turnover time for fungal culture and the critical nature of the diseases in ICU has led to the increased use of prophylactic and empiric fungal therapy. A systematic review was done in critically ill children and adults to see the effects of untargeted antifungal treatment. There was moderate grade evidence among the 22 studies reviewed of insignificant effect on the mortality (risk ratio = 0.93, 95% confidence interval = 0.79–1.09, $P = 0.36$), although the risk of invasive fungal infections was significantly reduced.[10] Hence, the role of untargeted antifungal administration before positive culture remains debatable and warrants further studies.

The emerging resistance to common antifungal drugs such as azoles and the rising incidence of NAC is a major concern in PICU. Many studies including Kaur *et al.*[11] done in adults have found similar results of higher incidence of NAC species with *C. tropicalis* being more followed by *C. glabrata*, *C. parapsilosis*, *C. krusei,* and *Candida kefyr*. Candida colonization is a common finding in ICU in almost 73% of patients;[12] however, most patients suffer no ill effects in the absence of immunosuppressed states or other risk factors.[13] Antifungal susceptibility indicated that 37.8% and 7.8% of the *Candida* isolates were resistant to fluconazole and amphotericin B, respectively.[11] Further studies are required in PICU to substantiate the same.

In this issue, Behera C *et al.*[14] in their retrospective observational study have tried to study the incidence, risk

factors of candidemia in PICU, associated mortality, and the sensitivity pattern over a period of 2 years in a tertiary care hospital. Out of 1034 cases, 36 cases were identified with candidemia. The study showed a male predilection with age groups between 6 and 14 years being most affected, though mortality was high in the younger age group (1–5 years). The risk factors were consistent with previous studies such as CVCs, immunosuppression, use of broad-spectrum antibiotics with anti-anaerobic activity, multiorgan dysfunction syndrome, and concurrent sepsis. Incidence of NAC group was higher with higher resistance and mortality. Most common among them was *C. tropicalis,* followed by *C. glabrata*, *C. parapsilosis*, and *C. krusei* (5.6%). Most of the isolates were sensitive to amphotericin B, followed by clotrimazole, voriconazole, and itraconazole and least to fluconazole and nystatin.

The results are consistent with many other studies highlighting the need for high-risk stratification and precautions to prevent the growing incidence of fungal infections and resistance to common antifungal drugs. This study has also identified Candiduria as an associated factor in 58.3% cases of Candidemia. Prophylactic antifungal in the presence of Candiduria with other risk factors and signs of fungal sepsis warrant early start of antifungals. However, whether it requires routine start of antifungal even in the absence of other factors remains debatable and needs further evidence.

This study emphasizes the burden of growing candidemia in the PICU units and the need to have stringent guidelines on invasive procedures to maintain asepsis, risk stratification to identify and initiate early treatment, and cautious use of antifungal therapy to curb the surge in resistant species. Overall, it is an important addition to the available evidence on fungal sepsis in order to have a more aware and cautious PICU care. However, further studies are required across the country for formulation of uniform policies based on Indian pediatric subpopulation and distribution of the species along with their resistance pattern.

Rakshay Shetty, Swarnika Mishra[1]

Department of Pediatric Intensive Care, Rainbow Children's Hospital, [1]Department of Pediatric Intensive Care, St. Philomena's Hospital, Bengaluru, Karnataka, India

Address for correspondence: Dr. Rakshay Shetty, Department of Pediatric Intensive Care, Rainbow Children's Hospital, Marathalli, Bengaluru, Karnataka, India.
E-mail: rakshayshetty@gmail.com

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Secondary bacterial infection in dengue fever in children: A reality or illusion?

Dengue fever is a common tropical infection, and its incidence has grown dramatically worldwide in recent decades. According to the World Health Organization, it causes 390 million viral infections per year, with 96 million infections manifesting clinically (with any severity of disease).[1] As per the National Vector Borne Disease Control Programme until November 2019, India, reported 136,422 cases, with 132 mortality,[2] which were slightly higher than the national average of the last 5 years.

Secondary bacterial infections in a child with dengue have the potential to adversely affect the clinical course of the disease and prolong the hospital stay. The incidence of secondary bacterial infection in dengue seems to be low; however, the pediatric literature is currently sparse in this regard. Cause of bacterial coinfection is not well understood, but some authors suggest that immunological alterations such as leukopenia, the proliferation of lymphocytoid and plasmacytoid cells, lymphocytolysis, lympho-phagocytosis, depletion of lymphocyte and breakdown of digestive epithelial barrier (endothelial damage or intestinal hemorrhage) help pathogens to enter the circulation.[3] Most of the documented infections are bacteremia or urinary tract infection (UTI) caused by enteric Gram-negative rods along with *Streptococcus pneumoniae*, *Staphylococcus aureus,* and *Haemophilus influenzae*. One case report shows coinfection by *Pseudomonas aeruginosa*.[3] In an adult study by Lee *et al*., it was found that 5.5% of the patients with dengue infection had bacteremia.[4] Another adult study conducted among patients with confirmed dengue cases with prolonged fever (>5 days), the incidence of secondary bacterial infection was 25%.[5] There are very few studies on this topic among children. In most of the cases, bacteremia is diagnosed. Although sterile pyuria is common, the incidence of culture-proven UTI is low. Adrizain *et al*. observed that there is a relatively higher use of antibiotics in private setup compared to teaching hospitals in suspicion of secondary bacterial infection.[6] The author himself, in his study of antibiotics usage, observed that in 203 dengue patients with various grades of severity, only 20 (9.8%) required antibiotics.[7]

In this issue, there is an article by Udayasankar *et al*. on secondary bacterial infection in dengue fever and associated risk factors, which is a retrospective observational study in children.[8] This is a good effort by the authors as literature is scarce in children. They observed 423 children, among which 83 children had persistent fever. Of these 83 children, 29 (34.9%) were culture positive confirmed sepsis and 7 had positive sepsis screen hence labeled as probable sepsis. They observed 8.5% (36/423) of all dengue patients had secondary bacterial infection, among which 6 had bacteremia and 20 had UTI. The incidence of secondary bacterial infection in all dengue cases and dengue with persistent fever is higher than as reported previously. The author reported a very high incidence of UTI and they could not provide any specific reasons behind this high incidence. Coinfection with bacterial pathogens is more in infancy and in severe dengue cases, which is similar as reported by Pandey, and Hongsiriwon.[3,9] Causative organisms observed by authors are similar to previous studies. The author observed that a longer duration of fever (>5 days) is associated with a higher incidence of secondary bacterial infection (P = 0.020). This is an important finding, and it may help to diagnose secondary bacterial infection in endemic regions like India.

Currently, we are at crossroads with national guidelines on the management of dengue fever not including antibiotics at any stage and many reports of the injudicious and high rate of antibiotic usage in dengue fever. However, antibiotic usage in a case actually complicated by secondary bacterial infection is crucial to improve outcomes. A balanced approach where unnecessary antibiotic usage as well as appropriate usage in dengue fever is need of hour. A national or state registry or multicenter studies may provide more insight and help in forming future treatment guidelines for dengue fever.

Pradeep Kumar Sharma

Department of Pediatric Critical Care and Pulmonology, Sri Balaji Action Medical Institute, New Delhi, India

Address for correspondence: Dr. Pradeep Kumar Sharma, Flat No. 48, Pocket-7, Sector-21, Rohini, New Delhi - 110 086, India.
E-mail: drsharma025@gmail.com

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Necrotizing pneumonia in children: Is it rare anymore?

Necrotizing pneumonia (NP), as term denotes, is characterized by the destruction and liquidation of lung parenchyma, resulting in cavity formation, air leaks, and/or intense suppuration. Therefore, it has protracted and severe clinical course unlike community-acquired pneumonia (CAP). Infection triggered vasculitis of intrapulmonary vessels and thrombotic occlusion, resulting in coagulative and liquefactive necrosis of the lung parenchyma.[1] Parapneumonic pleural effusions (PPEs) and empyema are the common results of this pathogenesis, and if necrotic regions extend to the pleura, bronchopleural fistula (BPF) may form. Rarely, thromboses of the multiple intrapulmonary vessels can result in pulmonary gangrene of an entire lobe.[1]

Although NP, described as relatively uncommon, is being increasingly recognized over the past decades[2] and nowadays, it is not uncommon to be seen in day-to-day practice of pediatricians and intensivists. This may be due to the evolution of antibiotic prescriptions, increased awareness, use of advanced diagnostic methods, and evolution of bacteria and host–pathogen interactions. Periodic evolution of bacteria and their virulence are well known. These may occur due to selection pressures in-response to antibiotic prescriptions, use of vaccines, and changing ecological factors. Incidence of NP in the present study is estimated to be 3.3% of children with pneumonia.[3] However, authors have excluded empyema and other complicated pneumonias, despite them being part of spectrum of NP. Authors have stated that lung abscess, NP, and empyema/PPE constituted 25.2% (352/1393) of total pneumonias, indicating higher true prevalence. *Staphylococcus* is emerging as the most common pathogen in the past two decades followed by pneumococcus. In developed nations, while there are reports of expanding nonvaccine serotype-induced pneumococcal NP (PNP) also, staphylococcal empyemas.[4-6] However, in general, PNP has been diminished there because of wide spread utilization of pneumococcal vaccine.[7,8]

Pathogenesis of NP is incompletely understood. Some of the bacterial virulence factors have been studied in this process. Staphylococcal α-toxin (pore-forming toxins) is shown to cause the activation of NLRP3 inflammasome and platelet–neutrophil aggregation-induced vasculitis/vessel clogging, leading to severe alveolar necrosis.[9] Panton–Valentine leukocidin (PVL) (pore-forming exotoxin linked to severe invasive infections) and methicillin-resistant *Staphylococcus aureus* have also been looked for association. However, findings are inconsistent unlike skin and soft tissue infections.[10-12] However, the role of PVL in causing rapidly progressive, hemorrhagic, NP has been well reported in CAP as well as hospital-acquired pneumonia.[13,14] Of pneumococci, serotype 3 (has thick capsule, evades opsonophagocytic, and is known to induce intense inflammation) and serotype 19A (has greater invasive potential, has a growth advantage over other serotypes, and is often resistant to antibiotics) have been seen closely associated with NP.[15,16]

Other bacteria including Gram-negatives (*Pseudomonas*, *Klebsiella*, *Legionella*, *Acinetobacter* sp., etc.) are also known to cause NP but are seen in small numbers or sporadic case reports. They are often seen in patients with comorbidities and hospital-acquired settings. Although studies are limited, viruses are known to attract secondary bacterial pneumonia and their interactions are well implicated in NP. With regard to the role of anaerobes (as routinely no efforts are made to culture or isolate them), adult studies have shown that they play a minor role in causing NP.[1]

Clinical features of NP are like CAP except being severe in nature. NP occurs in healthy individuals with no known risk factors or comorbidities. It manifests as prolonged and severe pneumonia; patients are often disproportionately sick and can have features of intense suppuration (empyema), pneumothorax/BPF, etc., that progress despite initial appropriate antibiotic therapy. It is often described as a complication of bacterial pneumonia. However, it may be possible that necrotic process could be the primary pathology from the beginning itself depending on host–pathogen interactions and pathogen virulence. Despite its serious nature, death is uncommon in NP. Apart from prolonged antibiotics, draining pleural fluid/pus, pneumothorax, and respiratory support, cardiovascular resuscitation and attention to hemodynamics, electrolyte imbalances, fluids, and nutrition are crucial for good outcome. Additional therapies such as lung or lobar resection, intravenous immunoglobulin, and extracorporeal membrane oxygenation are rarely needed in unresponsive cases, and evidence is limited to individual reports.

Thus, in recent decades, NP is increasingly recognized disease in children and not anymore uncommon. Additional molecular diagnostic tests apart from cultures may help increase the pathogen identification. Identification of serotypes is important to further understand the epidemiology, pathogenesis, prevention, etc. Further research on microbiology, host–pathogen interaction, and immunogenomic studies to identify the patients at risk of developing NP will help better understanding, treatment, and outcome.

Govind Benakatti

Department of Pediatric Intensive Care, NMC Royal Hospital, Abu Dhabi, UAE

Address for correspondence: Dr. Govind Benakatti, NMC Royal Hospital, Abu Dhabi, UAE.
E-mail: govind.pgi@gmail.com

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Prevention is better than cure: The vital role of the clinical pharmacist in the pediatric intensive care unit to prevent medication errors

Critically ill children require numerous medications during their management in the pediatric intensive care unit (PICU). In the United States, published data show that one error occurs for every five doses of medication administered.[1] In addition, pediatric patients are three times more likely to be involved in a medication error event than adult patients.[2] These errors occur even in the setting of processes already in place to improve medication safety, including unit dose dispensing, pharmacy compounding, automation, and computerized physician order entry (CPOE).[1] The clinical pharmacist plays a vital role in the PICU to optimize drug therapy, perform pharmacokinetic evaluations, mitigate adverse drug events, and support medication error prevention. The integration of a clinical pharmacist into patient care has been shown to not only reduce costs but also prevent errors, especially when available to round with the multidisciplinary intensive care unit team.[3,4] More recently, the involvement of clinical pharmacists during cardiopulmonary resuscitation is strongly encouraged to improve the process of care in a high-stress event in the PICU.[5] As pharmacologic agents and biologics become more complex due to drug development and novel therapeutic interactions, the clinical pharmacist assumes even greater importance to prevent medication errors, optimize patient care, and promote financial stewardship of limited resources in the PICU.

This prospective observational study conducted by Loni *et al.*[6] in the PICU of a secondary level hospital in Karnataka highlights that medication errors are quite common, with errors occurring during a quarter of observed patient days. Medication errors occurred in different steps of prescribing, transcribing, dispensing, and administering medications for critically ill children. Importantly, the study emphasizes the key role played by the clinical pharmacist to identify medication errors in different stages and to provide appropriate recommendations to optimize medication therapy in the PICU. The most common type of medication error found in this study was prescription errors (59%), with the most common prescription error being error related to dosage (76% of all prescription errors). This is not unexpected given the differences in pediatric pharmacokinetics and pharmacodynamics that affect drug response in critically ill children, the lack of commercially available pediatric formulations, and the complexity of weight-based dosing that spans multiple ages and developmental stages in children.[2] The study also classified medication errors using the National Coordination Committee for Medication Error Reporting and Prevention Index Severity Classification, with most errors falling in Category B (61%-the error did not reach the patient), followed by Category C (34%-the error reached the patient but did not cause harm). These findings support that the integration of a clinical pharmacist with extensive training in pediatric pharmacology is essential to provide optimized and safe care to this vulnerable population. Interestingly, when a pharmacist intervened, recommendations were accepted at a rate of 92%, suggesting that the incorporation of a clinical pharmacist into this type of clinical setting is well-received. The findings of this study are similar to a landmark adult study that observed that the presence of a pharmacist on rounds as a full member of the patient care team in a medical intensive care unit (ICU) was associated with a substantially lower rate of medication errors caused by prescribing errors.[3]

This prospective study is unique in its description of medical errors in the context of the health-care setting with limited access to technologies to improve medication safety such as CPOE, barcode-assisted medication administration, and new generation infusion devices with smart pump technology. This is a common scenario and this study provides further support that a clinical pharmacist can have a profound impact on the amount and outcomes of medical errors that occur within a pediatric ICU setting. A limitation of this study is that only medication errors identified by the pharmacist were included for evaluation, potentially resulting in bias with underreporting of the true rate of medication errors. In addition, the inclusion of a historical cohort group, would have allowed for a more accurate evaluation of the true impact of a clinical pharmacist on enhancing medication safety. Additional information regarding the timing of pharmacist intervention in relation to when errors occurred in the medication utilization

process would be helpful to ensure the best deployment of the pharmacist to match documented needs. It also remains unclear how often verbal orders to prescribe medications were utilized as this is often an important source of medication error.[7]

This study demonstrates that clinical pharmacists add high value to patient care and outcomes outside the drug dispensing process. Such involvement can result in practice changes that improve medication safety such as standardization of administration times, medication dilutions, and infusion rates; identification of interactions; and estimation of drug clearance and disposition. Increased involvement of clinical pharmacy services can provide ways to prevent medication errors and optimize overall patient care. In particular, the presence of the pharmacist on bedside rounds with the clinical team in the PICU serves as an immediate resource to optimize drug therapy and prevent medication errors. Limited access to in-house pharmacy resources or lack of qualified pharmacists is barriers to the delivery of high-quality care in the PICU. In the absence of a clinical pharmacist on site, alternative strategies and modalities to consult a clinical pharmacist for complex drug information questions either via telehealth or as an on-call service can mitigate dosing and medication selection errors for all providers in the PICU setting. Regardless of whether a clinical pharmacist is available in real time or not, we recommend dedicated pediatric-trained pharmacist involvement in quality improvement, guideline development, and policy implementation for improving therapeutics in the PICU. In the context of having a dedicated pediatric-trained pharmacist for the optimal care of critically ill children, the old adage of prevention is better than cure rings true…

Bridget Blowey, Karla V. Resendiz, Angela Grachen, Vijay Srinivasan[1]

Departments of Pharmacy Services and [1]Anesthesiology and Critical care Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA

Address for correspondence: Dr. Vijay Srinivasan, Department of Anesthesiology and Critical Care Medicine, The Children's Hospital of Philadelphia, 3401 Civic Center Boulevard, Philadelphia, PA 19104, USA.
E-mail: srinivasan@email.chop.edu

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Original Article

Candidemia in the pediatric intensive care unit in Eastern India

Chinmay Behera, Reshmi Mishra, Pratap Kumar Jena[1], Surya Mishra[2], Bandya Sahoo, Siba Brata Patnaik, Mukesh Jain

Departments of Pediatrics and [2]Microbiology, Kalinga Institute of Medical Sciences, [1]Department of Public Health, Kalinga Institute of Medical Sciences, Bhubaneswar, Odisha, India

Abstract

Background: Nosocomial infection, due to Candida, contracted in the pediatric intensive care unit (PICU), is emerging as a significant healthcare challenge. The incidence of non-albicans Candida as a cause of candidemia is on the rise, unlike in previous decades.

Materials and Methods: All the cases of candidemia confirmed by culture, admitted to the PICU during the study period of January 2017 to December 2019, were retrospectively studied. The prevalence, speciation, sensitivity pattern and risk factors of candidemia mortality were recorded and analyzed.

Results: There were 1034 admissions to the PICU in the study period, of which 926 blood samples were sent for culture and sensitivity. A total of 31 Candida non-albicans and five Candida albican species were isolated. C. tropicalis was the most common type (44.4%) of Candida species found, followed by C. glabrata (16.7%), C. parapsilosis (16.7%) and C. krusei (5.6%). The sensitivity of all Candida isolates to Amphotericin B, Clotrimazole, Voriconazole, Itraconazole, Ketoconazole, Nystatin, and Fluconazole was 94.4%, 91.7%, 88.9%, 86.1%, 77.8%, 52.8%, and 38.9% respectively. The use of a central venous catheter was a statistically significant contributor to mortality due to candidemia.

Conclusion: Non-albican Candida species are the predominant cause of candidemia this study. They are associated with higher fatality rates. Sensitivity of the Candida spp. was more common to Amphotericin-B than azoles.

Keywords: Antifungal susceptibility, non-albicans candida, pediatric intensive care

Address for correspondence: Dr. Reshmi Mishra, Department of Pediatrics, Kalinga Institute of Medical Sciences, Bhubaneswar, Odisha, India.
E-mail: docreshmis@gmail.com

INTRODUCTION

Millions of fungi exist in the environment as commensals. Less than 300 of these are pathogenic and usually cause opportunistic invasive fungal infections (IFIs).[1] Admission into the pediatric intensive care unit (PICU) is one of the significant risk factors for *Candida* IFIs.

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Preexisting bacterial infection, treatment with broad-spectrum antibiotics, immunocompromised status, recent surgery, parenteral nutrition, central line, dialysis, and mechanical ventilation are some of the known risk factors for *Candida* IFIs.[2]

The annual incidence of candidemia is 17–100 per million population, with a higher rate of occurrence in children.[3,4] As many as 10%–49% of the victims of candidemia run

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a risk of death.[5] Although *Candida albicans* had been traditionally found to be the usual cause of IFIs, the isolation of non-albicans Candida (NAC) such as *Candida glabrata, Candida tropicalis, Candida parapsilosis,* and *Candida krusei* has recently been increasingly reported. *C. tropicalis* is the most common species among the *Candida* isolated in the blood. Furthermore, resistance to fluconazole and other azoles, especially NAC, has become a menace.[6,7] This could be due to the increase in the empirical use of antifungal agents, primarily fluconazole.[8,9]

Studies exploring the various aspects of candidemia, reported from the eastern part of India, are scarce. This study was conducted to assess the burden of candidemia, speciation, sensitivity pattern, and risk factor of candidemia-associated mortality in the PICU of the tertiary care institute of Odisha.

SUBJECTS AND METHODS

Study design

A retrospective observational study was carried out using medical records.

Study setting

This study was conducted in the PICU of KIMS Medical College and Hospital, Bhubaneswar, Odisha, which is a 12-bedded unit.

Study duration

This study was conducted over a period of two years (January 2017 and December 2019).

Method

A predesigned case record form was used to collect data from the case records of patients with candidemia, confirmed on blood culture. Thirty-six cases of candidemia were recruited into the study after excluding the children who were already on antifungal prophylaxis at admission. The data on demographic patterns, clinical diagnosis, *Candida* speciation, drug sensitivity, risk factors such as the use of broad-spectrum antibiotics, intubation, and mechanical ventilation, days of catheterization, the presence of central line, corticosteroid therapy and multiple organ dysfunction, and disease outcome were retrieved.

Method of obtaining blood cultures

As a routine PICU protocol at KIMS, the blood samples from suspected patients with sepsis were collected in the specified bottles (BacT/Alert 3D [BioMerieux]) and sent to the central laboratory following all the standard precautions. The culture bottles were then loaded into a fully automatic BacT/Alert 3D system. Those culture bottles, which came out to be positive by this method, were further processed manually, first to get the causative organisms. A small amount of the broth from the positive bottle was inoculated into blood agar, chocolate agar, and MacConkey agar plate. The blood agar and chocolate agar plates were incubated in a carbon dioxide incubator, and the MacConkey agar plate was incubated in an ordinary incubator. After overnight incubation at 37°C, the plates were observed for any growth in a biosafety cabinet. The colonies with suspected *Candida* growth are usually tiny, whitish, dry, and pasty on all the culture plates. Initially, few representative colonies were used to observe the germ tube formation to know whether the colony is *C. albicans* or not (*C. albicans* only forms the germ tube). Few representative colonies were then inoculated onto CHROME agar and further incubated aerobically. The CHROME agar (HiMedia) is a novel, differential culture medium that is claimed to facilitate the isolation and presumptive identification of some clinically important yeast species. *C. albicans* forms greenish color colonies after an incubation of 24–48 h on CHROME agar. Thus, the colonies forming germ tube and forming greenish colonies on CHROME agar were presumptively differentiated as *C. albicans*, and the rest of the *Candida* species which were isolated were grouped under NAC. These colonies were now further evaluated for speciation and sensitivity determination using the fully automated VITEK 2 [BioMerieux] instrument which identifies the organism up to species level using its VITEK * 2YST ID card as well as gives the antifungal sensitivity pattern by minimum inhibitory concentration level.

Statistical methods

The data were processed using SPSS: IBM Corp, Armonk, NY, USA (version 25.0). Univariable analysis was presented as pie charts, bar diagrams, and tables. Categorical variables were expressed as percentage. The median and interquartile range (IQR) of age distribution were estimated. Bivariable analysis using Fisher's exact test was done to assess the factors associated with mortality due to candidemia considering various demographic and clinical characteristics. $P < 0.05$ (two-tailed) was considered statistically significant.

RESULTS

The total admission to PICU during the study period was 1034 cases, of which 926 blood samples were sent for microbiological assessment. Thirty-six (3.88%) cases were identified with *Candida* species in blood culture. The children were in the age range from 1 month to 14 years, with a median age of 4.54 years (IQR of 0.7–8 years). The majority of the children (47%) were in

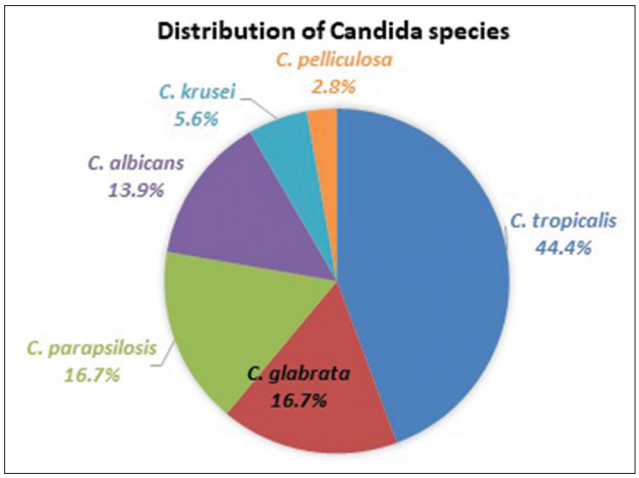

Figure 1: Percentage-wise distribution of isolated *Candida* species among children

the age group of 6–14 years, followed by infants (36%). The male children (66.11%) were more affected than the female.

The distribution of *C. albicans* and non-albicans species is detailed in Figure 1. *C. tropicalis* was the most common type of *Candida*, followed by *C. glabrata*, *C. parapsilosis*, and *C. krusei* (5.6%). The only case of *C. pelliculosa* isolated in the study period was in a 2-month-old baby with late-onset sepsis. The isolation of NAC species was relatively higher than *C. albicans* (31/36 vs. 5/36).

The clinical diagnosis and outcome of children detected to be having candidemia are summarized in Table 1. Nearly one-third of the children had sepsis (including scrub typhus), followed by patients with central nervous system infection (encephalitis and meningitis) who accounted for 10 (27.7%). The remaining cases were pneumonia (4,11.1%), Guillain Barre syndrome (3,8.3%) and others (acute leukemia, complicated malaria, chronic liver disease, acute pancreatitis seen in one case each). Out of 36 cases 5 died (sepsis:2, encephalitis:2, acute leukemia:1).

In this study, the presence of the central line ($P = 0.047$) was the only significant predictor of mortality among children with candidemia. Survival among female children was higher (92.9%) than their male (81.8%) counterparts, but it was not statistically significant. Similarly, survival among children in the age group of 1–5 years was lower than the other age groups, although it was not statistically significant. Influence of risk factors such as exposure to broad-spectrum antibiotics, fluconazole resistance, use of a mechanical ventilator, or urinary catheterization on the survival in children failed to show any statistically significant difference [Table 2].

Table 1: Distribution of underlying diseases among candidemia patients

Diseases	Frequency (*n*=36)	Death (*n*=5), *n* (%)	Survived (*n*=31), *n* (%)
Acute leukemia	1	1	0
Complicated malaria	1	0	1
Chronic liver disease	1	0	1
Empyema thoracis	2	0	2
Encephalitis	6	2 (33.3)	4 (66.7)
GB syndrome	3	0	3
Acute pancreatitis	1	0	1
Pneumonia with ARDS	3	0	3
Pneumonia with CKD	1	0	1
Pyogenic meningitis	4	0	4
Sepsis with MODS	8	2 (12.5)	6 (87.5)
Scrub typhus	5	0	5

ARDS: Acute respiratory distress syndrome, CKD: chronic kidney disease, MODS: Multi-organ dysfunction syndrome

All five deaths were associated with non-albicans IFIs (*C. glabrata* – 2 and *C. tropicalis* – 3). Multiple antibiotics (≥2) were used in 19 cases (52.77%). The most common antibiotic used was beta-lactam. Meropenem, vancomycin, and linezolid were the other commonly used antibiotics [Table 3].

Most of the *Candida* isolates were sensitive to amphotericin B (94.44%), clotrimazole (91.67%), voriconazole (89%), and itraconazole (86%) [Figure 2]. Lower sensitivity to fluconazole (39%) and nystatin (53%) was seen. The *C. albicans* were less sensitive (range: 20%–60%) to antifungals than non-albicans (range: 42%–100%), except to nystatin. *C. pelliculosa* was sensitive to all antifungal agents, and others had varied sensitivity [Table 4].

DISCUSSION

The prevalence of the nosocomial invasive *Candida* infection is on the rise, which is more or less similar to the trend of the increasing use of indwelling devices and modern medical procedures. The prevalence of candidemia in the PICU in our study was found to be 3.88%.

Several studies have shown *Candida*, particularly the albicans strain, as one of the major causes of bloodstream infection in the hospital setting.[4,7,10] However, gradually, there appears to be a shift toward the NAC species as a cause of candidemia. In this study, most of the isolates (86.1%) are NAC. A study by MacDonald *et al*.[11] found 58% of candidemia cases in children to be caused by NAC. The continuous exposure to prophylactic antifungal agents, particularly fluconazole, has led to emergence of NAC species as the predominant cause of candidemia.[12] In this study, *C. tropicalis* has been identified as the most prevalent *Candida* species (44.4%). Similar results suggesting the high prevalence of *C. tropicalis* in the range of 35.6% and 39.7%

Table 2: Factors associated with mortality among children with candidemia

	Death, *n* (%)	Survived, *n* (%)	*P**
Gender			
Female	1 (7.10)	13 (92.9)	0.628
Male	4 (18.20)	18 (81.80)	
Age group (years)			
<1	1 (7.70)	12 (92.30)	0.287
1-5	2 (33.30)	4 (66.70)	
>6	2 (11.80)	15 (91.20)	
Broad-spectrum antibiotic exposure			
No	2 (11.80)	15 (91.20)	0.988
Yes	3 (15.80)	16 (84.20)	
Central venous catheter			
No	0 (0.00)	17 (100)	0.047
Yes	5 (26.30)	14 (73.70)	
Urinary catheter			
No	0 (0.00)	15 (100)	0.062
Yes	5 (23.80)	16 (76.2)	
Mechanical ventilation			
No	0 (0.00)	15 (100)	0.062
Yes	5 (23.80)	16 (76.2)	
Candida species			
Albicans	0	5 (100)	1
NAC$	5 (16.1)	26 (83.9)	
Fluconazole sensitive			
No	5 (22.7)	17 (77.3)	0.134
Yes	0	14 (100)	

*Fisher's exact test. $NAC: Non-albicans candida

have been reported from South India.[13,14] The isolation of *C. glabrata* (16.7%) and *C. parapsilosis* (16.7%) was also found to be higher than *C. albicans* in this study. The incidence of *C. glabrata* is increasing remarkably, so is its resistance to the azole group.[15]

Studies suggest central venous catheterization as an important predisposing factor for candidemia.[16,17] In our study, the presence of a central venous line was significantly associated with high mortality in children with candidemia (19 children with $P = 0.047$). Considering this, the critical care society has strongly recommended removing the central line catheter as early as possible in the cases of candidemia.[18] *C. parapsilosis* has been particularly implicated in causing the intravascular catheter-related infection in neonates and pediatric age group.[19]

The presence of a urinary catheter is usually associated with urinary tract infection of fungal origin. Candiduria can sometimes be an indicator of impending sepsis in PICU-admitted patients.[7] The urinary catheter was present in 58.3% of the cases of candidemia in this study. Similar results have been obtained by Giri *et al.* (55.9%) and Xess *el al.* (55.6%).[7,10] In the present study, almost all the *Candida* species isolated (34/36) are found to be susceptible to amphotericin B, whereas fluconazole resistance was seen in two-third of the cases, which is different from the other Indian studies reported by Bhattacharjee and Kothari and Sagar.[20,21]

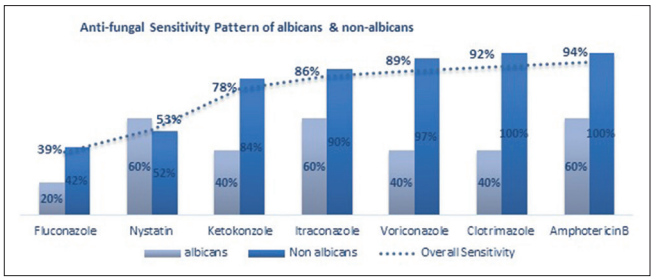

Figure 2: Comparative sensitivity pattern of albicans and non-albicans

A study on 595 cases of candidemia conducted by Badiee and Alborzi[22] demonstrated *C. albicans* to be having highest sensitivity to caspofungin (98.2%), followed by voriconazole (94%), amphotericin B (93%), ketoconazole (90.6%), and fluconazole (89.5%). On the other hand, the NAC isolates such as *C. krusei* and *C. glabrata* strains showed only 30%–40% sensitivity to fluconazole. The sensitivity to caspofungin was the highest (96%) and that to amphotericin B, ketoconazole, and voriconazole was in the range of 85%–93%.

Another study conducted by Hii *et al.*[23] on the resistance rates of NAC infections showed that *C. tropicalis* was the predominant non-albicans candidemia pathogen (42.4%) and showed 36.3% nonsensitivity to fluconazole. These findings closely resembled the findings of our study.

In our study, the sensitivity to amphotericin, clotrimazole, and voriconazole was high. The sensitivity to amphotericin B by NAC and albicans was 94% and 60%, respectively, followed by clotrimazole 92% and 40% and voriconazole 89% and 40%. Hence, these drugs could be a better choice of antifungals when started empirically. Similar findings also have been reported by Madhavan *et al.* and Balaram *et al.*[24,25] These findings may help in treating fluconazole-resistant strains.

As a protocol, antifungals are started in our unit in all high-risk patients including abdominal surgery, broad-spectrum antibiotic therapy, central line or urinary catheter, intensive care unit stay for more than 4 days, persistence of fever, and in cases, developing thrombocytopenia. Fluconazole is started in them empirically till the culture and sensitivity report is available.

There were five deaths (13.8%) in our study, all of which were from the non-albicans group. Dimopoulos *et al.*[26] similarly reported a higher mortality due to NAC candidemia than *C. albicans* in nonimmunosuppressed, nonneutropenic patients. Although the cause is unclear, delayed initiation of therapy or inappropriate treatment (owing to the slower

Table 3: Determinants influencing candidemia with albicans Vs NAC

Determinants		Candida groups		*P* Value
		Albicans	Non-albicans	
Age group	<1 Yr	2	22	0.623
	1-5 Yr	0	05	
	>5 Yr	3	15	
Gender	Female	1	13	0.628
	Male	4	18	
Broad spectrum	Yes	4	14	0.148
antibiotic exposure	No	1	17	
Urinary catheter	Yes	2	19	0.63
	No	3	12	
C.V. catheter[a]	Yes	3	16	0.999
	No	2	15	
Mechanical Ventilation	Yes	0	21	0.008
	No	5	10	
Use of Vasoactive	Yes	1	23	0.034
Agents	No	4	08	
Blood transfusion	Yes	1	3	0.466
	No	4	28	
Peritoneal dialysis	Yes	0	2	0.999
	No	5	29	
Fluconazole	Sensitive	1	13	0.628
	Resistant	4	18	
Outcome	Survived	5	26	0.999
	Death	0	5	

[a]Central venous catheter

Table 4: Species-wise sensitivity pattern of *Candida isolates*

Antifungal agent	Isolated *Candida* species from blood					
	Candida albicans (*n*=5), *n* (%)	*Candida krusei* (*n*=2), *n* (%)	*Candida glabrata* (*n*=6), *n* (%)	*Candida parapsilosis* (*n*=6), *n* (%)	*Candida pelliculosa* (*n*=1), *n* (%)	*Candida tropicalis* (*n*=16), *n* (%)
Nystatin	3 (60)	0	5 (100)	3 (50)	1 (100)	7 (46.7)
Amphotericin B	3 (60)	2 (100)	6 (100)	6 (100)	1 (100)	16 (100)
Clotrimazole	2 (40)	2 (100)	6 (100)	6 (100)	1 (100)	16 (100)
Ketoconazole	2 (40)	1 (50)	6 (100)	6 (100)	1 (100)	12 (75)
Voriconazole	2 (40)	2 (100)	6 (100)	6 (100)	1 (100)	15 (93.8)
Fluconazole	1 (20)	0	5 (83.3)	4 (66.7)	0	4 (25)
Itraconazole	3 (60)	1 (50)	6 (100)	6 (100)	1 (100)	14 (87.5)

growth of NAC isolates on primary culture) and severity of illness in patients with NAC candidemia may be the possible reasons. Patients on mechanical ventilation and the use of vasopressors were strongly associated with mortality in our study.

The mortality rate in this study was lower (13.8%) than that of other various other studies conducted in different parts of India.[7,16,25] A review article has suggested the mortality rate in the range of 10%–49%.[5]

CONCLUSION

NAC species were the more common cause of candidemia in this study, *C. tropicalis* being the most common. Overall, the *Candida* species were more sensitive to amphotericin, clotrimazole, and voriconazole than fluconazole. Non-albicans candidemia and the use of central venous catheters were associated with higher mortality rates. However, these findings need to be validated by more extensive prospective studies, which would help in a perfect choice of antifungal therapy.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Secondary bacterial infection in dengue fever and associated risk factors – An observational study in children

Sridhurga Udayasankar, Vijayanand Sivakumar[1], Raja Sundaramurthy[2]

Departments of Paediatrics, [1]Anaesthesia and Critical Care Medicine, and [2]Microbiology, Velammal Medical College Hospital and Research Institute, Madurai, Tamil Nadu, India

Abstract

Background: Dengue fever remains one of the leading causes of hospitalization among children in endemic areas. Clinical manifestations of dengue fever are highly variable. There are only a few pediatric dengue fever cases reported with secondary bacterial infection. Knowledge of prevalence, risk factors, and predictors of bacterial infection among children with dengue fever is essential to initiate antibiotics.

Objective: The objective of this study was to assess the prevalence of bacterial infection, analysis of risk factors, and predictors of bacterial infection among dengue fever patients with prolonged or recurrent fever after critical phase of illness.

Design: This was a retrospective observational study.

Setting: This study was conducted in the pediatric department of a tertiary hospital.

Patients: Children with dengue fever who present with persistent or prolonged fever even after critical phase were included in the study.

Results: Eighty-three children with dengue fever who had persistent fever for more than 5 days or recurrent fever were included in our study. Twenty-nine patients (34.9%) had definite secondary bacterial infection confirmed by positive culture and seven patients had probable secondary bacterial infection. The risk of secondary bacterial infection was higher in infants ($P = 0.054$), children who had fever >5 days on admission ($P = 0.020$), and children who had severe dengue ($P = 0.016$). The duration of hospital stay increased significantly in those with secondary bacterial infection ($P = 0.041$). No mortality was reported in culture-positive group.

Conclusion: Our study highlights the increased risk of multidrug-resistant secondary bacterial infection among infants and in children who presented with fever >5 days and severe dengue fever. Hence, a low threshold to work up for secondary bacterial infections and early initiation of empirical antibiotics is warranted in these patients.

Keywords: Dengue fever, immune paralysis, infants, secondary bacterial infection

Address for correspondence: Dr. Sridhurga Udayasankar, Department of Paediatrics, Velammal Medical College Hospital and Research Institute, Madurai, Tamil Nadu, India.
E-mail: drsridhurga@gmail.com

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INTRODUCTION

Dengue fever is the most widespread mosquito-borne arboviral infection in tropical and subtropical regions.[1] The estimated prevalence of dengue fever is 390 million infections annually, with 96 million of these infections being clinically apparent, threatening more than 40% of the world's population.[2,3] Clinical manifestations of dengue fever are highly variable, ranging from mild flu-like illness to severe life-threatening disease – dengue hemorrhagic fever or shock syndrome.[4,5]

Dengue fever is characterized by three phases – febrile, critical, and recovery. During the critical phase, there is an increase in vascular permeability due to endothelial cell dysfunction resulting in capillary leakage followed by coagulopathy, hemorrhage, and multi-organ dysfunction.[6] Although there is no specific treatment for dengue fever, early detection and supportive management is the key in reducing mortality as per the new clinical management guidelines for dengue (dengue with/without warning signs and severe dengue) by the World Health Organization (WHO).[7]

A majority of dengue fever patients recover with supportive management, but a few develop either cytokine storm manifesting as secondary hemophagocytic lymphohistiocytosis[8] or sepsis, due to over activation of compensatory anti-inflammatory response causing immune paralysis.[9] Many other hypotheses such as endothelial cell disintegration by antibodies against dengue nonstructural protein 1 and capillary leak leading to transgut migration of microbes are postulated for bacterial infections in dengue fever patients. The outcome of dengue fever with bacterial infection is worse than the severe dengue illness itself.[10,11]

Although there are many hypotheses, the exact prevalence of bacterial infections occurring either as concurrent or superadded infection among dengue patients is lacking in our setup.[1,12] Most of the studies are also carried out in adult population which may not be applicable to pediatric population. Dengue clinical management guidelines do not recommend the use of antibiotics during any of the stages of dengue due to sparse evidence of secondary bacterial infections in severe dengue patients.[7]

Hence, our present study is aimed to assess the prevalence of bacterial infection, analysis of risk factors, and predictors of bacterial infection among dengue fever children with prolonged or recurrent fever.

METHODS

This retrospective observational study was carried out in the pediatric department of a large tertiary care medical college hospital in South India after the institute ethical committee approval (IEC No: VMCIEC/18/2018). Children <16 years of age admitted between July and December 2017 were included in the study. Dengue fever was diagnosed in children with compatible clinical features (probable dengue as defined by the WHO progressing to develop either warning signs or shock) and laboratory findings (hemoconcentration, thrombocytopenia, leukopenia, or radiological signs of plasma leakage). This was confirmed either by positive NS1 antigen and/or immunoglobulin M (IgM) antibodies by enzyme-linked immunosorbent assay (ELISA) against dengue (Panbio Dengue NS1, IgM, IgG ELISA-Standard Diagnostics, Gyeonggi, Republic of Korea). Isolated IgG ELISA-positive patients with no other clinical signs were excluded from the study.

Out of these dengue-positive cases, we included children who had persistent or recurrent fever even after the critical phase. Critical phase was defined as per the WHO criteria and classified as warning signs and severe dengue. Children were considered to have recovered once the warning signs subsided or hemodynamic instability improved with a decrease in hematocrit and improving platelet count. Children who continued to have fever through critical phase into recovery phase (fever >5 days) were defined as persistent fever, and children who became afebrile during the course and then developed fever during recovery phase were defined as recurrent fever. These children were started on antibiotics as per hospital antibiotic policy (BL/BLI – injection Pip–Taz). These children were investigated for bacterial infections. These children were investigated for bacterial infections with complete hemogram, C - Reactive Protein (CRP), Chest Xray (In children with respiratory symptoms), blood culture, urine culture, cerebrospinal fluid analysis (in children with seizures, altered sensorium), serology for bacterial infection (Widal, Scrub antibody). Those who had any one positive culture were considered as definite secondary bacterial infection following dengue fever. Based on these, participants were divided into two groups: one with definite secondary bacterial infection and the other group whose cultures were negative. Among those with culture negative, probable secondary bacterial infection was considered if CRP was positive (>6 mg/L) or leukocytosis (>15,000/cu mm).

The demographic, clinical, and laboratory data were retrieved from case records. These parameters were

compared between children who had secondary bacterial infection (definite and probable) and those who did not have any evidence of secondary bacterial infection.

Statistic analysis

Categorical variables were presented by frequency distribution and analyzed using univariate analysis (Chi-square test). Risk factors for bacteremia were further assessed using multivariate analysis. Any $P < 0.05$ was considered statistically significant.

RESULTS

During our study period, 423 children were admitted in our pediatric department with a diagnosis of dengue fever. Eighty-three children with persistent or recurrent fever were included in the study. Twenty-nine children (34.9%) had any one culture positive which was labeled as definite secondary bacterial infection, and 54 children had culture negative. Among 54 children who had culture negative, 7 had sepsis screen positive (positive CRP or leukocytosis) and labeled as probable secondary bacterial infection. Six children had elevated serum ferritin and the rest 41 were inconclusive. Those six children who had high ferritin were worked up for hemophagocytic lymphohistiocytosis and were excluded from further analysis. The number of children who had probable secondary bacterial infection was too less; hence, both groups – culture-positive sepsis and probable sepsis – are combined together for further analysis. The prevalence of secondary bacterial infection in our study population was 8.5% (36/423). On analyzing the 29 children with secondary bacterial infection, 6 had bacteremia, 20 had urinary tract infection (UTI), 2 had UTI with bacteremia, and 1 had bacteremia with CSF culture positive. Organisms and their resistance patterns are depicted in Table 1.

Analysis of demographic details of the study participants revealed 35 males and 42 females. The baseline characteristics of the study population are given in Table 2. Sixteen males and 20 females had secondary bacterial infection, and there was no significant difference between them. While analyzing the age group, secondary bacterial infection was highest among infants (7/10) ($P = 0.054$). Characteristics of fever analysis showed that secondary bacterial infection was higher in children (13/19) with longer fever duration (>5 days), with $P = 0.020$. Of those 36 children, 27 had persistent fever and 9 had recurrent fever. Seven out of eight children with severe dengue developed secondary bacterial infection ($P = 0.016$). Length of hospital stay was longer among children with secondary bacterial infection compared to children who recovered without bacterial infection ($P = 0.041$). A comparison of the hematological parameters did not show any significant difference between both the groups.

The demographic, clinical and hematological parameters of both groups are compared in Table 3 and 4. Table 4 shows the risk associated with the independent variables sex, age groups, fever days, severity of illness, length of hospital stay, and hematological parameters and the dependent variable on multivariate analysis.

DISCUSSION

Despite the powerful existence of the National Vector Borne Disease Control Programme (NVBDCP), dengue itself remains one of the biggest concerns in India with the high disease burden and frequent outbreaks leading to 1.88 lakhs positive cases and 325 death in 2017 as per NVBDCP data.[13] Secondary bacterial infection in dengue still remains an area to be addressed, and also, it is the need of the hour to make a decision when to start the antibiotics along with routine supportive management. Our study is

Table 1: Secondary bacterial culture isolate and resistance pattern of organisms

	Number of isolate	
Type of culture	**Organism isolated**	**Resistance pattern**
Blood culture (6)	*Staphylococcus aureus* (2)	MRSA (2)
	Escherichia coli (2)	ESBL (2)
	Coagulase-negative *Staphylococcus* (1)	MRCONS (1)
	Streptococcus pneumoniae (1)	-
Urine culture (20)	*Escherichia coli* (10)	ESBL (6); CRE (4)
	Enterococcus faecalis (5)	-
	Klebsiella pneumonia (2)	CRE (2)
	Enterobacter aerogenes (1)	ESBL (1)
	Acinetobacter baumannii (1)	CRAB (1)
	Pseudomonas aeruginosa (1)	-
Urine and blood (2)	*Pseudomonas aeruginosa* (2)	-
Blood and CSF (1)	*Enterobacter aerogenes* (1)	ESBL (1)

MRSA: Methicillin-resistant *Staphylococcus aureus,* MRCONS: Methicillin-resistant coagulase-negative *Staphylococcus,* ESBL: Extended-spectrum beta-lactamase, CRE: Carbapenem-resistant Enterobacteriaceae; CRAB: Carbapenem-resistant *Acinetobacter baumannii*, CSF: Cerebrospinal fluid

Table 2: Baseline characters of study population (*n*=77)

Parameters	*n* (%)
Gender	
Male	35 (45.5)
Female	42 (54.5)
Age group	
Infant	10 (13.0)
Toddlers	16 (20.8)
School age and adolescence	51 (66.2)
Fever days	
<5	58 (75.3)
>5	19 (24.7)
Fever pattern	
Persistent	58 (75.3)
Recurrent	19 (24.7)
Lowest TC	
Normal (5000–15,000)	26 (33.8)
Abnormal (<5000, >15,000)	50 (64.9)
Lowest ANC	
Normal (500–1500)	40 (51.9)
Neutropenia (>1500)	30 (39.0)
Severe (<500)	6 (7.8)
Lowest platelet	
Normal (150–450)	18 (23.4)
Thrombocytopenia (<150, >450)	58 (75.3)
Highest MPV	
Normal (7–10.5)	63 (81.8)
Abnormal (<7, >10.5)	13 (16.9)
Clinical presentation	
No warning sign	36 (46.8)
Warning sign	33 (42.9)
Severe	8 (10.4)
Length of hospital stay	
≤5	31 (40.3)
6–10	39 (50.6)
>10	7 (9.1)
IV fluid duration	
<2	53 (54.5)
>2	24 (45.5)
IV drug duration	
<3	42 (54.5)
>3	35 (45.5)

ANC: Absolute neutrophil count, TC: Total count, MPV: Mean platelet volume, IV: Intravenous

one of the few studies in children describing secondary bacterial infection associated with dengue and risk factors associated with it.[14,15]

According to our study, children with dengue fever who developed secondary bacterial infection were 8.5% similar to the study results of Pothapregada *et al.* (7.2%) but higher compared to the results of Pancharoen and Thisyakorn (0.5%).[16,17] Six out of 29 (20.7%) definite secondary bacterial infection children had bacteremia which was in concordance with the study results of Leo *et al.*,[18] who reported that 14.3% of the dengue patients had secondary bacteremia. Few other studies by Lahiri *et al.,* Ong *et al.*, and Lee *et al.* had reported a higher rate of bacteremia 44.4%, 42.9%, and 37.5%, respectively.[19-21] This difference may be attributed to the difference in the study population group as most of the studies were done in adults. None of our children who developed bacteremia had risk factors such as central line and arterial line. Only one child was ventilated for altered sensorium.

Among our bacteremia isolates, 2 (33.3%) were methicillin-resistant *Staphylococcus aureus* and 2 (33.3%) were *Escherichia coli (E. coli)* which is discordant from the other study results as many had reported Gram-negative bacteremia as the most common. *Staphylococcus* infections are also raising concerns in our setup.

Among these isolates extended spectrum beta lactamases producing enterobacteriaceae and carbapenem resistant enterobacteriaceae were almost equal (ESBL - 7 and CRE - 6). 2 children with *Pseudomonas aeruginosa* had urosepsis with positive blood culture. None of these children with confirmed urinary tract infection were catheterised during hospital stay. In children with confirmed or probable secondary bacterial infection, only 2 children were catheterised, one with probable sepsis and another child with *enterobacter* meningitis. The reason for this high incidence of UTI could not be explained with the present study and needs further evaluation.

On comparing the demographic details of both the groups, there was no statistically significant difference between males and females. In our study, the odds of secondary bacterial infection is high in infants and decreases with age (odds ratio [OR] – 5.5; $P = 0.054$). This may be explained by the immature immune system in infants making them vulnerable to secondary bacterial infection.

Children who had fever more than 5 days on admission had significantly higher secondary bacterial infection than children who had fever less than 5 days on admission (OR 4.94, $P = 0.020$). The odds of secondary bacterial infection was higher in children with severe dengue (OR – 22.5; $P = 0.016$). This can be explained by an increase in intervention and gut translocation of microbes. Although some studies have shown an association of hematological parameters and secondary bacterial infection, our study findings have not made any significant association between secondary infection and hematological parameters lowest total count, absolute neutrophil count, platelet count, and mean platelet volume observed anytime during the illness which is similar to the study results of Kumar *et al.*[22]

It was also noted that children with secondary bacterial infection had significantly prolonged hospital stay than children who recovered without any infection. This shows the additional health-care burden imposed by secondary

Table 3: Comparison of demographic, clinical, and hematological parameters

	Parameters	Sepsis (*n*=36), *n* (%)	No sepsis (*n*=41), *n* (%)	Total	OR (95% OR)	*P*
Gender	Male	16 (45.7)	19 (54.3)	35	1.0 (ref)	
	Female	20 (47.6)	22 (52.4)	42	1.080 (0.439–2.654)	0.868
Age group	Infant	7 (70.0)	3 (30.0)	10	3.930 (0.906–17.037)	0.067
	Toddlers	10 (62.5)	6 (37.5)	16	2.807 (0.880–8.958)	0.081
	School age and adolescence	19 (37.3)	32 (62.7)	51	1.0 (ref)	
Fever days	<5	23 (39.7)	35 (60.3)	58	1.0 (ref)	
	>5	13 (68.4)	6 (31.6)	19	3.297 (1.096–9.916)	0.034
Fever pattern	Persistent	27 (46.6)	31 (53.4)	58	0.968 (0.343–2.732)	0.951
	Recurrent	9 (47.4)	10 (52.6)	19	1.0 (ref)	
Lowest TC	Normal (5000–15000)	15 (57.7)	11 (42.3)	26	1.0 (ref)	
	Abnormal (<5000, >15000)	21 (42.0)	29 (58.0)	50	0.531 (0.203–1.386)	0.196
Lowest ANC	Normal (500–1500)	18 (45.0)	22 (55.0)	40	1.0 (ref)	
	Neutropenia (>1500)	17 (56.7)	13 (43.3)	30	1.598 (0.616–4.148)	0.335
	Severe (<500)	1 (16.7)	5 (83.3)	6	0.244 (0.026–2.286)	0.217
Lowest platelet	Normal (150–450)	11 (61.1)	7 (38.9)	18	1.0 (ref)	
	Thrombocytopenia (<150, >450)	25 (43.1)	33 (56.9)	58	0.482 (0.164–1.421)	0.186
Highest MPV	Normal (7–10.5)	28 (44.4)	35 (55.6)	63	1.0 (ref)	
	Abnormal (<7, >10.5)	8 (61.5)	5 (38.5)	13	2.000 (0.589–6.794)	0.267
Clinical	No warning sign	13 (36.1)	23 (63.9)	36	1.0 (ref)	
presentation	Warning sign	16 (48.5)	17 (51.5)	33	1.665 (0.635–4.365)	0.300
	Severe	7 (87.5)	1 (12.5)	8	12.385 (1.368–112.096)	0.025
Length of	≤5	9 (29.0)	22 (71.0)	31	1.0 (ref)	
hospital stay	6–10	21 (53.8)	18 (46.2)	39	2.852 (1.050–7.744)	0.040
	>10	6 (85.7)	1 (14.3)	7	14.667 (1.539–139.793)	0.020
IV fluid duration	<2	24 (45.3)	29 (54.7)	53	1.0 (ref)	
	>2	12 (50.0)	12 (50.0)	24	1.208 (0.460–3.174)	0.701
IV drug duration	<3	17 (40.5)	25 (59.5)	42	1.0 (ref)	
	>3	19 (54.3)	16 (45.7)	35	1.746 (0.705–4.324)	0.228

ANC: Absolute neutrophil count, TC: Total count, MPV: Mean platelet volume, OR: Odds ratio, IV: Intravenous

Table 4: Risk factors analysis of secondary bacterial infection using multivariate analysis model

Parameters	Sepsis (*n*=36), *n* (%)	No sepsis (*n*=41), *n* (%)	Total	OR (95% OR)	*P*
Gender					
Male	16 (45.7)	19 (54.3)	35	1.0 (ref)	
Female	20 (47.6)	22 (52.4)	42	1.025 (0.322–3.257)	0.967
Age group					
Infant	7 (70.0)	3 (30.0)	10	5.526 (0.970–31.483)	0.054
Toddlers	10 (62.5)	6 (37.5)	16	1.336 (0.318–5.612)	0.693
School age and adolescence	19 (37.3)	32 (62.7)	51	1.0 (ref)	
Fever days					
<5	23 (39.7)	35 (60.3)	58	1.0 (ref)	
>5	13 (68.4)	6 (31.6)	19	4.948 (1.286–19.037)	0.020
Lowest TC					
Normal (5000–15,000)	15 (57.7)	11 (42.3)	26	1.0 (ref)	
Abnormal (<5000, >15,000)	21 (42.0)	29 (58.0)	50	0.649 (0.192–2.198)	0.487
Lowest platelet					
Normal (150–450)	11 (61.1)	7 (38.9)	18	1.0 (ref)	
Thrombocytopenia (<150, >450)	25 (43.1)	33 (56.9)	58	0.332 (0.086–1.278)	0.109
Clinical presentation					
No warning sign	13 (36.1)	23 (63.9)	36	1.0 (ref)	
Warning sign	16 (48.5)	17 (51.5)	33	1.805 (0.454–7.174)	0.402
Severe	7 (87.5)	1 (12.5)	8	22.580 (1.775–287.269)	0.016
Length of hospital stay					
≤5	9 (29.0)	22 (71.0)	31	1.0 (ref)	
6-10	21 (53.8)	18 (46.2)	39	1.960 (0.497–7.728)	0.336
>10	6 (85.7)	1 (14.3)	7	14.100 (1.119–177.751)	0.041

OR: Odds ratio

infection prolonging need for antibiotic therapy and hospital stay. However, there was no mortality, though one of the patients with *Enterobacter* meningitis had mild neurological deficit on follow-up. One child who had urosepsis presented to PICU with septic shock.

Limitations

The limitation of our study is that it is a retrospective study, data retrieved from case sheets, which has its own limitation. A larger sample size and a prospective study is needed.

CONCLUSION

Secondary bacterial infection in children with dengue fever was higher in infants, children with severe dengue, and children who had fever >5 days on admission. Secondary bacterial infections result in prolonged hospital stay. Hence, a low threshold to work up for secondary infection is warranted in infants and children with severe dengue, and early initiation of antibiotics needs to be considered in appropriate situation.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Utility of a clinical pharmacist in the pediatric intensive care unit to identify and prevent medication errors

Ramaning Loni, Siddu Charki[1], Trimal Kulkarni[1], Mahesh Kamale[2], Laxman H. Bidari[2]

Department of Pediatrics, Aditya Birla Memorial Hospital, Pune, Maharashtra, [1]Department of Pediatrics, Shri BM Patil Medical College and Hospital, [2]Dr. Bidari"s Ashwini Hospital and Postgraduate Centre, Vijayapura, Karnataka, India

Abstract

Background: Medication errors (MEs) in the pediatric intensive care units (PICUs) are common, predictable, serious, and preventable. Patients in the intensive care unit (ICU) are more vulnerable to increased MEs due to the complexity of underlying critical illness.

Aim: The aim of the study was to determine the incidence, types, adverse effects, and outcome of MEs identified by a clinical pharmacist in the PICU.

Subjects and Methods: This prospective observational study was conducted in the PICU of Dr. Bidari's Ashwini Hospital, Vijayapura, using daily observation of medical records from February 17, 2018, to November 30, 2019, using NCC-MERP guidelines to define the ME.

Results: The incidence of MEs was 250/1000 patient days. Prescription errors were most common with 59.3% (3007), followed by administration errors with 21% (1100). Dispensing and transcription errors were 10.4% (528) and 8.6% (441), respectively. In prescription error, dosage error was predominant with 76% (2286), followed by documentation error in 15% (451), In transcription errors, incorrect drug dose was the most common error with 47% (208), followed by the wrong drug in 23% (102). In the case of dispensing errors, a supply of incorrect medicines was most common with 61% (321), followed by the unavailability of medicines with 24% (126). In administration errors, medicines given at the wrong time duration were observed in 55% (603), followed by orders not carried by nurses at an appropriate time in 23% (255). National coordination committee for ME reporting and prevention index severity classification includes Category B, the most common with 61% (3096) incidence, followed by Category C with 34% (1725).Total 23 patients developed probable adverse side effects. The mortality was only 1% (28) in this study, which was crude mortality of our PICU.

Conclusions: (i) Prescription errors were the most common MEs followed by administration errors. (ii) The role of the clinical pharmacist was vital in identifying and avoiding the existing burden of MEs in the PICU. (iii) Reinforcement of structured training of the medical and paramedical staff is essential regarding the safe medication practices.

Keywords: Clinical pharmacist, medication errors, pediatric intensive care unit

Address for correspondence: Dr. Ramaning Loni, Aditya Birla Memorial Hospital, Chinchwad, Pune - 411 033, Maharashtra, India.
E-mail: raj2031979@gmail.com

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INTRODUCTION

Medication errors (MEs) in the pediatric intensive care units (PICUs) are common, predictable, serious, and preventable.[1] The prevention of MEs forms a quality control measure for ensuring patient safety and avoiding patient harm.[1,2] Patients admitted to an intensive care unit (ICU) experience 1.7 times more medical errors each day when compared to non-intensive care patients, and some may be life-threatening.[1,2] MEs in the United States alone (inpatient department and outpatients) may account for more than 7000 deaths yearly.[3] The costs of MEs and the incidence of adverse drug events (ADEs) are extremely high.[4] MEs can lead to high morbidity, unnecessary hospital stay, diagnostic investigations, and even iatrogenic mortality.[4,5]

The magnitude of MEs is definitely higher in intensive care setup due to the complexity of the underlying disease condition and other factors.[4,5] The goal of the World Health Organization with its global patient safety challenge strategy is to reduce the severe patient harm associated with MEs by 50% within the next 5 years duration as the children have the highest risk of drug-related preventable harm. To help this global campaign, it is essential to know the actual burden of the errors and related ADEs in seriously ill children admitted to the PICU.[6] The incidence of MEs has been reported to be 100–400/1000 patient days in children.[7] Medications errors can any happen at many stages from prescription, dispensing, transcription, and till the administration of medications. There is a need for the development and optimization of patient safety profiles and policies to block the drug-related patient harm. The rate of MEs declined with structured training before and after pediatric cardiopulmonary resuscitation (CPR), but documentation errors could not be eliminated completely in a study done by Sankar *et al*.[8] The cognitive burden in the form of physical stress and social burden on the duty doctors are the main contributing factors associated with prescription and transcription errors.[9]

Even though lot of research is available on MEs in children, to improve the quality of care and patient safety in our hospital, this study was undertaken.

SUBJECTS AND METHODS

This prospective observational study was conducted in 20-bedded secondary level care, PICU from February 17, 2018, to November 30, 2019 (22 months), catering general pediatric critical care, pediatric cardiac critical cases, and all other pediatric subspecialties patients also. Daily review of medical records was performed by a full-time clinical pharmacist in the PICU. The following records were reviewed: doctor's order sheet, daily plan sheet, transcription sheet, nursing charts and notes, and drug dispensing by in-house pharmacy outlet. All data were reviewed by a clinical pharmacist, consultant pediatric intensivist, and senior consultant pediatrician to confirm the type of the errors. All the verbal orders given during emergencies like cardiac arrest were entered in the drug order sheet within a few hours of the administration and checked by the consultant on duty on the same day. The clinical pharmacist intervened to prevent MEs in conjunction with medical staff. The clearance from the ethical committee of the hospital was approved.

ME is defined as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health-care professional, patient, or consumer [Figure 1].[10]

Harm

It includes impairment of the physical, emotional, or psychological function or structure of the body and/or pain resulting therefrom.

Monitoring

Monitoring is done to observe or record relevant physiological or psychological signs.

Intervention

It may include a change in therapy or active medical/surgical treatment.

Intervention necessary to sustain life

It includes cardiovascular and respiratory support (e.g., CPR, defibrillation, intubation, etc.).

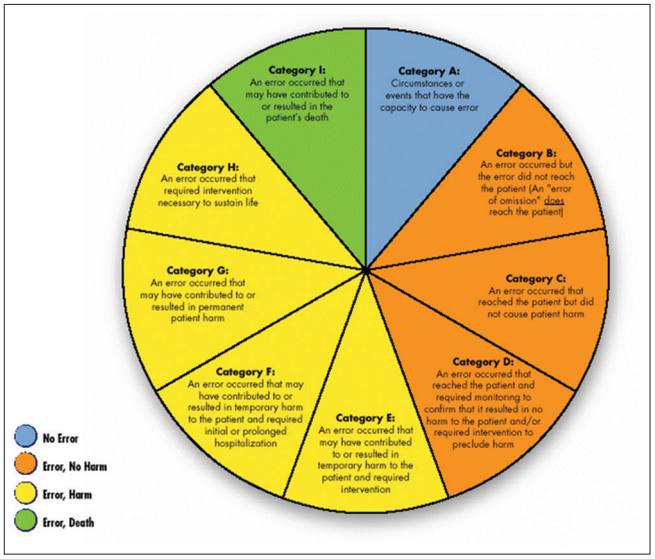


Figure 1: NCC -MERP Index for Categorizing Medication Errors[10]

According to the NCC MERP index [Figure 1], the severity of MEs has categorized into A to I Category, i.e., from no error, no harm, to error resulting in the death or might have contributed to death of the patient.

Aim and objective

The aim and objective of the study was to determine the incidence and types, ADEs, and outcome of MEs in the PICU

Inclusion criteria

All children admitted to the PICU in the age group between 1 month of life to 18 years of age were included in the study.

RESULTS

The incidence of MEs was 250/1000 patient days. Prescription errors were most common with 59.3% (3007), followed by administration errors with 21% (1100). Dispensing and transcription errors were 10.4% (528) and 8.6% (441), respectively [Figure 2]. In prescription error, the dosage error was predominant with 76% (2286), followed by documentation error in 15% (451), and drug interaction and therapeutic duplication errors in 4% (120) each, respectively, with least one, medical reconciliation error in 1% (30) [Figure 3].

In transcription errors [Table 1], the incorrect drug dosage was the most common error with 47% (208), followed by the wrong drug in 23% (102), improper dilution in 21% (90), missing the drug to transcribe in 8% (36) with the least one, route of administration not written with 1% (05). In case of dispensing errors, wrong medicines supplied due to improper handwriting was the common with 61% (321), followed by unavailability of medicines with 24% (126), and delayed dispensing of medicines in 12.6% (67), whereas wrong patient medicines supply was the least with 2.4% (14) [Figure 4]. In administration errors, medicines given for wrong time duration observed in 55% (603), followed by orders not carried by nurses at an appropriate time in 23% (255), inappropriate dilution in 9% (101), oxygen therapy not started in time or continued beyond the stop order in 8% (87), wrong intravenous (iv) fluid chosen in 4.5% (48), iv medications continued through an iv catheter which was extravasated in 0.5% (06) [Table 2]. The National Coordination Committee for Medication Error Reporting and Prevention Index Severity Classification

Table 1: Transcription errors

Type of error	Numbers	Percentage
1.Wrong drug	102	23%
2.Incorrect drug dosage	208	47%
3.Improper drug dilution	90	21%
4.The Route of administration not written	05	1%
5.Misses the drug to transcribe	36	8%
Total	441	100

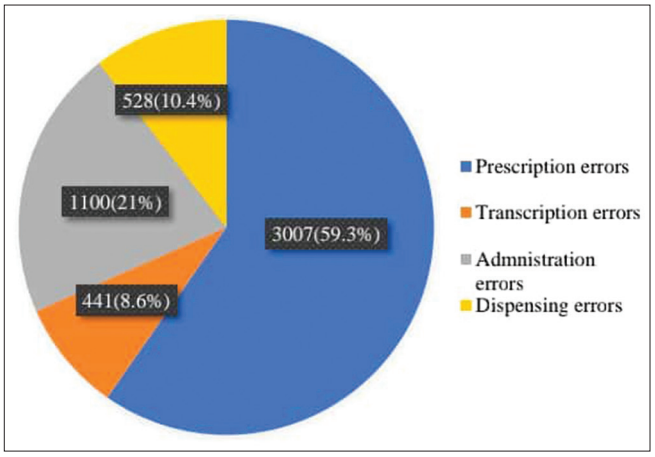


Figure 2: Prescription errors were most common with 59.3% (3007), followed by administration errors with 21% (1100). Dispensing and transcription errors were 10.4% (528) and 8.6% (441), respectively

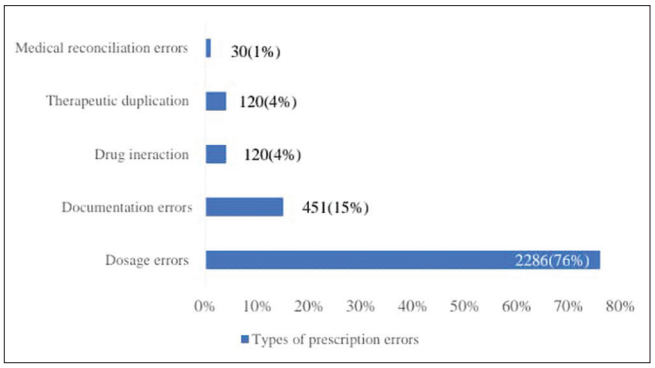


Figure 3: In prescription error, dosage error was predominant with 76% (2286), followed by documentation error in 15% (451), and drug interaction and therapeutic duplication errors in 4% (120) each, respectively, with least one, medical reconciliation error in 1% (30)

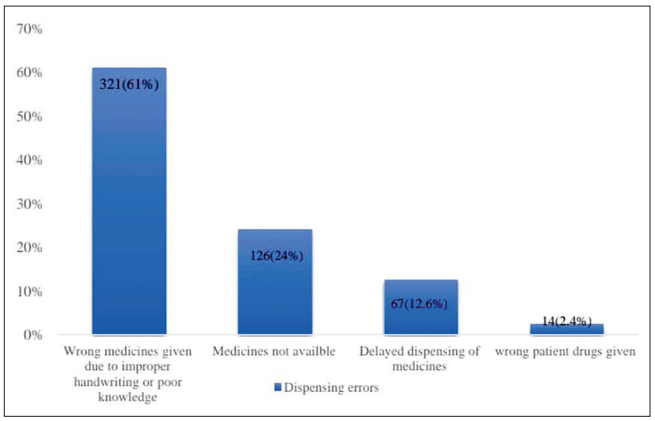


Figure 4: The wrong medicines supplied due to improper handwriting was the common with 61% (321), followed by unavailability of medicines with 24% (126), and delayed dispensing of medicines in 12.6% (67), whereas wrong patient medicines supply was the least with 2.4% (14)

includes Category B, the most common with 61% (3096) incidence, followed by Category C with 34% (1725). A total of 23 patients developed ADEs (Probably) like electrolytes disturbances in the form of hypernatremia in 4 patients, hyperkalemia in 3 patients, renal complication like acute kidney injury, pRIFLE injury stage in 7 children, and thrombocytopenia in 4 patients, QTc prolongation in 3 children, and hypotension in 2 patients due to MEs, but all of them improved [Table 3]. These complications are not completely explained either by medication errors itself or due to the underlying disease condition.

The mortality was only 1% (28) in this study, which was crude mortality of our PICU and 99% (2792) of the children admitted in the PICU improved and discharged.

DISCUSSION

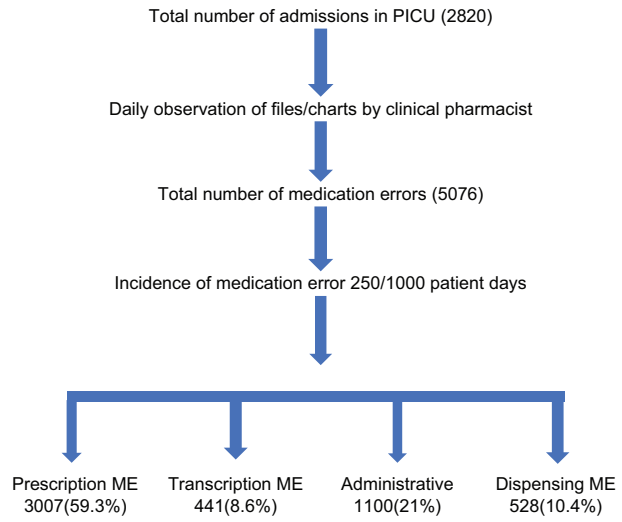
The incidence of MEs [Flow Chart 1] in our study was 250/1000 days or 1.8 MEs per medical record audited, which is comparable to the other studies showing a ME rate of 100–400/1000 patient days in children using direct observation of medical records which is frequently used tool for identifying MEs.[7] The daily chart review or direct observation method is a widely established methodology for identifying MEs in the medical field as compared to other tools like self-reporting.[11] Different studies have proven that pharmacist-led medication reviews have decreased the number of hospital admissions.[12] A systematic review of 38 studies of primary care interventions that were designed to reduce drug-related adverse events proved that most fruitful interventions included a medication review conducted by a pharmacist or other clinicians and medication review by a primary care physician as one component of multicomponent interventions.[13]

In our study [Figure 2], the incidence of prescription, administration, dispensing, and transcription errors was 59.3%, 21%, 10.4%, and 8.6%, respectively, as compared to the study done by Zakharov *et al*.,[14] where prescription, administration, and dispensing errors were 36.8%, 43%, and 20.2%, respectively. The prescription and transcription errors (usual responsibility of medical staff) accounted for 69% of the total MEs, whereas administration errors (usual responsibility of nursing staff) of 21% with the least by pharmacy outlet responsible for dispensing errors of 10.4%.

The most common ME in our study was a prescription error (59.3%) which is comparable to other studies showing prescribing error between 40% and 71.4% in 16 studies.[15,16] The most frequent prescription sub error was dosage

Table 2: Administration errors

Types of error	Numbers	Percentage
1.Medicines given in short time or longer time from prescribed time duration	603	55%
2.Orders not carried by nurses at appropriate time	255	23%
3.Inappropriate dilution	101	9%
4.Oxygen therapy not started in time or continued beyond the stop order	87	8%
5.wrong iv fluid	48	4.5%
6.Medications as iv continued though intracath was extravasated	06	0.5%
Total	1100	100



Flow Chart 1: Flow chart of the study

Table 3: Adverse drug events

System	Type of adverse events with numbers	Reason for error
1.Metabolic	Hypernatremia (04)	IV Sodium bicarbonate therapy, using NS as diluent in most of times
	Hyperkalemia (03)	Tacrolimus, use of Kcl in the maintenance fluids in excessive time, Acute kidney injury
2. Renal	AKI (p RIFLE) Injury stage (07)	Vancomycin use, other nephrotoxic drugs, diuretics etc.
3.Cardiovascular	QTc prolongation (03)	Combination of QTc prolonging drugs such as Azithromycin, fluconazole, and anti-emetic drugs (Domperidone)
	Hypotension (02)	Use of diuretics freely along positive pressure ventilation
4.Hematological	Thrombocytopenia (04)	Heparin/Warfarin therapy Ranitidine Cyclosporine
Total	23	

error, with 76% out of total prescription errors which are comparable to many other studies.[17-19] In some studies, they have found administration error as the most frequently occurring ME, whereas, in our study, administration error was the second most common with 21%. The transcription error [Table 1] noticed in 8.6% of total errors in which the incorrect drug dose was written by staff, it is more as compared to the study done by Haghbin *et al*.[16] with 4.88%. In dispensing error with 10.4% in our study, wrong drugs supplied due to poor handwriting/poor knowledge about the drugs were most common, which is comparable to other studies.[17,20]

In administration error, the common subtype was medications given for the wrong time duration in 55% of cases [Table 2]. This could be because of nurses who do not adhere to strict drug orders or negligence toward timing importance.

The ME severity according to the NCC-MERP categorization [Figure 5] (an error has happened but not entered the patient body) was the most common category (B) with 61%, followed by Category C (an error has happened and entered the patient body but did not lead to any harm) with 34%, while the Category A (circumstances or situations that can lead to an error) 2.4% and Category D (error happened and reached the patient but needs monitoring and or interventions) with 2.6% were the least. Our study is comparable to other studies showing no harm in more than 78% of the studies.[18,19,21,22] Category D contributed little with only 2.6% of the errors where we monitored the child for error-related adverse events.

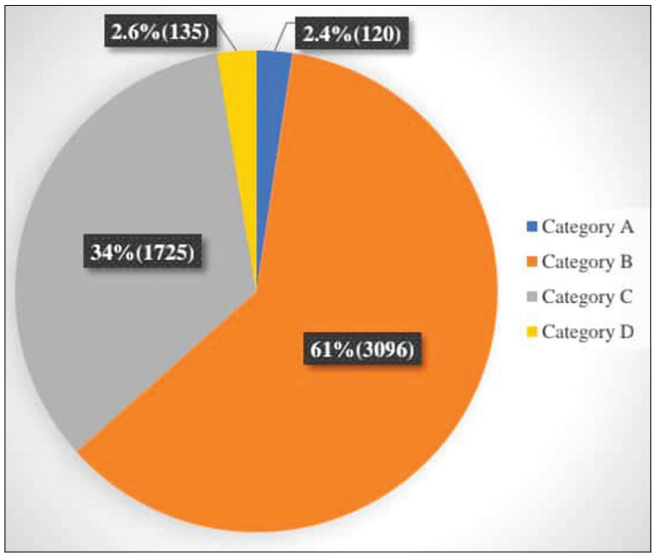


Figure 5: National Coordination Committee for Medication Error Reporting and Prevention Index Severity Classification includes Category B, the most common with 61% (3096) incidence, followed by Category C with 34% (1725)

The observed ADEs were noticed in 0.81%[23] of the total of 2820 patients and less than 0.1% of the total MEs. The ADE rate in our study (0.81%) is very much less as compared to the study done by Kaushal *et al*.,[24] which has reported 2.3% of pediatric inpatients. These ADEs are not entirely explained by MEs alone but by the underlying disease processes too. The ADE included hypernatremia in 4 patients, hyperkalemia in 3 patients, renal complication like acute kidney injury, pRIFLE injury stage in 7 children, and thrombocytopenia in 4 patients, QTc prolongation in 3 children, and hypotension in 2 patients due to MEs, but all of them improved [Table 3]. All of the above ADEs belonged to Category D of the NCC MERP severity classification. These are comparable to other studies.[24,25] These errors could be preventable in more than one-third of the total MEs by not only using computerized physician order entry, bar code system, centralized drug delivery, and structured training program but also using clinical pharmacist assistance.[25-27]

In 92% of MEs, clinicians accepted the advice and suggestions by the clinical pharmacist, but in only 8%, we had biased decisions due to bias in the literature itself.

Almost 99% (2792 patients) of the study population survived, but only 1% (28) of them died as they had underlying critical illness and multi-organ dysfunction syndrome and all of them had mild MEs severity that means they belonged to Category B (17 patients) and Category C (11 patients) as per the NCC-MERP severity categorization. This is our crude PICU mortality rate [Figure 6].

CONCLUSIONS

- Prescription errors were the most common MEs followed by administration errors

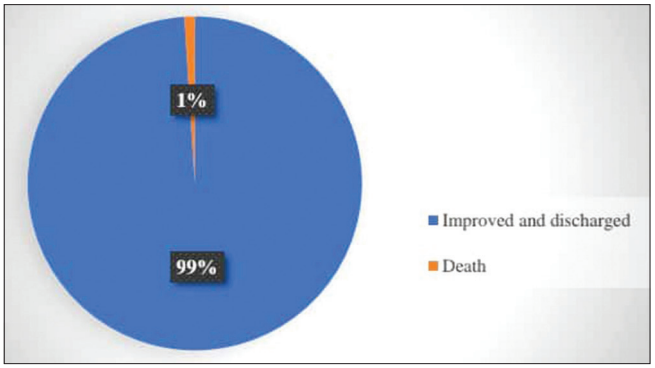


Figure 6: The mortality was only 1% (28) in this study, which was crude mortality of our PICU and 99% (2792) of the children admitted in the PICU improved and discharged

- The role of the clinical pharmacist was vital in identifying and avoiding the existing burden of MEs in the PICU.
- Reinforcement of structured training of the medical and paramedical staff is essential.

Limitation of the study

The causative factors are not studied, and recognizing the exact incidence of the ADEs was difficult to evaluate.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

A retrospective study of etiology, clinical features, management, and outcomes in children with necrotizing pneumonia

Maaz Ahmed, K. S. Sanjay, M. L. Keshavamurthy, G. V. Basavaraja

Department of Pediatric Medicine, Indira Gandhi Institute of Child Health, Bengaluru, Karnataka, India

Abstract

Introduction: Necrotizing pneumonia (NP) is a severe and emerging complication in children with community-acquired pneumonia (CAP). The study was conducted to analyze the etiology, clinical features, treatment strategies, and outcome of NP in children admitted in a single pediatric tertiary referral care center.

Materials and Methods: The study is a retrospective chart review which included children above 1 month and below 18 years who were admitted at Indira Gandhi Institute of Child Health, from January 2015 to December 2018, with community-acquired NP.

Results: During the study period, 1393 cases of CAP were admitted in our institute. Three hundred and fifty-two cases (25.2%) of complicated pneumonia were admitted which include cases of NP, lung abscess, and empyema. Children who were diagnosed with NP were 3.3% ($n = 46$) of all CAP cases. All the cases with NP were immunocompetent, with the most common organism isolated being *Staphylococcus aureus* followed by *Streptococcus pneumoniae*. NP is associated with complications such as empyema, pneumothorax, and bronchopleural fistula. All the children in the study group survived except for mortality in one case.

Conclusion: NP can be well managed with conservative approaches such as prolonged antibiotic therapy and pleural drainage. Although there are commonly associated with local complications, in general the clinical outcome is good.

Keywords: Bronchopleural fistula, community-acquired pneumonia, necrotizing pneumonia, *Staphylococcus aureus*

Address for correspondence: Dr. G. V. Basavaraja, Professor and Incharge, Pediatric Intensive Care Unit, Department of Pediatric Medicine, Indira Gandhi Institute of Child Health, 1st Block, Siddapura, Jayanagar, Bengaluru - 560 029, Karnataka, India.
E-mail: basavgv@gmail.com

INTRODUCTION

Necrotizing pneumonia (NP) is a rare but emerging and most severe complication of community-acquired pneumonia (CAP).[1-3] NP is due to the destruction of normal architecture of lung parenchyma leading to multiple, thin-walled, small cavitary lesions within areas of lung consolidation.[4] NP or cavitary pneumonia is frequently associated with empyema and bronchopleural fistula (BPF). NP is a part of spectrum between lung abscess and pulmonary gangrene.[4,5] The cause of lung

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necrosis is due to the direct cytotoxic effect of toxins of invasive bacteria. Secondary changes in microvasculature of lung-like intravascular thrombosis have also been noted. Such changes lead to reduced concentration of antibiotics in the diseased area of the lung parenchymal tissue. As a result, there is persistence of infection which consequently leads to destruction parenchyma of the lung, transforming the area into a cavity. The cavity is either filled with gas or pus due to discontinuity with bronchial tree.[2,4,6,7]

NP is usually seen in previously healthy children with progressive pneumonia even while on appropriate antibiotics and generally has a prolonged clinical course.[4] As there are less number of studies on children with NP.[1] Hence, the aim of the study is to analyze the etiology, clinical characteristics, management, and outcome of NP in children admitted in a single pediatric tertiary referral care center.

MATERIALS AND METHODS

The study included children above 1 month and below 18 years admitted at Indira Gandhi Institute of Child Health, a tertiary care referral center, from January 2015 to December 2018, with community-acquired NP. It is a retrospective chart review.

To identify the study group, initially all cases of CAP were segregated from the electronic database of our institute. The children with suspected NP as complication of CAP were included in the study group. The diagnosis of NP was established after reviewing the chest X-ray and contrast-enhanced computed tomography (CECT) thorax by two radiologists who were blinded to the clinical features. The case definition of NP is, a child with signs and symptoms of pneumonia with a specific radiological pattern. The specific radiological pattern includes either multiple airfilled spaces observed as lucencies (areas of low attenuation) or air and fluid spaces, within the areas of consolidation of lung parenchyma. There can also be numerous thinwalled cavities (non-enhancing necrotic lung tissue) encircled by lung parenchyma.

The details of children such as demographics, past medical history, etiology (based on the culture results of blood and pleural fluid culture), clinical data (symptoms and examination findings), and laboratory and radiological data were documented. The data on specifics of treatment strategies, complications, and outcome were also recorded in a standard data collection form. After the case selection, the electronic data were collected from patients' electronic records, and wherever necessary, the medical records were used to complete the data.

The lung abscess has a single cavity with rim of enhancement. It differs from NP in having different underlying causes and treatment and hence has been excluded from the study. The study was conducted after the approval of the Institutional Ethics Committee.

Statistical analysis

The variables in the results of the study were summarized by standard descriptive statistics. The comparison between different groups based on clinical presentations, various interventions, and complications of NP was done using nonparametric, Fisher's exact test, or Mann–Whitney *U*-test. $P < 0.05$ was considered as statistically significant.

RESULTS

Demographic and clinical data

During the 3-year study period, 1393 cases of CAP were admitted in our institute. There were 352 cases (25.2%) of complicated pneumonia which included 46 (3.3%) cases of NP, 7 cases of lung abscess, and 299 cases of empyema.

The median age in the study group was 4.7 years (1 year 6 months–16 years). The study group included 26 males and 20 females. The past medical history (to look for underlying diseases and comorbidities), of the children with NP revealed four cases that had recurrent history of upper respiratory tract infection and two cases suffered viral infection prior to presentation with NP. Type I diabetes mellitus and oculocutaneous albinism were present in one case each. None had prior history of asthma or congenital heart disease. No immunodeficiency was noted in any of the cases in the study group.

The most common symptoms at presentation were fever (95%), cough (88%), and hurried breathing (63%). Chest pain and abdominal pain were also a part of presenting complaints in one patient each. The median range of number of days of fever before admission was 7 days (interquartile range [IQR]: 5–10 days). Examinations findings at admission include dullness on percussion and decreased breath sounds on auscultation in 69%. Crackles on auscultation were heard in 48% of the patients with NP. Three cases were initially treated as tuberculosis with antitubercular therapy for 2 weeks. These three children had persistent fever and clinical deterioration despite antitubercular therapy; hence, CECT thorax was done which was suggestive of NP. The treatment was reviewed, and appropriate antibiotics were initiated for which the children responded.

Laboratory data

The significant laboratory parameters included acute phase reactants such as C-reactive protein (CRP) with mean of

78.9 mg/dl (range: 6–100 mg/dl), white blood cells of 15,900 cells/mm^3 (range: 2200–42,100), neutrophils of 73% (IQR: 66–79), anemia (mean hemoglobin: 8.8 g/dl), and hypoalbuminemia (mean serum albumin: 2.9 mg/dl). Pleural fluid analysis was done in 35 cases, with a median high cell count of 28,000 cells (IQR: 15,000–50,000 cells) with polymorphic predominance, high pleural fluid protein of 3.7 g/L (IQR: 3–4.2 g/L), high pleural fluid lactate dehydrogenase of 9800 U/l (IQR: 5270–14,098 U/l), and low pleural fluid glucose of 26 mg/dl (IQR: 17–34 mg/dl).

Radiological data

All the cases underwent chest X-ray and CECT scan of lungs [Figure 1]. The chest radiographs of 39 children revealed unilateral consolidation with 22 cases involving the right lung and 17 cases involving the left lung and 7 cases had bilateral consolidation. At admission, chest X-ray revealed 9 cases with pneumothorax and 27 cases with empyema. In the CECT thorax of 46 children, there was consolidation with cavities, loss of architecture, and decreased parenchymal enhancement. Cavitary necrosis with low attenuation varying from homogeneous to patchy was seen in single lobe in 6 cases, multiple lobes but unilateral in 33 cases, and in bilateral lungs in 7 cases. Parapneumonic effusion/empyema was seen in 39 cases, of which 1 case had bilateral empyema. Thirteen cases had pneumothorax and eight cases had BPF.

Microbiological data

Blood cultures were sent in all cases. Thirteen blood cultures were positive, of which six cases grew *Streptococcus pneumoniae*, four cases were methicillin-sensitive *Staphylococcus aureus,* and three cases grew methicillin-resistant *S. aureus (MRSA). S. aureus* was seen in four cases of pleural fluid. Bronchoalveolar lavage was done in five cases where only one showed culture positive for *MRSA.*

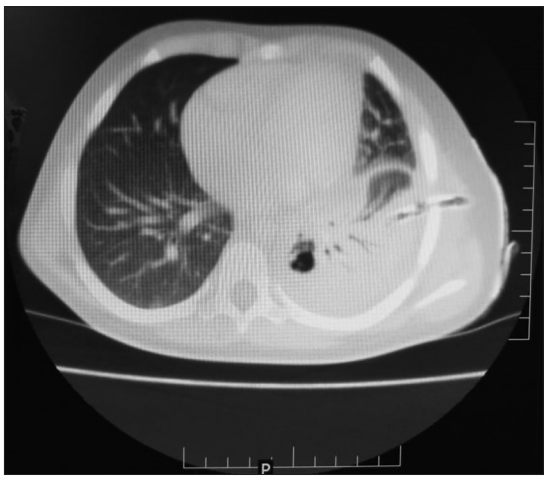

Figure 1: Contrast-enhanced computed tomography chest of a 5-year-old child with air space within the areas of consolidation of lung parenchyma suggestive of necrotizing pneumonia

Management and outcome

The median duration of hospital stay and antibiotic therapy for the children with NP was 25 days (IQR: 19.5–33) and 30 days (IQR: 24–34), respectively. The most common first-line antibiotics prescribed were amoxicillin with clavulanic acid and cefuroxime. The most common second-line antibiotics include ceftriaxone, vancomycin, and meropenem. A combination of two drugs was given for all patients.

Bronchoscopy was done in five patients, wherein thick pus was seen in one case. Three children required noninvasive ventilation (NIV) for 3 days each. One child responded to NIV as first-line therapy and the other two children were given NIV support while weaning from mechanical ventilation. Seventeen children required mechanical ventilation support for a median duration of 7 days (IQR: 5–11).

Video-assisted thoracoscopic surgery (VATS) was done in eight children, of which one case required bilateral VATS. Twelve cases underwent thoracotomy and decortication. Only one case received fibrinolytic therapy with urokinase. Chest drain was inserted in 39 cases. All the eight cases who had BPF underwent thoracotomy except for one who underwent VATS. All cases with BPF had chest drain inserted during the course of treatment for more than 7 days. All the cases of NP survived except for mortality in one case.

DISCUSSION

The current study which includes 46 patients with NP is one of the largest case series of pediatric NP analyzed in the subcontinent to best of our knowledge. The cohort of NP has mostly immunocompetent children, with the most common organism isolated being *S. aureus*. Despite prolonged hospital stay and associated complications such as empyema, pneumothorax, and BPF, the overall outcome is good. Table 1 enumerates the summary and comparison of the present study with two other large retrospective studies in children with NP by Sawicki *et al.* and Lemaître *et al.*[1,6]

The children in the study group had similar features with respect to age and demography as cases in other studies.[1,8,9] The most common symptoms were fever and cough for about 7 days before admission to hospital similar to a study by Sawicki *et al.*[1] The persistence of fever in most of the

Table 1: Summary and comparison of the present study with two other large retrospective studies in children with necrotizing pneumonia by Sawicki *et al*. and Lemaître *et al*.[1,6]

Author	Sawicki *et al.*	Lemaitre *et al.*	Present study
Type of study	Retrospective study	Retrospective study	Retrospective study
Number of patients	80 patients	41 patients	46 patients
Duration of studies	15-year review	5-year review	3-year review
Clinical presentation	Fever and cough were the major symptoms		Fever and cough were the major symptoms
Pathogens	*S. pneumonia* -18 Methicillin-sensitive *S. aureus* - 5 Methicillin-resistant *S. aureus* - 3 Coagulase-negative staphylococci - 4 Others - 8	Methicillin-sensitive *S. aureus* - 12 Methicillin-resistant *S. aureus* - 1 *S. pneumonia* - 7 Others - 1	*S. pneumonia* - 6 Methicillin-sensitive *S. aureus* - 8 Methicillin-resistant *S. aureus* - 3 cases
Complications	Empyema - 69 (86%) Bronchopleural fistula - 10 (13%)	Empyema - 26 (63%)	Empyema - 39 (85%) Bronchopleural fistula - 8 (17%)
Surgical interventions	ICD - 47 (68%) ICD and surgery - 16 (23%) Thoracentesis - 6 (9%)	ICD - 26 Thoracentesis - 10 Video-assisted thoracoscopic surgery - 6	ICD - 38 (85%) Video-assisted thoracoscopic surgery - 8 (18%) Thoracotomy and decortication - 12 (26%)
Outcome measures	Median hospital days - 12 Median antibiotic days - 28 Mortality - 0	Median hospital days - 26 Median antibiotic days - 42 Mortality - 0	Median hospital days - 25 Median antibiotic days - 30 Mortality - 1

S. pneumonia: Streptococcus pneumonia, S. aureus: Staphylococcus aureus, ICD: Inter costal drainage

children could be due to the pyrogens generated as a result of inflammation and parenchymal destruction.[1] Leukocytosis, high CRP, and anemia were found to be associated with children with NP in this study.[1,2,4,10] Hypoalbuminemia was also observed which could be secondary to protein loss in pleural fluid or affected pulmonary tissue.[1]

Thirty-seven percent of the cultures were only positive in our study, whereas other studies have 8%–55% of the patients, which could be due reasons like our use of traditional culture methods. All the children with NP received antibiotics before hospitalization which could have sterilized the blood/pleural fluid.[4] It is also possible that causative organisms could be viruses, anaerobic bacteria, or atypical organisms such as *Mycoplasma pneumoniae* which were not tested in our study.[1,2,6,11-13]

S. aureus was isolated in 11 cases (23.9%) as the most common organism in our study, of which three were MRSA. *S. aureus* was also a common causative organism in 13 cases (61.9%) in a study of 41 cases of NP, all of which were strains encoding genes of Panton–Valentine leukocidin and resistant to methicillin except one.[6] In another retrospective study of eighty cases of NP analyzed by Sawicki *et al*., eight cases (10%) with *S. aureus* were identified, of which 3 cases were methicillin resistant.[1] Six cases *of S. pneumoniae* were seen in our study, but serotyping was not done. S. *pneumoniae* was the most common causative organism as per the systematic review and in a number of studies where serotype 3 is associated with high risk of NP and complications such as hemolytic uremic syndrome.[1,2,4,10,14-20]

NP should be considered in a child with pneumonia who is sick with persistence of fever even after 3–5 days of appropriate antibiotics and significantly raised markers of inflammation in blood for which chest X-ray and CECT thorax play a major role. The CECT thorax is most sensitive in diagnosing cases of NP.[2,4,21-23] With increased use of CECT thorax in cases with complicated pneumonia, there is an increased yield of diagnosis of NP, thereby facilitating better management of children.[1,2,4]

NP is commonly associated with local complications in children. Empyema was seen in 39 (85%) cases in our study where the incidence of empyema in other studies has been reported in the range of 63%–97%.[2,6] Chest drain was placed in 83% ($n = 38$) of the cases similar to another study where 87.5% of the cases were treated with placement of chest drain.[2] Surgical intervention was done in the form of VATS in 17% of the cases ($n = 8$) and thoracotomy and decortication in 26% of the cases ($n = 12$). There are no randomized control trials to compare the efficacy of pleural drainage with or without fibrinolytic versus VATS in cases with NP.[2] The severity of disease and conditions such as adhesions, location, and volume of pleural fluid directly influences the selection of just pleural drainage or VATS or thoracotomy.[24] Pleural drainage is sufficient in most of the cases like in our study, but early VATS is indeed justified.[2,7]

BPF was seen in eight cases with incidence of 17%, whereas studies have shown an incidence between 15% and 67% of the cases with NP.[1,2,25,26] In our study, all children who had chest drain placement for more than a week developed BPF. This could be due to the pleura becoming friable secondary to inflammation as it is adjacent to the necrotized pulmonary tissue.[1]

The only mortality was a case that had MRSA isolated in culture, but we could not test the strain. Lethal strain of *S.*

aureus ST398 which caused NP has been documented in a case report.[27] A case series of four children reported a high mortality with Panton–Valentine leukocidin-associated *S. aureus*. Thus, in such cases, an aggressive approach to start early empirical combination antibiotic therapy, which could also include a toxin-suppressing agent, may be crucial to avert mortality.[28] The limitation of the study is that we could not investigate viral etiology and serotyping of isolated bacteria as it is a retrospective study. The study was conducted only at one center also that all children had received antibiotics before admission.

CONCLUSION

NP can be well managed with conservative approaches such as prolonged antibiotic therapy and pleural drainage though there are commonly associated with short-term local complications, in general the clinical outcome is good.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Review Article

Quality indicators and improvement measures for pediatric intensive care units

Farhan Shaikh

Department of Pediatric Intensive Care, Rainbow Children's Hospital, Hyderabad, Telangana, India

Abstract

Quality and patient safety is an integral part of pediatric critical care. Quality indicators (QIs) or key performance indicators (KPIs) are crucial to measure various aspects of quality and patient safety in pediatric intensive care. If we want a system which gives us reproducible results, it is crucial that various aspects of structure, process, and outcomes in that system are measurable and reproducible. It is crucial that the data used for measurements are accurate and they are analyzed using appropriate tools, and the KPIs/QIs calculated from the data are appropriately validated. These QIs/KPIs should be compared to the "accepted" international or national benchmarks on a periodic basis so that the team of doctors, nurses, and administrators are aware of the performance of their unit. In India, there are no national benchmarks available to compare the QIs/KPIs of our pediatric intensive care units (PICUs), and there is a dearth of such benchmarks for PICUs at international level too. In this review article, we aim to discuss the various aspects of data collection, data validation, and measurement of some important QIs of a PICU. We have also tried to gather some international benchmarks for some important QIs, which can be used by PICUs for their comparisons. Eventually, the best thing will be to develop a national database from various PICUs across India so that a national benchmark is created.

Keywords: Key performance indicators, pediatric intensive care unit, quality and patient safety in pediatric intensive care, quality indicators

Address for correspondence: Dr. Farhan Shaikh, Rainbow Children's Hospital, Banjara Hills, Hyderabad, Telangana, India.
E-mail: farhanshaikh74@gmail.com

INTRODUCTION

Providing medical care to a patient with latest gadgets and the most updated scientific knowledge is the most obvious practice in any pediatric intensive care unit (PICU).

In this endeavor, the treating team often tends to ignore the other crucial aspect of critical care, which is providing care with utmost attention to patient safety and high quality.

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In the last two decades, there is increased public awareness, media attention, and legal intercession in the way health care functions. There is also a growing insistence from health insurance companies to bring transparency, accountability, and cost-effectiveness in health-care system.

In this chapter, we shall discuss the important aspects of quality indicators (QIs) and their appropriate utilization in the implementation of quality and patient safety practices.

The Institute of Medicine (IOM) report[1] on safety revealed that there is a health-care safety crisis. Their data indicated

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that approximately 44,000 to nearly 100,000 patients die annually in US hospitals due to error.[1]

This was equal to one Jumbo Jet plane crashing every 2nd day!

Moreover, these were the data from one developed country; the scenario in a developing country would be unimaginable!!

Apart from developing and monitoring of QIs, there are many other tools to improve quality and patient safety in intensive care units, which are beyond the scope of the present article.

In this article, we shall restrict our discussion on different types of QIs, which can be used in a PICU, and various means of collecting reliable data so that the calculated QIs in turn are meaningful.

"QUALITY INDICATORS" AND "BENCHMARKING"

The IOM has defined health-care quality as "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge."[1]

This definition insists that the services provided in health-care industry should be audited and various standards of services must be "measured."

These measurable components of health-care service are known as "quality indicators" or "key performance indicators."

These QIs should be compared with nationally or internationally accepted QIs, known as "benchmarks," to understand "the degree to which health services for individuals and populations match with the desired health outcomes and are consistent with the current professional knowledge."

"QIs" help in the assessment of the quality of service provided; analyze the various outcomes of intervention, treatment, and adverse events (AEs); audit various managerial and therapeutic processes; and thus help explore opportunities for further improvement.

Concept of "benchmarking"

Benchmarking is a technique in which an organization measures its performance against that of the reputed organizations, determines how those organizations achieved their performance levels, and uses the information to improve its own performance. Subjects that can be benchmarked include strategies, operations, and processes.

ROLE OF "QUALITY INDICATORS IN PEDIATRIC INTENSIVE CARE UNIT"

PICU is a potentially dangerous place in terms of patient safety and quality of care.

PICU care is unique because:

- Sick patients vary depending on their age, size, and the underlying medical conditions
- There are many complex invasive and noninvasive procedures involved
- There is continuous usage of high-risk medications in complex dosing and frequency regimes, and there is constant use of complex lifesaving equipment and
- There is a complex interaction between technology and potentially erring humans.

Thus, it is very important to device reliable methodologies to identify important areas, where quality of care can be measured (QIs) and analyzed and reliable corrective and preventive actions can be planned accordingly.

HOW TO SELECT APPROPRIATE QUALITY INDICATORS FOR PEDIATRIC INTENSIVE CARE UNIT CARE?

The simplest approach is to follow the Donabedian's[2] model of "structure," "process," and "outcome."

1. Structure: This encompasses facility attributes:
    - Layout of the PICU in terms of its location in the hospital and utilization of available space
    - Overall infrastructure (physical lighting, air quality, water quality, and available workforce [nurses (nurse: patient ratio), number of doctors, etc.])
    - Available equipment (ventilators, cardiac monitors, syringe pumps, hemodialysis and/or continuous renal replacement therapy [CRRT] machine, extracorporeal membrane oxygenation [ECMO], etc.)
    - Medical gas supply, electricity supply (including availability of adequate backup supply of gas, water, and electricity)
    - Availability of isolation and quarantine facilities
    - Efficient and effective air-handling system
    - Effective fire safety system
    - Efficient water and electricity supply and utilization
    - Presence of infection control nurse (ICN)
    - Presence of clinical pharmacist.

2. Process: This includes various aspects of patient care:
   - Open versus closed PICU system
   - 24-h intensivist presence
   - Identifying patients by two identifiers
   - Process of pain assessment and management
   - Process of prescription audits and prevention of prescription and administration errors
   - Turnaround time for availability of blood products
   - Turnaround time for availability of important lab results
   - Response time for short and long transports by hospital ambulance
   - Standardized procedures are followed to adhere to various infection control activities (adhering to hand hygiene, adhering to "bundle" approach to prevent ventilator-associated pneumonia [VAP], Central line associated blood stream infection (CLA-BSI) and catheter-associated-urinary tract infection [CA-UTI], adhering to antibiotic stewardship, etc.)
   - Standardized protocols being followed to manage various clinical conditions (using clinical guidelines and algorithms in the management of diabetic ketoacidosis, dengue hemorrhagic fever, acute respiratory distress syndrome, septic shock, etc.)
   - Emphasis on patient- and family-centered care
   - Emphasis on excellent communication between doctors and nurses
   - Standardized process to address breakdown of equipment, gas supply, and electricity failure
   - The treating team following standard procedures during admission, discharge, death, or left against medical advice situations
   - Process to manage "nonavailability of bed" situation
   - Process to handle grievances of patient's family members
   - Process for managing patient's family request for organ donation

   "Process" also includes ensuring the well-being and safety of the treating team:
   - Process for selection of adequately qualified staff for the PICU
   - Process for induction training and education of newly joined doctors and nurses
   - Process for handling complaints and grievances of the PICU staff (doctors and nurses)
   - Process of ensuring prompt response following a needlestick injury
   - Process preexposure prophylaxis of health-care workers
   - Process of ensuring adequate number of doctors and nurses per shift
   - Process of ensuring adequate ongoing training and education of the doctors and nurses
   - Training of hospital staff in fire and nonfire emergencies (including handling of difficult/violent family members, child abduction, and disaster management).
3. Outcome: This includes various clinical, nonclinical, or administrative aspects of patient care:

   Clinical outcomes:
   - Mortality rate (MR)
   - Average length of PICU stay
   - Average ventilator days
   - Survival rates of patients on high-frequency oscillatory ventilation (HFOV) or ECMO or CRRT therapy
   - Survival of postliver transplant patients, or postcardiac surgery patients, etc.

   Nonclinical outcomes:
   - Patient satisfaction survey reports
   - Number of admissions per month and per year
   - Average PICU bed occupancy
   - PICU utilization rate
   - PICU equipment utilization rate

In addition to the above-mentioned Donabedian's approach of "structure," "process," and "outcome," certain other QIs which are useful are derived from two important aspects of care delivery, namely (a) improvement based and (b) accountability based.

a. "Improvement-" based quality indicators include:
   - Return to PICU within 48 h
   - Incidence of iatrogenic pneumothorax
   - Percentage of unplanned extubation (UE)
   - Incidence of re-intubation
   - Adverse drug reactions
   - Antibiotic stewardship-related indices.

b. "Accountability-" based quality indicators include:
   - Incidents of medication errors (including prescription, dispensing, and administration errors)
   - Safe injection practices
   - VAP rate
   - Catheter-related bloodstream infection (CRBSI) rate/catheter-associated-bloodstream infection (CA-BSI) rate
   - CA-UTI rate
   - Surgical-site infection (SSI) rates
   - Percentage of adherence to hand hygiene
   - Incidence of pressure sores
   - Fall from bed

- Incident of sentinel events
- Equipment breakdown
- Deviation from standardized protocols
- Air and water quality monitoring
- Fire safety
- Disaster preparedness
- Outbreak management.

Some examples of the commonly used QIs with their benchmark are as follows:

1. PICU MR:
   PICU MR = (total number of deaths/total number of PICU admissions in the same period) × 100

   This gives a rough guide to the death rate in a unit; however, they are not "adjusted" with the disease severity.

2. Standardized mortality rate (SMR)
   SMR = (observed MR/risk-adjusted expected rate) × 100

   Risk-adjusted MR can be calculated from various severity scoring systems such as PRISM-3 or PIM-2. The scoring is as follows:
   - = 100 – Hospital's MR and the expected average rate are the same
   - >100 – Hospitals' MR is higher than the expected average MR
   - <100 – Hospitals' MR is lower than the expected average MR
   - Higher SMR does not necessarily mean that the hospital is unsafe, as this is a snapshot method and simultaneous assessment of other QIs must be done to draw a logical conclusion. Single parameter-based judgment on performance level is not advocated.[3]

3. Unplanned extubation
   The incidence of UE is reported in two ways. The first approach divides the number of UE by the number of ventilated patients (percentage). This calculation is confounded by the possibility of disproportionate rates of ventilated patient turnover. Adopting this first method, intensive care units that have a high number of short-term ventilations would have lower incidences of UE because the denominator of the formula would be large; therefore, to avoid this confounding possibility, Little *et al*.[4] recommended calculating incidence as a function of the number of UE per 100 intubation days. This model incorporates the concept of days at risk for UE and allows comparisons among different PICUs.

   (no. of UEs/no. of intubation days) × 100

   Studies conducted within the past 20 years indicate that UE occurs with a rate of 0.11[5] to 2.7[6] events/100 intubation days. A multicentric study conducted to examine extubation failure in 16 PICUs revealed UE rate of 1.02/100 intubation days.[7]

4. Incidence of re-intubation
   Accidental extubation and subsequent re-intubation can lead to prolonged stay, longer ventilation, and higher nosocomial pneumonia and mortality.

   (no. of re-intubations within 48 h of extubation/total no. of extubation) × 100

   Benchmark: 12%[8]
   - Too low re-intubation rate hints toward very conservative ventilation strategy
   - Too high rate signifies aggressive extubation policy and poor sedation/analgesia or extubation planning.

5. Incidence of decubitus (pressure) ulcer
   Prolonged uninterrupted pressure over bony prominences causes necrosis and ulceration.

   Depending on tissue damage, ulcers are classified into four stages.
   - Stage 1 indicates superficial color change
   - Stage 2 represents partial-thickness skin loss
   - Stage 3 denotes full-thickness skin loss
   - Stage 4 denotes deep and extensive tissue damage involving muscle, tendon, or bone.

   Hip and buttock sores represent 67% of all pressure sores.

   (No. of pressure ulcers/no. of patients admitted) × 1000

   OR

   (No. of pressure ulcers/no. of patients admitted) × 100

   Benchmark: 17%–24% in PICU population[9] and 3%–11% or 18–22/1000 patient-days in some other studies.[10]

6. Average length of stay (LOS) in PICU
   Total occupied bed days/number of patients in a given time frame (weekly/monthly/yearly)

   The total duration of hours and days in which patients are treated in the unit with midnight bed occupancy is taken for the calculation of numerator.

   Calculation of "mean" overestimates LOS, as outliers in both ways erroneously influence the calculation.

   Calculating the median of LOS can avoid this problem.

   If calculated and analyzed properly and stratified on the basis of diseases and underlying clinical conditions, this can be a sensitive parameter to analyze the quality of care provided for various clinical conditions, discharge process in PICU, and mortality/morbidity pattern of the unit.

7. Readmission in PICU within 48 h:
   The Society of Critical Care Medicine's QI Committee has ranked this indicator as the top indicator for judging ICU quality.

   (no. of readmitted patients/total no. of patients managed in the ICU) × 100

   Benchmark: 4%[8]

   Zero readmission rate over few months reflects a conservative approach; this will increase LOS in ICU causing risk of nosocomial infection, iatrogenic complications, and nonavailability of beds for the deserving patients.

   A higher readmission rate indicates premature decision to shift out patients, and such units should adopt sound discharge planning and discharge criteria to prevent readmissions within 48 h.

8. Incidence of fall from bed:
   A fall can be accidental or anticipated in a patient with risk factors (sedation, neurodeficit, etc.). Accidental fall can cause injuries, prolonged stay, and patient dissatisfaction.
   (No. of patient falls/total no. of patient-days in the same period) × 100
   Benchmark: 0%[8]

9. Medication errors:
   Medication errors can be of prescription, administration, dispensing, monitoring, and transcription errors.

   Medication error rate = (no. of error/no. of bed days) × 1000

   Median of 24.1/1000 patient-days in neonatal/pediatric ICUs

   Wrong dose: 105.9 errors/1000 patient-days in the ICU.[11]

   A Dutch study used a passive observer to determine the frequency and causes of drug administration errors in the ICUs of two hospitals. A 33% error rate was observed, with wrong administration technique as the leading type of error.

   The investigators determined that the systems for operating the ICUs made a difference in the rate of errors. The ICU with full-time intensive care physicians and approved pharmacy protocols for drug administration had fewer errors (21.5% vs. 70.2%).

   This factor and other system issues, such as staffing on certain days (errors were observed more frequently on a Monday) and lack of familiarity with nursing protocols on nasogastric (NG) administration of medication, were suggested as interventions to improve medication safety.[12]

10. AEs/error rate
    Patients in PICU are at high risk for complications due to their underlying medical conditions, various invasive procedures, use of high-risk medications, and technology-based interventions.

    As per the IOM report,[1] nearly half (45%) of the AEs are preventable.

    AEs/error rate = (no. of error/no. of bed days) × 1000

11. Needlestick injury rate
    Needlestick injuries can cause transmission of blood-borne pathogens. Needlestick injury can occur due to lack of awareness in safe handling of sharps (syringe needles, recapping of needles, suture needles, etc.) and their safe disposal.

    Needlestick injury rate = (no. of incidences of needlestick injuries/patient-days in that period) × 100

    The aim is to keep the incidence of needlestick injuries to 0% by better training and awareness of staff and sound biomedical waste segregation practices.

12. Infection control quality indicators

Nosocomial infection causes direct and indirect impact on the mortality and morbidity in the PICU patients.

Nearly 80% of the nosocomial infection in any hospital belong to the following four main categories:

- VAP
- CA-BSI or CRBSI
- CA-UTI
- SSI.

12a. VAP

VAP refers to nosocomial pneumonia occurring 48 h or more after the initiation of invasive mechanical ventilation. Centers for Disease Control and Prevention (CDC) criteria (PNU 1, PNU2, and PNU3 categories: CDC Device-associated module, 2017) are used to identify VAP.

Indian studies have shown VAP rates ranging from 15% to 45%. The incidence rates of VAP are higher in developing countries with limited resources.[13]

(no. of patients diagnosed as VAP as per CDC criteria [PNU1, PNU2, or PNU3]/no. of ventilator days) × 1000 days.[14]

12b. CA-BSI or CRBSI

CRBSI remains the most common nosocomial infection in pediatric ICUs, resulting in significant morbidity, mortality, and added health-care costs.

Very few studies expressing CRBSI data in terms of device utilization frequencies as denominator are available in India and other developing countries.

(no. of CLABSI/no. of central line-days) × 1000

For surveillance purposes, CA-BSI is used rather than CR-BSI as the diagnostic criteria, as CR-BSI criteria are more stringent.[15]

CA-BSI rates are higher in developing countries than that of the developed countries due to various factors. A study by Parameswaran *et al.* from a tertiary care center in South India shows the incidence of CRBSI as 8.75/1000 catheter-days.[16]

12c. CA-UTI:

Urinary tract infections diagnosed after 48 h of urinary catheterization are included in the numerator.

(no. of UTI/no. of catheter-days) × 1000

An incidence of 2–5/1000 catheter-days is reported in many studies.[17]

12d. Hand hygiene audit (percentage of adherence)

(No. of missed moment/no. of available opportunities) × 100

The unit should strive to keep the compliance above 80%

Individual moments from the WHO recommended that "five moments" of hand hygiene should also be audited individually. The data can be interpreted using the Pareto chart to understand the most commonly missed moments.

13. Percentage of transfusion reactions:

Every transfusion of blood product should be monitored for transfusion reaction. Transfusion reactions can be analyzed using the following formula:

(No. of transfusion reactions/no. of transfusions administered) × 100

The aim should be to keep this rate at 0%.

14. Bed occupancy rate:

(No. of inpatient days in a given month/no. of available bed days in that month) × 100

The no. of inpatient days is calculated by multiplying the number of patients admitted during the study period with the number of days the patients were kept in PICU.

The no. of available bed days is calculated by multiplying the number of beds in PICU with the total number of days (if calculating bed occupancy for a month, then multiply by 30 and if for 1 year, then multiply by 365).

This indicator helps hospital management in planning resources.

15. Nurse: patient ratio

Based on our experience and unit practice, a safe ratio between patients and nurses can be as follows:

- For very sick patient (ventilated patients on high-ventilator settings, multiple inotropes, HFOV, CRRT, or ECMO, etc.): 1 patient: 2 nurses
- For sick patients (ventilated on moderate settings, those on continuous positive airway

pressure (CPAP)/high-flow nasal cannula (HFNC) with severe distress, on multiple inotropes): 1 patient: 1 nurse
- For moderately sick patients (on CPAP/HFNC but stable, hemodynamically stable, etc.): 2 patients: 1 nurse
- For stable patients (on low-flow oxygen or room air, feeding on NG or direct oral feeds,): 3 patients: 1 nurse

ATTRIBUTES OF QUALITY INDICATORS

The key to continuous quality improvement is availability of reliable and robust data.

A clear understanding of availability and limitations of the data is crucial in developing strong and reliable QIs.

The inaccuracy in the data can be due to:
- Passive or "voluntary reporting" of various incidents, which is the most common method of data collection, carries inherent risk of underreporting and thus, erroneous data[18]
- Erroneous data collection can also be due to inexperience or lack of knowledge of the person who is collecting the data, in that particular process. If the person collecting the data does not have knowledge in that domain, the data collection can be erroneously collected or wrongly interpreted
- Errors in data entry due to human and/or machine errors
- Errors in coding due to human factors or lack of training, etc.
- Inability to adjust the data depending on the severity of illness
- Possibility of incomplete data collection. For example, if data were collected for some other purpose and then decided to use them for calculating QI or safety parameter, there is a risk of data being incomplete as it was originally not collected for this purpose.

DATA VALIDATION FOR RELIABLE DATA COLLECTION

Voluntary reporting of AEs is the most commonly used method for data collection in health care. However, voluntary reportings have been shown to capture only 2%–8% of all harms.[18]

One more commonly utilized method is direct observation and detailed chart reviews.

This method requires workforce and is labor intensive. Although more reliable than voluntary reporting, it too carries the risk of personal bias and personal interpretation errors.[19]

Doctors, nurses, and coordinators working within the PICU can also be trained and made "quality champions," "infection control champions," and "medication safety champions," who help the quality team, ICNs, and clinical pharmacists in their audits and data validation.

Data validation can be done through various indirect means. For example, an "interdepartmental cross audits can be a useful tool for data validation. Quality champions, infection control champions, and medication safety champions of one department can be sent to other departments for auditing, for example, a trained team from neonatal intensive care unit audits pediatric intensive care and *vice versa*. This provides opportunity for "peer review" and validation of data collected by the regular auditing team.

One more effective strategy, known as the "trigger tool," has been found to be superior to voluntary occurrence reports and conventional unfocused chart review in the identification of AEs.[20]

David C. Stockwell and his team[18] used a novel pediatric-specific list of triggers and found 40 harms/100 admissions among children hospitalized at six large freestanding children's hospitals. Nearly one-half of the harm was deemed preventable.[2,15,16] One of the every four pediatric admissions in their study had at least one identified harm. They found trigger tools far superior to voluntary reporting in detecting harm.[18]

A trigger is defined as an occurrence, prompt, or flag found on review of the medical chart that triggers further investigation to determine the presence or absence of an AE.

AEs are defined as an injury, large or small, caused by the use (including nonuse) of a drug, test, or medical treatment.

Harm is defined as an unintended physical injury resulting from or contributed to by medical care that requires additional monitoring, treatment, or hospitalization or that results in death.[19]

Some examples of "trigger tools" are:
- Using "Pediatric Ventilator-Associated Events (PedVAE) to screen for the possibility of VAP
- Use of naloxone in PICU patients should trigger the team to investigate for opioid-related AE
- Any positive blood culture in a patient after 48 h of

insertion of a central line should trigger investigation for the possibility of CA-BSI
- Any patient receiving intravenous antihistaminic (Pheniramine) and/or hydrocortisone during or immediately after transfusion of a blood product should trigger an investigation for possible transfusion reaction which could have been missed in the "voluntary reporting" system
- Return to PICU in 48 h should trigger to investigate any lacunae in the discharge process
- LOS in PICU longer than the usual trend of the unit for a particular medical condition should trigger to investigate for any iatrogenic complication (iatrogenic infections, air leaks, pressure sores, adverse drug reactions, etc.).

The Institute for Healthcare Improvement has come up with a list of global trigger tools which can be used for capturing reliable data and add more value to the calculated QIs.[21]

Various units can device their own trigger tools to capture their data.

ANALYSIS AND PRESENTATION OF DATA[20]

The data which are collected by various methods (voluntary reporting, auditing of patient records, use of trigger tools, patient feedbacks, managerial reports, etc.) are converted into "QIs" by using various formulas/calculators. These QIs are then presented in graphical or pictorial format for better visual appeal and understanding.

For example, analysis of AEs can be done in different ways as follows:
- AEs/1000 patient-days
- AEs/100 admissions; and
- Percent of admissions with an AE.

"AEs/1000 patient-days" is the traditional measure and is the recommended measure to track the harm rate over time.

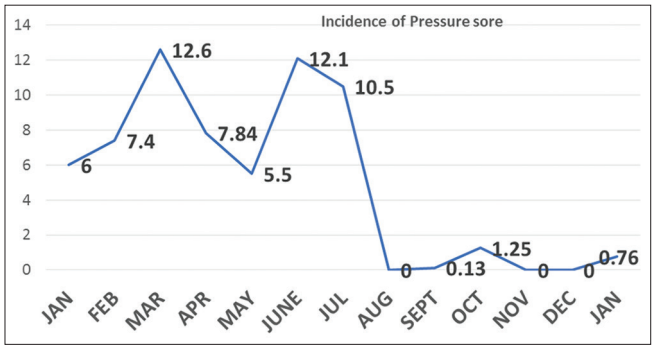

Figure 1: A run chart showing incidence of pressure sores/1000 patient-days, in a pediatric intensive care unit over 1 year. There is reduction in incidence from September due to implementation of some quality improvement measures

Data should be presented in a run chart [Figure 1] with "AEs/1000 patient-days" on the Y-axis and time in 2-week increments on the X-axis.

"AEs/100 admissions" is another presentation of rate. It provides a more easily understood representation of harm. Data should be presented in a run chart similar to "AEs/1000 patient-days."

It should be noted that the conversion from "AEs/1000 days" to "AEs/100 admissions" simply entails a switch from the number of patient-days (1000) to records reviewed (admissions).

"Percent of admissions with an AE" is a convenient way to present the information to lay persons, although it diminishes the number of events because some patients may have more than one AE during a hospital stay. Thus, it is less sensitive to improvement than the two rate measurements.

In addition to the run chart representations, the team can present categories of harm in a "bar chart" in order to depict the volume of harm in each category.

Data are also often presented by the "type of AEs." The types of events have commonly been defined as infections, medications, and procedural complications.

Hospitals find this categorization to be useful in prioritizing areas for improvement in work.

The Pareto chart [Figure 2] is one useful tool which depicts the "80:20" rule (80% of the events are due to 20% of the causes).

IMPLEMENTATION OF QUALITY AND PATIENT SAFETY IMPROVEMENT METHODS

The Plan-Do-Study-Act (PDSA) cycle is a simple yet effective tool for continuous quality improvement.[22]

Once a team has set an aim, assembled appropriate team, and "Planned" a workflow, they will start the work (Do), and after some time period they will make an re-assessment (Study) whether their strategy is leading to an improvement or not, if the target is still not achieved or partially acheived , the team shall start the work with some appropriate changes in strategy once again (Act). The same cyckle of Plan, Do, Study and Act will repeat.

The PDSA cycle [Figure 3] is shorthand for testing a change – by planning it, trying it, observing the results, and acting on what is learned. This is the scientific method, used for action-oriented learning.

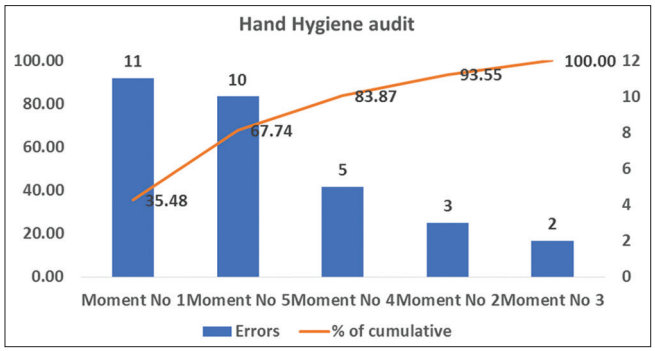

Figure 2: Pareto chart utilizing 80:20 rule (80% of the events are due to 20% of the causes). In this chart, we can see Moment #1 and Moment #5 are the most commonly missed moments out of the WHO's Five Moments of hand hygiene

QUALITY AND PATIENT SAFETY IS A CONTINUOUS "TEAM" EFFORT.

The entire team of PICU (doctors, nurses, technicians, housekeeping staff, and administrative staff) forms the "quality team."

An ICN performs various infection control-related audits (hand hygiene audits, adherence to various infection prevention bundles such as VAP bundle, CABSI bundle, and CAUTI bundle) and surveillance activities (water quality, air quality, and surveillance swabs on regular intervals). The ICN is also responsible for ensuring that all health-care staff had received prophylactic immunization (hepatitis B vaccine, H1N1 prevention vaccine, etc.).

The ICN also ensures that adequate isolation measures (air-borne/droplet/contact isolations) are followed for patients in need of isolation in PICU.

The ICN is also actively involved in continuous training and education of doctors and nurses in infection control activities, personal protection, needlestick injury, etc.

Clinical pharmacists perform daily prescription audits, ensure appropriate labeling of medications and appropriate dilution of infusions, and ensure that inappropriate drug combinations are avoided.

Clinical pharmacists also check the crash trolleys and medication trolleys for sound inventory control and appropriate segregation of medications in different categories (look-alike drugs, sound-alike drugs, high-risk drugs, narcotics, emergency drugs, etc.).

Clinical pharmacists are also involved in the training and education of nurses in safe medication practices.

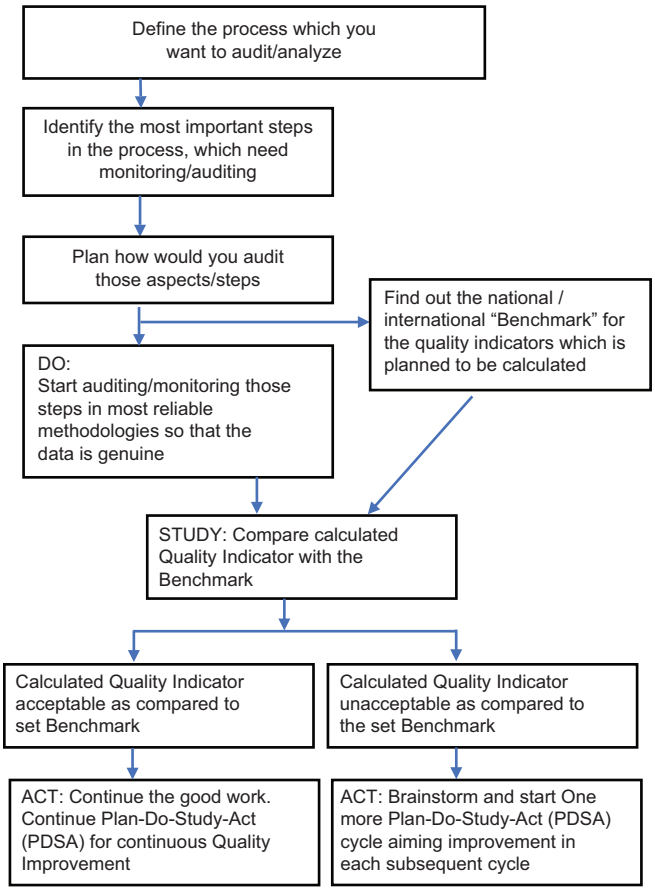

Figure 3: Plan-Do-Study-Act cycle

A quality executive from the department of quality will be involved in collecting data and performing document audits and audits of various "structure-," "process-," and "outcome-" related parameters on a daily basis. He/she maintains the data and shares the data with the physicians and nurses on regular intervals. The quality executive also maintains an "events report" register in collaboration with the PICU in-charge nurse. This register keeps record of all AEs and events which deviated from the routine process. This register is an important source of data which is used for the calculation of various QIs.

The in-charge nurse of a PICU is a crucial link between PICU physicians (consultants and resident doctors), PICU nurses, ICNs, clinical pharmacists, housekeeping staff, biomedical engineering staff, maintenance engineering staff, human resources department, and hospital's operations and management division.

The in-charge nurse of a PICU maintains optimum patient: nurse ratio, ensures training and education of the PICU nurses, and ensures that all PICU equipment are calibrated and are in sound working condition.

The in-charge nurse should carry a "checklist" to ensure the availability of emergency drugs, airway equipment, and other lifesaving equipment (ventilators, cardiac monitors, defibrillators, etc.).

The PICU in-charge nurse ensures efficiency in:

- Structured hand overs between nurses
- Monitoring patients' vital parameters and their accurate entry in patients' medical records
- Taking complete patient consents
- Monitoring patients' pain, sedation, and analgesia
- Screening of various risk factors (e.g., pressure sores, thrombophlebitis, and falls from bed) at regular intervals
- Implementation of various "checklists" to implement patient safety activities (e.g., VAP bundle, CABSI bundle, CA-UTI bundle, head injury bundle, and septic shock management bundle).

The PICU consultants must carry one "huddle round" in the morning to discuss new admissions in the previous day, any patient-related clinical care issues, and any other events from PICU.[23]

Consultants, fellows, and residents in the PICU should meet once in a week and discuss the important events of the previous week such as cancellation of procedures, refused admissions, delayed PICU shift outs, delayed procedures, and readmission in 48 h.

The resident doctor can adopt "checklists" for various clinical conditions (e.g., septic shock management checklist, diabetic ketoacidosis checklist, and trauma care checklist).

The team of doctors should use standardized communication tools (e.g., ISBAR) and "structured" hand-off tools while exchanging patient information at the time of change of shift.[24]

The entire team of PICU staff (medical and paramedical staff) should meet once in a month to discuss all the QIs, patient feedbacks, and patient safety-related events.

SUMMARY

- Quality and patient safety is everybody's business!
- The entire team should work in a blame-free atmosphere where audits are carried out with the sole aim of improving quality and safety and not finding faults or blame individuals
- In resource-limited setups with shortage of workforce, sometimes, it may not be possible to recruit designated ICN, clinical pharmacists, or quality executives. In such a scenario, these responsibilities can be shared among the doctors and nurses of the PICU
- Daily morning huddles and regular meetings on weekly and monthly intervals should be planned to ensure that PDSA cycle is maintained.

Future directions

The QIs of PICU should be compiled over months and years. The data should be shared between various units with an aim for eventual development of regional benchmarking and eventually national benchmarking.

These benchmarks will provide a direction to the PICUs across the country, who are in pursuit of perfection in critical care delivery to sick children.

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Conflicts of interest

There are no conflicts of interest.

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Case Report

Pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus 2 – An emerging problem of PICU: A case series

Bal Mukund, Manoj Sharma[1], Ankit Mehta[2], Ashutosh Kumar[3], Vivek Bhat

Department of Pediatrics, INHS Kalyani, Visakhapatnam, Andhra Pradesh, [1]Department of Pediatrics, Military Hospital, Jammu and Kashmir, [2]Department of Pediatrics, Wockhardt Hospital, Ahmedabad, Gujarat, [3]Department of Pediatrics, Research and Referral Hospital, New Delhi, India

Abstract

Among rising number of coronavirus disease 2019 cases in children, there has been a rapid rise in cases of pediatric multisystem inflammatory syndrome associated with severe acute respiratory syndrome coronavirus 2 (PIMS-TS) with clinical features either simulating Kawasaki disease or toxic shock syndrome. We report three children who initially presented with fever, multisystem involvement, and features of hyperinflammation satisfying the World Health Organization criteria for PIMS-TS clinically and on laboratory investigations. All patients were treated with immune modulation by intravenous immunoglobulin and/or methylprednisolone and recovered to discharge.

Keywords: Coronavirus disease 2019, inflammatory markers, intravenous immunoglobulin, Kawasaki disease, pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus 2, World Health Organization

Address for correspondence: Dr. Ashutosh Kumar, Department of Pediatrics, Research and Referral Hospital, New Delhi, India.
E-mail: ashuarnav@gmail.com

INTRODUCTION

Coronavirus disease 2019 (COVID-19) triggered by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to around 16 million infections and approximately 6.5 lakhs deaths world over as of July 26, 2020.[1] In adults, it has manifested with severe hypoxemia in acute-phase and profound inflammatory response with cytokine storm leading to multi-organ dysfunction syndrome contributing to high mortality in symptomatic patients. Fortunately, the risk of infection and acute disease in children has been consistently low. On May 1, 2020, the Royal College of Paediatrics and Child Health (RCPCH) published clinical management guidelines for children with presentation of pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) infection and proposed a case definition.[2] These guidelines were formulated because health authorities at the UK reported a number of seriously ill children with clinical signs of circulatory shock and/or hyperinflammatory states with features consistent with diagnosis of Kawasaki disease (KD) or toxic shock syndrome. The same syndrome has been called multisystem inflammatory syndrome in

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children (MIS-C) associated with COVID-19. Among these children, some tested positive for SARS-CoV-2 infection or had exposure to them from a positive contact. Similarly, on April 7, 2020, a classic case of KD with COVID-19 was reported from the USA.[3] In France, on May 12, 125 suspected cases were reported, 65 cases were provisionally diagnosed as PIMS-TS, and additionally, 15 were noted to have probable links with COVID-19.[4] From India, Rauf *et al*. were first to report a similar case from South India on May 28, 2020.[5]

A causal association between SARS-CoV-2 infection and PIMS-TS has not yet been proven. It is, however, hypothesized that it probably reflects a dysregulation of immune response to this virus and may hence occur as a late reaction to SARS-CoV-2 infection. It is also not known why only a subset of children manifest with PIMS-TS among large number of positive/exposed cases among children and adolescents. Probably, the inflammatory reaction is also influenced by the genetic background of the individuals resulting in rarity of this condition. One possible mechanism that causes KD or PIMS-TS in children could be antibody-dependent enhancement (ADE) where the presence of antibodies can be detrimental when their levels are too low to provide protection but high enough to enable the virus an abode for spread and immunomodulate. ADE has been demonstrated in SARS-CoV-2 *in vitro*, where antibodies to spike protein improve the ability of novel strains of the virus to enter host cells.[6,7] In order to establish the causality of SARS-CoV-2 infection in PIMS, Bradford Hill's nine causality criteria were applied, where it was found that these criteria partially met (i.e., 2+) in consistency and temporality and minimally met (1+) in strength, coherence, and plausibility and not met (−/±) in specificity, biological gradient, experiment, or analogy as per the European Centre for Disease Prevention and Control report dated May 15, 2020. The report also said that the onset of symptoms of PIMS-TS was estimated to be 2–4 weeks after COVID-19 infection.[8] The World Health Organization (WHO) in its scientific brief report dated May 15, 2020, proposed diagnostic criteria for PIMS-TS in children and the Centers for Disease Control and Prevention (CDC) published similar criteria on May 14, 2020 [Table 1].[9,10]

Clinical management of PIMS-TS has been supportive. On suspicion, efforts should be made to exclude bacterial sepsis and viral infections such as Epstein–Barr virus, in addition to investigation of household members for COVID-19 infection. Treatment with intravenous immunoglobulin (IVIG) has been a predominant management option. Methylprednisolone, heparin, and anti-inflammatory agents like tocilizumab have also been tried. A few children with PIMS-TS have required inotropic support, mechanical ventilation, and extracorporeal membrane oxygenation. There is a need for continuous surveillance and additional data from the Indian subcontinent so that a better understanding of the complications and ideal modality of treatment can be recommended. Till mid-May, 5 fatalities have been documented with PIMS-TS, 3 in the USA, and 1 each in France and the UK. Since most of these children present with myocardial involvement or coronary abnormalities, a long-term follow-up is required.[11] Case details of the three cases are enumerated below [Table 2].

Table 1: WHO and CDC criteria for PIMS-TS/Multisystem Inflammatory Syndrome in children (MIS-C)

WHO criteria - PIMS-TS dated May 15, 2020, in children with features of typical/atypical Kawasaki disease or toxic shock syndrome
Children and adolescents 0-19 years of age with fever≥3 days
AND any two of the followings
Rash or bilateral nonpurulent conjunctivitis or mucocutaneous inflammation signs (oral, hands, or feet)
Hypotension or shock
Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echo findings or elevated troponin/NT-proBNP)
Evidence of coagulopathy (by PT, PTT, or elevated D-dimers)
Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain)
AND elevated markers of inflammation like CRP, procalcitonin, or ESR
AND no other microbial cause of inflammation like bacterial sepsis, staphylococcal or streptococcal shock syndromes
AND evidence of COVID-19 (by RT-PCR, antigen or serology positive) or likely contact with patients with COVID-19
CDC criteria published on May 14, 2020
An individual <21 years of age presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization with multisystem organ (≥2) involvement (cardiac, renal, respiratory, hematological, gastrointestinal, dermatological, or neurological)
AND no alternate plausible diagnosis
AND positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test or COVID-19 exposure within 4 weeks prior to onset of symptoms

WHO: World Health Organization, PIMS-TS: Pediatric multisystem inflammatory syndrome associated with SARS CoV-2, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, PT: Prothrombin time, PTT: Partial thromboplastin time, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, COVID-19: Coronavirus disease 2019, RT-PCR: Reverse transcription-polymerase chain reaction, CDC: Centers for Disease Control and Prevention

DISCUSSION

There are a growing number of media reports and publications from around the world including India that a SARS-CoV-2-related inflammatory syndrome is emerging. Although PIMS-TS or MIS-C has been compared with KD, there are some differences such as an older age at presentation in former (mean age: 7 vs. 3 years in KD) with high incidence of shock and myocardial involvement,

Table 2: Case details

Demographics and clinical details	Case 1	Case 2	Case 3
Age in years	12	7	6.5
Gender (male/female)	Male	Male	Male
Presenting features in days	Fever - 6	Fever - 5, body ache	Fever - 9, irritability
Examination findings	Lethargy, ↓feeding	Irritability - 4	Rash [Figure 4], swollen hand and feet - 6
Others	Poor intake, urine output - 2, abdominal pain - 1 Hepatosplenomegaly with lymphadenopathy (on bedside USG)	Nonpurulent conjunctivitis, cracked lips, generalized erythematous rash periungual excoriation-D11 [Figure 3]	Red lips - 3 Strawberry tongue, cervical lymphadenopathy+ Cardiac rub+
Shock	Present- hypotensive	No	No
Inotropes	Adrenaline - 80 h	No	No
Respiratory failure and support	Yes, PF ratio - 85.7, OI - 16.9 NIV, awake prone, MV	No but distress + Low flow	Yes Low flow
AKI	Yes, AKI stage 2	No	No
Rash	Yes	Yes	Yes
PRISM III-24	24	13	12
Bedside 2D echo	Contractility 35% Normal coronaries	Moderate RV dysfunction, normal coronaries	Pericardial effusion - 5 mm Normal coronaries
Counts (in cumm)	29,500, P94L4	13,600, P81L12	29,300, P90L05
Poly, lympho (%), platelets in cumm	76,000	5.6 lakhs	5.3 lakhs
LDH U/L	740	345	825
Procalcitonin ng/ml	5.91	Not done	Not done
CRP in mg/dl/ESR	69/52	134/not done	13/72
NT-ProBNP pg/ml	4692	900	Not done
INR/D-dimer in ng/ml	1.8/not done	1.6/4000	1.4/not done
IL-6 pg/ml	12.81	150	Not done
Tropical fever workup/cultures	Negative	Negative	Negative
X-ray	ARDS/cardiomegaly [Figure 1]	Normal	Cardiomegaly
CT chest/angiography	CT chest- bilateral ground-glass opacities/consolidation [Figure 2]	CT angio for PTE - normal	Not done
COVID-19 test	RT-PCR positive	Contact with uncle who was COVID-19+	IgG ab to COVID-19+
TSS/KD criteria	TSS	KD	KD
WHO-criteria PIMS-TS	MV,NIV and awake prone fulfilled	fulfilled	fulfilled
Respiratory support	NIV/O_2 by low flow	O_2 by low flow	O_2 by low flow
Treatment	IVIG - 2 g/kg, methylprednisolone Azithromycin and supplements Injection furosemide for CCF	IVIG - 2 g/kg Aspirin	IVIG - 2 g/kg Aspirin
Response in hours	96, CRP/counts improved by day 5, AKI by D4	36, improvement in inflammatory markers	48 - afebrile, echo-decrease effusion
Length of stay days	32	16	20

PIMS-TS: Pediatric multisystem inflammatory syndrome associated with SARS CoV-2, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, COVID-19: Coronavirus disease 2019, RT-PCR: Reverse transcription-polymerase chain reaction, AKI: Acute kidney injury, CCF: Congestive cardiac failure, IVIG: Intravenous immunoglobulin, NIV: Noninvasive ventilation, MV: Mechanical ventilation, OI: Oxygenation index, KD: Kawasaki disease, TSS: Toxic shock syndrome, CT: Computed tomography, PTE: Pulmonary thromboembolism, ARDS: Acute respiratory distress syndrome, IL-6: Interleukin-6, INR: International normalized ratio, LDH: Lactate dehydrogenase, RV: Right ventricular, PF: PaO_2/FiO_2, USG: Ultrasonography

similar to that seen in our series.[12] Our patient's age profile matched PIMS-TS profile reported so far. Initial clusters were reported from the UK and Europe. However, it is increasingly reported with fever, features of hyperinflammation, and multi-organ dysfunction with laboratory evidence of COVID-19 positivity or with definite exposure to the virus from positive cases. Our cases had similar features of multi-organ involvement including all three of them depicting involvement of heart either with echo evidence as in all three, and biochemical evidence in two (markedly raised NT Pron BNP).[13] Table 2 depicts clinical features, investigations, and treatment summary of our patients. PIMS-TS generally has higher inflammatory markers, elevated NT-proBNP/BNP, and lymphopenia. All our patients in the series had raised inflammatory markers. In accordance with the RCPCH, WHO, and CDC guidelines, common bacterial sepsis and EBV infections were excluded. In all our patients, all cultures and common tropical infection mimics such as enteric fever, scrub typhus, and dengue were excluded. Most of the published literature had either reverse transcriptase–polymerase chain reaction positivity to COVID-19 virus or IgG antibody positivity or definite exposure to a positive case. Fortunately, the approach of early recognition, prompt investigation, and appropriate therapy with treatments often used for KD have worked in PIMS-TS as well with high rate of recovery. Nonetheless, the ideal and optimum treatment for PIMS-TS remains uncertain.

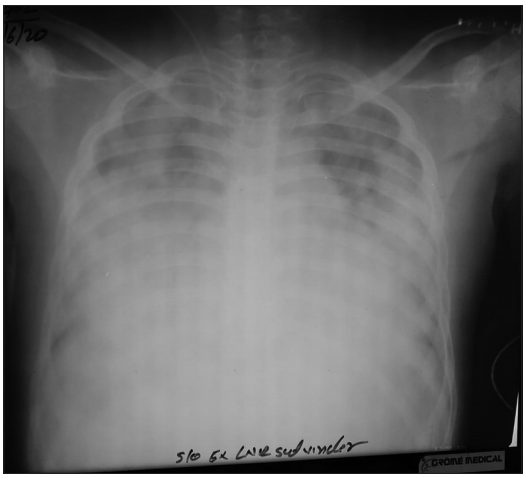

Figure 1: Chest X-ray depicting bilateral opacities and cardiomegaly

Figure 3: Periungual excoriation

The majority of patients in literature have been treated with immunomodulatory therapy with IVIG, steroids, and fewer with anakinra, infliximab, or tocilizumab.[14,15] Patients with cardiac involvement require aggressive therapy with ICU admission and early immunomodulation, as has been observed by Belhadjer *et al*.[16] We managed all our patients with steroids and IVIG, and all children recovered satisfactorily. A well-randomized controlled trial is required before IVIG or steroid can be recommended in PIMS-TS. The first reported child with possible PIMS-TS from India required steroid pulses in addition to IVIG. However, none of our children required steroid pulses.[5] None of our patients required tocilizumab. With the COVID-19 pandemic still progressing in India, more such cases will be reported in the future; hence, general pediatricians should be aware of this entity and should refer them to higher centers with PICU facilities for optimum management. Mortality is rare with early treatment, and in a recently published study by Feldstein *et al*. from the USA, out of 186 patients, only 24 died.[17] Further research is needed to understand immunobiology, spectrum, best therapy, and follow-up of such patients, particularly those involving the heart, and for this, multiple registries have been started by the WHO, RCPCH, and others.

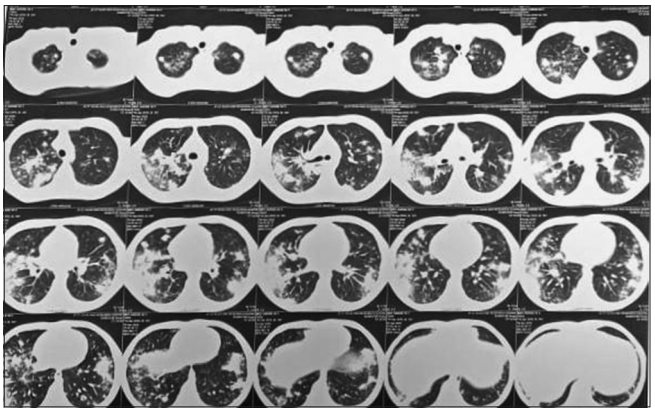

Figure 2: Computed tomography chest showing bilateral ground-glass opacities and consolidation

Figure 4: Generalized body rash

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Conflicts of interest

There are no conflicts of interest.

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Case Report

Pertussis: Resurgence of a forgotten entity

Mukesh Kumar Jain, Sibabratta Patnaik, Bandya Sahoo, Reshmi Mishra

Department of Pediatrics, Kalinga Institute of Medical Sciences, KIIT University, Bhubaneswar, Odisha, India

Abstract

Pertussis is a serious and life-threatening infection of infancy. Recurrent apnea with a paroxysm of cough is the early clue for its diagnosis. The rate of pertussis increased worldwide with the occurrence of regular outbreaks globally, including India. The resurgence of pertussis is multifactorial, and it includes antigenic shifts in bacteria, decreasing vaccine immunity, reduced duration of protection by acellular pertussis vaccine, and improved method of surveillance and diagnosis. Family members, especially mothers and siblings, are an important source of pertussis transmission to vulnerable infants. Maternal vaccination for pertussis during pregnancy should be done as many cases of infantile pertussis was found before primary immunization. A 45 days infants admitted to the pediatric intensive care unit with recurrent apnea and bradycardia, require prolonged mechanical ventilation with intense cardiorespiratory monitoring. Real-time polymerase chain reaction of the nasopharyngeal swab for pertussis was positive. Successfully discharged after a long course of hospitalization.

Keywords: Apnea, infancy, pertussis, polymerase chain reaction

Address for correspondence: Dr. Bandya Sahoo, Department of Pediatrics, Kalinga Institute of Medical Sciences, KIIT University, Bhubaneswar - 751 024, Odisha, India.
E-mail: bandyasahoo@gmail.com

INTRODUCTION

Pertussis is a serious infection with high mortality in infancy. Although a vaccine-preventable disease, its remains a significant public health threat as a reemerging infection. Over the last few decades, the incidence of pertussis increased among young adults and its a matter for grave concern.[1,2] Parents, especially mothers and siblings have been implicated as important sources of pertussis transmission in vulnerable infants.[3] Recently, many public health studies have suggested that maternal immunization during pregnancy can decrease pertussis in infants in a cost-effective manner.[1,4] Although the exact cause of resurgence is not clear, various factors such as antigenic shifts in bacteria, waning vaccine immunity, reduced duration of protection by acellular pertussis vaccine, and improved method of surveillance and diagnosis are held responsible.[5] Here, we describe a case of infant pertussis with the classical presentation.

CASE REPORT

A 45 days, 3.5 kg female, twin 2 presented to the emergency with the complaints of cough for 3 days, decreased feeding, and breathing difficulty for 1 day. She was born at 36 weeks (late preterm) with a birth weight of 2 kg, with uneventful postnatal history, was feeding well and healthy till the 42nd day of life. On examination, she was sick looking, irritable with tachypnea (respiratory rate-70/min) and subcostal retraction, SpO2 was 90% on room

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air and heart rate of 180/min. She had coarse crackles on the left side. The patient was shifted to the pediatric intensive care unit and was treated as a case of severe pneumonia with intravenous fluid, oxygen, and antibiotics. Initial investigation revealed Hb-13.5 g/dl, Total Leukocyte count (TLC) of 18,000/uL with 72% neutrophils and 29% lymphocyte, platelet-3.7 lakh/Cumm, C-reactive protein (Q)-14.9 mg/l, and chest X-ray showed bilateral infiltrate.

On day 2, the patient having repeated episodes of seizures, desaturation, and apnea. Gradually the severity and frequency of apnea increased, requiring bag and mask ventilation. Blood gas and sugar were normal during such episodes. On day 3 of admission, the patient continued to have recurrent life-threatening apnea, bradycardia accompanied by paroxysmal cough, which requires intubation, and mechanical ventilation. 2 D echo was structurally normal with moderate pulmonary arterial hypertension (PAH). Neurosonogram and cerebrospinal fluid study are normal. Serum procalcitonin was negative (0.22 ng/ml). Blood culture revealed no growth after 48 h. Repeat hemogram on day 4 showed Hb-13 gm/dl, TLC-12,600/uL with predominant lymphocytosis 69%, and on day 5 showed a similar trend with Hb-13 g/dl, TLC-7660/uL with lymphocytes 70. On day 5 of admission, pertussis was suspected because of recurrent apnea with predominant lymphocytosis. However, a positive history of contact from either parent could not be obtained. Nasopharyngeal swab for pertussis polymerase chain reaction (PCR) was sent, and azithromycin was started. There was no clinical evidence of gastroesophageal reflux, such as persistent vomiting, arching, or failure to gain weight. The patient continued to have frequent episodes of desaturation and bradycardia on mechanical ventilation. Gradually over 2 weeks, the frequency of apnea and desaturation reduced, and the baby was extubated. Postextubation, patient was hemodynamically stable and tolerated oral feeds. The patient was discharged after 24 days of hospital stay with stable vitals and intermittent cough. PCR for pertussis was came out to be positive.

DISCUSSION

Severe cases of Bordetella pertussis manifest with recurrent episodes of apnea along with bradycardia, desaturation, and sudden death have been reported.[6,7] Unvaccinated newborn babies and young infants, as in our case, are at more risk. Two-thirds of all infants admitted to the hospital have apnea as it is a major symptom of pertussis.[1] Once infants develop apnea with pertussis, it is usually recurrent in nature and lasting for a prolonged period, the median duration of 19 days (range: 1–76 days).[8] Although numerous virulence factors of B. pertussis, such as pertussis toxin and adenylate cyclase toxin have been identified, the exact pathogenesis of apnea in pertussis is not yet clear.[9] Therefore, the management of patients with recurrent apnea needs early diagnosis and intense cardiorespiratory monitoring for a better outcome.

Central nervous system dysfunction such as seizures, encephalopathy is found in 10%–20% of cases, whereas hyperleukocytosis in 21%–35% of cases.[10] PAH was found in 33% of cases, and it is possibly due to obstruction of pulmonary vasculature by excessive lymphocytes in pertussis. Mortality in critical pertussis varies between 4.8% and 55%.[11] The predictors of mortality include younger age, comorbidities, need for ventilation, inotropes use, PAH, and a fast course.[11]

Bordetella pertussis is a human-specific, Gram-negative, pleomorphic, aerobic coccobacillus that is transmitted through droplets. This microorganism grows on Bordet–Gengou medium between 35°C and 37°C. Although many serological tests are available, they are not always helpful, and therefore specific test like PCR is required for better results.[7] Lymphocytosis is a major and useful diagnostic clue for pertussis infection in infants and young children.[12] However, some infants may have normal lymphocyte counts in the early stage of the disease, as seen in our cases.[13] Lymphocytosis is also a marker of disease severity and is associated with a bad prognosis in infants and may responsible for the development of pulmonary hypertension or the need for extracorporeal membrane oxygenation.[10]

Antibiotic is not helpful either in treating recurrent apnea or in changing the course of the diseases but only reduces the risk of disease transmission. Macrolide such as azithromycin is recommended for 5 days as the first-line antibiotic.[13] No effective treatment has been established for repetitive apnea caused by pertussis. Therefore, this disease needs intense cardiorespiratory monitoring for a better outcome in infancy.

The rate of pertussis is increasing worldwide, with regular upsurge being reported globally, including India.[14,15] The resurgence of a vaccine-preventable disease such as pertussis causing increasing hospitalization, costs, and mortality is a worrisome trend and has led to calls for a relook of immunization schedules[14,15] Critical pertussis occurring before primary immunization highlights the importance of maternal immunization against pertussis.

CONCLUSION

Recurrent apnea with paroxysmal cough is early sign to suspect pertussis in early infancy. Common sources of infections are family members, especially mothers and siblings. Intensive cardiorespiratory monitoring is of paramount importance. Azithromycin is the drug of choice, but it only prevents further transmission. Antepartum immunization of mothers will be perhaps helpful to prevent such infections.

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Case Report

A rare cause of pulmonary hemorrhage in the intraoperative period

Anurakti Dev Singla, Anil Sivadasan Radha[1], Girish Warrier[2], Meena Trehan[3]

Department of Pediatric Cardiac Sciences, Artemis Hospitals, Gurugram, Haryana, [1]Medical Services, Apollo Adlux Hospitals, Ernakulum, [2]Department of Pediatric Cardiac Sciences, Aster Hospital, Calicut, Kerala, [3]Department of Pediatric Cardiac Sciences, Apollo Health City, Jubilee Hills, Hyderabad, Telangana, India

Abstract The perioperative morbidity and mortality in pediatric cardiac surgery can be due to a multitude of factors. Timely identification of the problem helps in altering the treatment strategy and improving the outcome.

Keywords: Cardiac intensive care, central venous catheter, unilateral pulmonary edema

Address for correspondence: Dr. Anurakti Dev Singla, Department of Pediatric Cardiac Sciences, Artemis Hospitals, Sector 51, Gurugram, Haryana, India.
E-mail: anurakti07@yahoo.co.in

INTRODUCTION

Mitral valve replacement in the younger population is increasingly being done, especially for the mitral valve affected by rheumatic heart disease. The perioperative course can be unusual sometimes, and we should be ready to explore and identify the problem.

CASE REPORT

A 12-year-old girl presented with palpitations and exertional dyspnea, New York Heart Association functional Class III.[1] She was on irregular Benzathine penicillin prophylaxis for the past 5 years after an episode of fever and arthritis. On initial examination, the patient had brisk and bounding pulses with a heart rate of 130/min with respiratory distress and tachypnea and saturation of 98% on room air. She had a hyperdynamic apical impulse felt in the 6th left intercostal space with a late systolic left parasternal thrust and palpable second heart sound. Her first heart sound was normally heard, second heart sound was widely split with a loud pulmonic component; and she had a soft Grade 3/6 pansystolic murmur at the apex, radiating to the axilla and back with a rumbling, and low-pitched flow mid-diastolic murmur. Her systemic examination was noncontributory. There was no evidence of rheumatic activity on blood investigations. On chest radiograph, she had gross cardiomegaly with pulmonary artery enlargement and pulmonary plethora. Her electrocardiogram was suggestive of sinus tachycardia with prominent left ventricular forces and left atrial enlargement. The two-dimensional echocardiogram showed rheumatic involvement of the mitral valve evident from thickened, nodular, and echogenic mitral valve leaflets with severe mitral regurgitation due to prolapse of all segments of the anterior mitral leaflet, lack of mobility of posterior mitral leaflet, and annular dilatation. She had dilated left atrium (LA), left ventricle (LV), and pulmonary artery with pulmonary arterial hypertension. She was stabilized with inhaled oxygen, decongestive therapy, and inotropic support and was planned for

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elective mitral valve repair (if feasible)/replacement. In the operating room, after initial preoxygenation, she was electively intubated and mechanically ventilated using narcotic-based anesthesia. Neck central line was secured using a posterior approach. After sternotomy followed by adequate heparinization, she was taken under normothermic aortobicaval cardiopulmonary bypass (CPB) with antegrade crystalloid cardioplegic arrest. As seen after left atriotomy, the valve was unsuitable for repair because of severe subvalvular pathology and fixed posterior mitral leaflet. Hence, a 25 mm St. Jude mechanical valve was used to replace the mitral valve. After coming off bypass, there was transient hypotension which did not respond to volume replacement and inotropes. At the same time, there were copious pink frothy secretions from the endotracheal tube. The LA pressure was measured directly and the mean was 5 mmHg. Transesophageal echocardiography (TEE) was done to check LV function, valve position, and function and for residual paravalvular regurgitation, which were normal and were consistent with normal LA pressure. After achieving hemodynamic stability, the patient was shifted to the intensive care unit (ICU). However, the unexplained endotracheal tube bleeding persisted. The chest radiograph revealed a good position of the endotracheal tube, neckline, and chest tubes in the expected position with diffuse haziness of the right lung [Figure 1]. Hence, the causes of unilateral pulmonary edema, and pulmonary hemorrhage were considered. Repeat TEE was done to look for pulmonary vein issues. On TEE, we realized that echo contrast was seen coming into LA, although there was no Patent foramen ovale (PFO). To our surprise, the tip of the neckline was in the right upper pulmonary vein (RUPV) and thus into LA. Due to the side holes in the canula, part of the drugs administered was entering LA and part of it seeping into the lung. This could explain unilateral haziness on chest radiograph and hypotension not responding to inotropes. The neckline was removed, bleeding was stopped, inotropes were decreased, and the patient was extubated the next day. There was a radiological improvement in 48 h [Figure 2], though it took 2 weeks for full recovery. In retrospect, the cannulation was difficult according to the anesthetist.

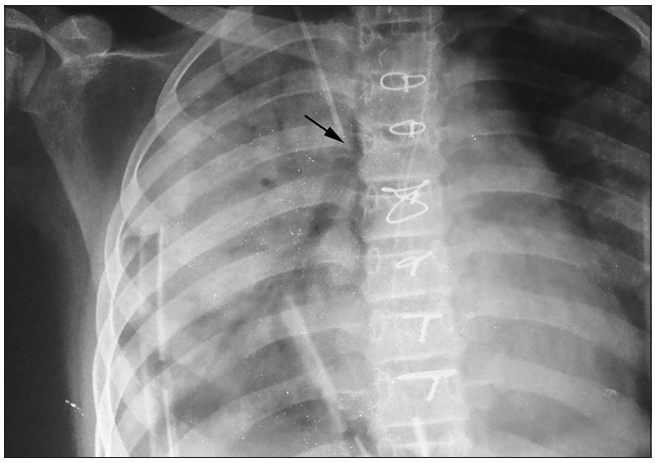

Figure 1: Chest radiograph taken in anteroposterior view showing unilateral haziness (right side) with neckline tip (black arrow) apparently in expected position

DISCUSSION

Bilateral diffuse pulmonary edema in a patient undergoing mitral valve replacement can be a manifestation of underlying left ventricular dysfunction, prosthetic valve dysfunction, residual paravalvular leak, and extensive chordal resection. LV dysfunction can be due to the inflammatory response syndrome resulting from CPB and also due to increased cross-clamp time, inadequate myocardial protection, and preoperative ventricular dilatation and dysfunction.[2,3]

Our patient had a refractory unilateral pulmonary edema; volume replacement indeed worsened the hemodynamics. Paradoxically, the common attributable factors were absent. Being unilateral, it made us suspect injury to RUPV, which can rarely happen during LA closure. The abnormal placement of the central venous catheter was realized during a TEE evaluation to check for the RUPV status. In the review of literature of unilateral pulmonary edema (UPE) in postoperative patients, it shows that most reported cases of acute UPE have resulted from severe eccentric MR with the jet predominantly affecting RUPV, leading to a larger increase in mean capillary pressure in the right side.[4,5]

UPE has also been reported due to variation in the pulmonary venous pressure associated with left heart failure, anomalous

Figure 2: Chest radiograph taken in anteroposterior view after neckline removal showing reduced lung plethora

vascular distribution, asymmetric pulmonary perfusion due to pulmonary artery agenesis or hypoplasia, local emphysematous changes, and pulmonary inflammatory diseases. UPE following systemic-pulmonary artery shunts can be explained on the basis of preferential flow resulting from such a shunt.[6,7] UPE can also be reexpansion edema after the rapid evacuation of pneumothorax or a presentation of acute rheumatic fever.[8] Contralateral bronchial obstruction or stenosis causes hypoxia of one lung with resultant pulmonary capillary endothelial damage and lymphatic insufficiency and cause UPE.[9] On rare occasions, compression of a pulmonary vein outlet by a myxoma or atrial wall hematoma or destruction of the pulmonary vascular bed of the right lung can cause UPE.[10] Misplacement of a central venous pressure monitoring catheter into a pulmonary artery can present with UPE as well.[11]

We tried to think about all the possible issues to conclude what went wrong. We present this case to draw attention to an uncommon cause of pulmonary edema in the intraoperative period, where the central venous line put through the jugular access inadvertently reached the RUPV. Anatomically, RUPV courses posterior to the distal end of superior vena cava (SVC) and can be cannulated if our puncture is directed toward the posterior wall of SVC. All the central lines are taken with ultrasound guidance; still, this complication can occur on rare occasions. To prevent this from happening, we should either check the echocardiography to ascertain the position of the neckline by seeing bubble contrast in the right atrium or take venous blood gas samples to be sure that it is not in RUPV. Any unexplained pulmonary edema in operating room or ICU should involve a detailed evaluation of the quantity of volume replacement, intactness of the secured lines for delivery of inotropes, a watch on the CPB time, ventricular dysfunction, residual valvar or paravalvular leak, prosthetic valve dysfunction, increased LA pressures owing to the narrowed mitral orifice or pulmonary venous issues. Logical thinking, stepwise analysis, and an open mind help in identifying uncommon causes for common problems.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initial s will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

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Case Report

Acyclovir crystalluria: The utility of bedside urine routine microscopic examination

Puneet Jain, Ramachandran Rameshkumar, Ponnarmeni Satheesh, Subramanian Mahadevan

Department of Pediatrics, Division of Pediatric Critical Care, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India

Abstract

Acyclovir, an acyclic nucleoside, is commonly used for the treatment of viral infections. Acyclovir is well tolerated in children. However, severe nephrotoxicity has been shown to occur in some children. One of the mechanisms for acyclovir-induced nephrotoxicity is acyclovir-induced crystalluria. Prompt attention to urine microscopy examination can help avoid drug-induced nephrotoxicity. Here, we report a case of a seven-year-old febrile comatose child who received intravenous empirical acyclovir therapy and developed cloudy urine. Bedside urine microscopic examination shows fine-needle-shaped crystal. The urine was cleared within 12 h of stopping the acyclovir and adequate intravascular hydration. A child recovered without evidence of acute kidney injury.

Keywords: Acyclovir, children, complications, crystalluria, microscopy, urine examination

Address for correspondence: Dr. Ramachandran Rameshkumar, Department of Pediatrics, Division of Pediatric Critical Care, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry - 605 006, India.
E-mail: krramesh_iway@yahoo.co.in

INTRODUCTION

Urine microscopy is a low-cost investigation that can provide useful and relevant information in a broad spectrum of clinical situations.[1] The presence of crystals in urine is a common finding in the routine examination of urine. A variety of drugs sulphadiazine, acyclovir, triamterene, piridoxilate, and primidone may cause crystalluria. Although acyclovir is well tolerated, it may lead to severe nephrotoxicity.[2] Acyclovir crystalluria is an uncommon side effect of the commonly used drug. Timely detection of acute kidney injury (AKI) and prompt intervention is necessary to prevent morbidity. Prompt attention to urine microscopy observation can help to avoid drug-associated renal toxicity. We highlighted the utility of art and science of urine microscopic examination in a report of the seven-year-old febrile comatose child who developed acyclovir-induced crystalluria.

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CASE REPORT

A seven-year-old developmentally normal boy with no significant history was brought to the emergency department with a history of fever for the past three days and altered sensorium for one day. There was no history of seizures, jaundice, or recent vaccination. Examination findings were terminal neck rigidity, and upper motor neuron signs but no papilledema. The provisional diagnosis of acute febrile encephalopathy was considered. The child was managed with supportive care, osmotherapy (3%-saline),

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and intravenous antimicrobials (ceftriaxone, 50 mg/kg/dose every 12 h and acyclovir, 10 mg/kg/dose every 8 h over 1-h infusion). The lumbar puncture was done after finding an unremarkable study of contrast-enhanced computer tomographyof the head examination. The child was on mechanical ventilation for three days for disordered control of breathing.

On the day three of stay, his urine changed to cloudy appearance. His serum creatinine levels were within the normal range (0.6 mg/dL). The specific gravity of urine was 1.020. Microscopy of urinary sediment revealed abundant, colorless, transparent, and fine-needle-shaped crystals [Figure 1]. The macroscopic and microscopic picture of urine suggested acyclovir-induced crystalluria is the most likely diagnosis. The drug was stopped, and adequate hydration ensured to maintain adequate urine output. Renal function and urine output were normal during the stay. Urine was clear of crystals within 12 h. Cerebrospinal fluid (CSF) examination showed hypoglycorrhachia (CSF sugar 38 mg/dL and blood sugar 84 mg/dL), the protein of 75 mg/dL and 60 cells with 80% neutrophils. Since the CSF picture suggestive of pyogenic meningitis and polymerase chain reaction for herpes virus in CSF was negative, acyclovir was not restarted.

DISCUSSION

The urine microscopy is one of the few tests which can be done at the bedside and at a low cost. A variety of drugs such as triamterene, sulphadiazine, acyclovir, piridoxilate, and primidone may cause transient crystalluria.[3] Factors leading to precipitation of crystals within renal tubular lumen are an overdose, dehydration, and hypoalbuminemia.[4]

The incidence of acyclovir-induced renal impairment has been reported to be 16% in adults.[5] Acyclovir crystals are birefringent and needle-shaped[3] [Figure 1], and the abundance of these crystals give urine a silky and opalescent macroscopic appearance. Needle-shaped crystals are not unique to acyclovir drug. Endogenous causes of needle-shaped crystals are uric acid, calcium phosphate, tyrosine, and bilirubin crystals, whereas drug-related needle-shaped crystals are formed by acyclovir, atazanavir, ciprofloxacin, and amoxicillin.[6] As laboratory technicians do not have access to medical records, timely reporting of moderate to abundant crystalluria to clinician is of paramount importance to raise concern for the risk of acute kidney injury (AKI). Therefore, long needle-shaped crystals, with bright birefringence under polarized light microscopy that readily dissolve with the addition of saline, acid, or base in the urine of patients receiving acyclovir intravenously is most likely due to acyclovir crystalluria.

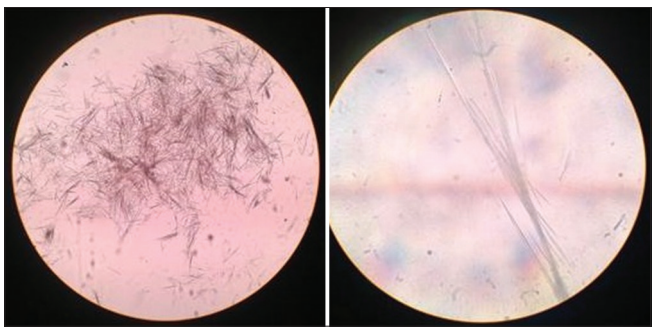

Figure 1: Multiple needle-shaped crystals observed under light microscopy

The acyclovir can cause crystalluria though it is an uncommon side effect of commonly used drugs.[7] The occurrence of acyclovir-induced crystalluria increases when high dosages are given intravenously, and when accorded to dehydrated patients.[5] Additional risk factors are preexisting AKI, concurrent administration of nephrotoxic agents, and rapid intravenous infusion.[4] In the index case, acyclovir dose and duration of infusion were as per standard recommendations. The identifiable risk factor in the index case is restricted maintenance fluid (80% of daily requirement) and coadministration of ceftriaxone as a combination of ceftriaxone and acyclovir may result in nephrotoxicity. Vomiero *et al*. reported that a combination of ceftriaxone and acyclovir resulted in an increased incidence of renal impairment as compared to monotherapy in meningoencephalitis cases. However, they did not find evidence of crystalluria in their cases.[8]

Drug-induced crystalluria may be asymptomatic or in association with erythrocyturia or leukocyturia.[1] In the index case, crystalluria led to cloudy urine. The primary mechanism of acyclovir-induced nephrotoxicity is thought to be because of crystalluria.[5,9,10] However, clinical evidence of nephrotoxicity in the absence of crystal formation suggests that acyclovir may cause direct insult to renal tubular cells. Gunness *et al*. reported that renal biopsies from the patients receiving acyclovir demonstrated flattened vacuolated, bulging epithelial cells, and no evidence of crystals.[2]

Treatment of acyclovir nephrotoxicity is mainly supportive and modification of drug or discontinuation in addition to maintaining a high urinary flow rate with intravenous fluids and furosemide.[4] In the index case, the drug was stopped and good urine output was achieved with adequate hydration. Subsequently, urine was clear of crystals within 12 h, and renal function tests were also within the normal range.

CONCLUSION

This case highlights the utility of art and science of urine microscopy. Acyclovir is recommended mainly for acute meningoencephalitis in tropical countries. Hence, daily microscopic examination of urine in patients who were receiving Acyclovir may help in early detection of crystalluria, and necessary intervention can be done accordingly. The low-cost investigation and feasibility to perform bedside, it should be more widely used by clinicians. In the clinical context, timely recognition and prompt intervention can prevent drug-induced kidney injury.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient's parents have given their consent for images and other clinical information to be reported in the journal. The patient's parents understand that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Case Report

Giant asymmetrically peaked T-waves in a child with raised intracranial pressure due to acute central nervous system infection: A case report and review of the literature

Puneet Jain, Ramachandran Rameshkumar, Ponnarmeni Satheesh, Chitamanni Pavani

Department of Pediatrics, Division of Pediatric Critical Care, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India

Abstract

Although various changes in electrocardiogram (ECG) were reported with normal serum potassium levels in acute intracranial pathology, giant asymmetrical T-wave change has not been reported. We report a case of a previously healthy male child who presented with acute febrile illness and features of raised intracranial pressure. Full standardized ECG shows normal sinus rhythm and tall, broad, and giant asymmetrically peaked T-wave. Serum potassium, echocardiography, and cardiac injury marker were normal. The child managed with supportive care and antimicrobials and showed recovery in 7 days.

Keywords: Central nervous system infections, children, ECG changes, raised intracranial pressure

Address for correspondence: Dr. Ramachandran Rameshkumar, Department of Pediatrics, Division of Pediatric Critical Care, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry - 605 006, India.
E-mail: krramesh_iway@yahoo.co.in

INTRODUCTION

An electrocardiogram (ECG) is one of the most valuable diagnostic tools that record the heart's electrical activity as waveforms. By interpreting these waveforms accurately, we can identify rhythm disturbances, conduction abnormalities, and electrolyte imbalances. ECG changes have also been reported in many noncardiac illnesses.[1] Awareness of characteristic ECG changes in cardiac and noncardiac illnesses such as raised intracranial pressure (ICP) may alert the treating physician for early recognition and timely life-saving interventions. The various ECG changes have been described in a myriad of central nervous system (CNS) lesions. These changes include bradycardia, extrasystoles, abnormal ST-T deflection, prominent U-waves, prolonged QT intervals, and tall, deeply inverted, large upright, or notched T-waves.[2]

CASE REPORT

We describe a case of an 8-year-old developmentally normal male child who presented with complaints of fever for 4 days, altered sensorium for 1 day, four episodes of vomiting, and one episode of a generalized tonic–clonic seizure. On examination, the child was hemodynamically stable with unremarkable system examination except for the low modified Glasgow coma scale (9/15) and upper motor neuron signs. A provisional diagnosis of acute

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meningoencephalitis was considered and was managed with antiraised ICP measures and empirical antiviral therapy.

Full standardized ECG [Figure 1] showed sinus rhythm, normal axis, heart rate of 60/min, and normal QRS complex duration and PR and QT intervals. However, T-wave abnormalities in this ECG were detected. T-waves were tall, broad, and asymmetrically peaked. T-waves were inverted in V1, V2, avR, and bifid in V3 (marked with an arrow), whereas large upright T-wave was noticed in V4, V5, and V6. The largest amplitude was seen in V4 – 1.8 mV (marked with a small arrow) with a T/QRS ratio of 1.28 which qualifies for giant T-wave. This tall T-wave cannot be explained by hyperkalemia which is a common cause of tall T-wave in our clinical practice as serum potassium level was within the normal range (serum potassium: 4.4 mEq per dL) and normal troponin I. Echocardiography examination was also normal. T-wave abnormality disappeared once the CNS pathology resolved. ECG was normal at discharge. The child was discharged after 7 days of hospital stay with the normal neurological state.

DISCUSSION

The observed ECG findings in the index case were correlated with the ECG findings described in the literature in association with neurologic diseases except for giant asymmetrical T-wave. Tall upright peaked T-waves may be seen in hyperkalemia or myocardial ischemia besides as a normal variant. In 1947, Byer *et al*. reported large, upright T-waves in patients with arterial hypertension and symptoms and signs of encephalopathy, together with prolongation of the QT interval.[3]

Burch *et al*. in 1968 reported that prominent upright T-waves are frequently associated with prominent U-waves, prolonged QT interval, and T–U fusion as ECG manifestation of intracranial diseases.[4] In their study, 55 patients with ECG changes thought to be secondary to intracranial lesions, the more typical ECG findings of prolonged QT interval, and large T-wave inversion were seen in only 17 (31%) of the 55 patients, whereas 38 (69%) had the type of upright T-waves.

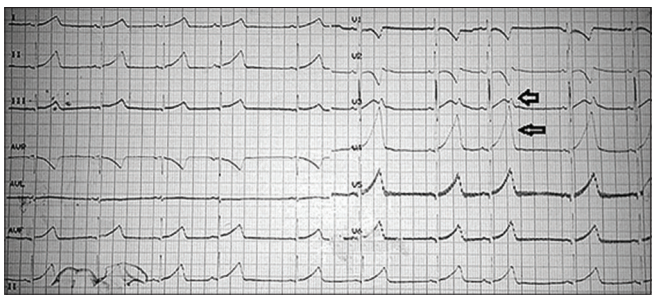

Figure 1: Full standardized ECG shows giant asymmetrically peaked T-waves

In a case series of seven patients with varying intracranial conditions and with no evidence of cardiovascular disease, Jachuck *et al*. studied electrocardiographic abnormalities associated with raised ICP.[2] It was observed that two patients with normal ICP showed no ECG abnormalities, whereas the remaining five patients had different ECG changes. All five patients had T-wave abnormality. T-waves were flat in three patients, notched in one patient, and tall in the other. ECG changes were studied objectively with ICP changes, and it was suggested that tall T-waves are an early ECG manifestation of rising ICP.

As the ICP increases, the tall T-waves became flat and reverted to normal as the ICP with normal ICP. The T-waves became progressively inverted if ICP rises significantly. These T-wave changes were usually seen in the standard leads II, III, aVL, and aVF. Other ECG changes noticed were progressive ST depression with increasing ICP and prominent U-waves. These findings not only confirm the association between ECG abnormalities and CNS diseases but also suggest that many of the ECG abnormalities are related to changing ICP. In addition, it has to be kept in mind that elevated T-waves in ECG can be seen as normal variation in young patients and athletes. Even some medications are also associated indirectly with T-wave abnormalities such as antiarrhythmic, digoxin, and diuretics.[5]

In a study of 161 patients with neurologic diseases by Póvoa *et al*., the most frequent abnormality observed was ventricular repolarization (23.7%). The presence of T-waves (4.6%) and prolonged QT intervals (8.8%) was the most characteristic of brain injuries.[6] The peculiarity of the index case is the asymmetrically peaked giant T-waves which are different from the ECGs described in other studies.

The exact pathophysiology of this condition remains unclear. Several different mechanisms have been proposed such as the involvement of the neurohormonal system, increased catecholamine levels, and sympathetic outflow. Excess of catecholamines in association with enhanced adrenal production and activation of the calcium channels leads to an increase in calcium levels in cytosolic and mitochondria, as well as the release of free radicals, causing contraction band necrosis and ECG alterations.[6]

Byer *et al*. reported that large, upright T-waves in the human electrocardiogram, together with prolongation of

the QT interval, may often be due to the predominant involvement of ischemic changes in the endocardial surface of the left ventricle muscle layers.[3] A clinically significant prevalence of myocardial injury in patients with acute neurologic illness has been demonstrated by Dixit *et al*.[7] and confirmed by the finding of the elevated cardiac troponin I level. Kono *et al*. also reported that patients with subarachnoid hemorrhage and ST-segment elevation may demonstrate transient corresponding regional wall motion abnormalities.[8] T-wave changes in the index patient can also be explained by autonomic disturbances caused by raised ICP.

This report highlights the importance of ECG in noncardiac illnesses, including alterations of the CNS, and should be considered in the diagnosis of diseases resulting in ECG changes, especially when the clinical history does not suggest cardiac disease.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the parents have given their consent for their child's images and other clinical information to be reported in the journal. The parents understand that their child's name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Case Report

Point-of-care ultrasound in pediatric cardiac masses: A case series

Jangam Sachin S, Shobhavat Lakshmi, Mishra Jayashree, Solomon Rekha, Pathak Nakul

Department of Pediatric Critical Care, Bai Jerbai Wadia Hospital for Children, Mumbai, Maharashtra, India

Abstract

The utility of point-of-care ultrasound (POCUS) is well supported by evidence In the Indian scenario, there are no standard guidelines or special training for POCUS in the pediatric intensive care unit. We present here a case series of nine patients with intracardiac masses in whom POCUS performed by pediatric intensivist helped in the management of critically ill patients. The final diagnosis of these patients included left atrial myxoma, two cases of thrombus, four cases of infective endocarditis (IE) with unusual organisms, and two cases with diagnostic confusion about IE/thrombus/cardiac tumor. In all these patients POCUS helped in deciding the line of management such as choice of antimicrobial therapy, site of the central venous catheter, and timely involvement of cardiologist and cardiothoracic surgeon. One of the children presented with obstructive shock and bedside ultrasound helped in the diagnosis of a left atrial mass and early surgery with a good outcome.

Keywords: Cardiac masses in pediatric patients, infective endocarditis, point of care ultrasound

Address for correspondence: Dr. Sachin Shankar Jangam, Shivkrupa Niwas, Plot No-19, Ashtha Bypass, Madhavnagar Road, Kalanagar, Sangli - 416 416, Maharashtra, India.
E-mail: jangamsachin2007@gmail.com

INTRODUCTION

Point-of-care ultrasound (POCUS) is emerging as a reliable and valid tool for clinicians for bedside diagnosis, clinical decision-making as well as timely intervention for optimum patient management. Recently, the American Academy of Pediatrics, in its policy statement, recommended the establishment of training and credentialing programs for POCUS to improve the care of pediatric patients.[1] The technological advances in the field of ultrasound have made it easier to provide POCUS by first responders. The smaller size and easy portability of ultrasound machines coupled with a better understanding of ultrasound techniques and improvements in imaging quality have made it possible to use ultrasound as a great tool of examination. In the context of neonatology, it has been already widely adopted tool for neurosonogram and neonatal two-dimensional echocardiogram.[2] The areas where the point of care sonography routinely used in pediatric intensive care units (PICUs) are for fluid responsiveness, preload estimation, lung ultrasound, intracranial pressure monitoring, functional 2 d echo for cardiac contractility, cardiac output, and detection of pleural and pericardial effusion. Furthermore, ultrasound-guided central line placement, pericardiocentesis, or thoracocentesis is now standard of care.[3] The advantages of POCUS include

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rapid detection of problems and timely intervention which can be done at the bedside in patients who cannot be moved to the cardiology or radiology department because of their critical condition.[4]

The concept of POCUS in pediatric intensive care with intracardiac masses is more compelling than its use in adults because pediatric cardiology itself is in budding shape in India and children are more likely to succumb to the disease process if the diagnosis and timely involvement of respective specialist is not done in time.

We present a case series including nine patients with intracardiac masses from Bai Jerbai Wadia Hospital for Children, Mumbai diagnosed over 2½ years (January 2017–May 2019) in whom POCUS played a major role in diagnosis and management. The patients were diagnosed to have atrial myxoma, cardiac thrombus, bacterial, and fungal infective endocarditis (IE). In all these case POCUS helped us in the diagnosis and management of patients before a cardiology reference could be made.

CASE REPORT

Case 1

A 45-day-old male infant was admitted with severe respiratory distress with oxygen saturation of 90% on oxygen with hood. He had a low pitched rumbling mid-diastolic murmur and required ventilator support for respiratory failure. Chest X-ray showed bilateral pulmonary plethora and bedside POCUS showed large left atrial mass measuring 15 mm × 15 mm causing almost complete obstruction to blood flow across the mitral valve [Figure 1] which was confirmed by a pediatric cardiologist. Because of pulmonary edema refractory to medical line of management the cardiothoracic surgeon was involved and the patient underwent removal of mass under cardiopulmonary bypass. POCUS helped in the detection of obstructive cardiac mass leading to timely surgical intervention. Histopathological examination revealed atrial myxoma. Postsurgery patient was stable and was discharged 2 weeks later.

Figure 1: A 45-day-old infant with refractory pulmonary edema

Case 2

A 18-month-old boy, known case of nephrotic syndrome with documented episode of bacterial peritonitis and shock 2 months earlier was admitted with respiratory failure and shock. He required ventilator support along with fluid resuscitation and inotropic support. POCUS showed a mobile right atrial mass [Figure 2]. It was decided to place a central venous catheter in the femoral vein rather than the internal jugular vein (IJV) so that mass could not be disturbed or dislodged. With the differential diagnosis of IE and thrombus, the patient was treated with appropriate antibiotic therapy (meropenem and vancomycin) and low molecular weight heparin (LMWH). Detection of cardiac mass in this helped us to decide the site of the central line, collection of the appropriate number of blood culture for IE, and also to start LMWH and proper antibiotics. Complete disappearance of mass on follow-up 2 D Echo and the presence of predisposing factor (IJV catheter during first admission and nephrotic syndrome) pointed toward the possibility of it being intracardiac thrombus.

Case 3

A 12-year-old boy who was a known case of end-stage renal disease awaiting renal transplant was admitted to PICU with respiratory failure. At the time of admission, he had left IJV dialysis catheter. POCUS showed right atrial mass measuring 13 mm × 14 mm at the tip of the catheter suggestive of thrombus or vegetation. He was started on Piperacillin-Tazobactum, vancomycin, fluconazole, and LMWH empirically. The patient improved to the above treatment and was eventually extubated on the 6th day

Figure 2: A 18-month-old child with nephrotic syndrome with right atrial mass

of admission. Cardiothoracic and vascular surgeon was involved after stabilization and advised removal of mass by open heart surgery but his parents opted for medical management. He was listed for renal transplant but the child succumbed to his illness after 6 months.

Case 4

A 12-year-old boy diagnosed to be have acute myeloid leukemia (M2-Stage) on chemotherapy developed febrile neutropenia. He was started on Piperacillin-Tazobactum, vancomycin, amikacin, and fluconazole. On the day 4, he developed shock and was shifted to PICU. POCUS showed hypoechoic mass measuring 4 cm in the right ventricle [Figure 3]. As this child had an immunocompromised state differential of the fungal ball was considered and was started on a parenteral antifungal (voriconazole and amphoterecin B). The mass was removed by open heart surgery and biopsy confirmed as mucormycosis [Figure 4]. Hence in this case, POCUS helped us in considering antifungal drugs and the involvement of cardiologist and cardiothoracic surgeon in time. Despite all medical and surgical management child succumbed on the 10th day of admission.

Case 5

A 3½-year-old male child was admitted with a history of fever, breathing difficulty, and convulsions. The central nervous system examination revealed left hemiparesis with left side upper motor neuron type of facial palsy. He had a history of unsuccessfully attempted ventricular septal defect (VSD) device closure 9 months earlier. POCUS echo showed the presence of VSD along with vegetations over anterior leaflet of the mitral valve. Appropriate blood cultures were collected and the patient was empirically started on LMWH for suspected thrombus as well as antibiotics for IE. Blood culture grew rapidly growing nontuberculous *Mycobacteria*. Magnetic resonance images (MRI) of the brain showed nonhemorrhagic infarct. The patient was started on clarithromycin, linezolid, rifampicin ethambutol, and ofloxacin after infectious disease expert consultation. He was stabilized and was transferred to ward with neuro deficit after 2 weeks; he had a complicated hospital course and died of septic shock 2 months later.

Case 6

A 10-year-old boy was admitted with pneumonia and septic shock. He had a history of multiple admissions since 1 year of age and was diagnosed case of hyper immunoglobulin M syndrome with failure to thrive. He had chronic diarrhea, chronic eczema, chronic suppurative otitis media, hepatomegaly, and iron deficiency anemia. POCUS showed 1.2 cm × 1.2 cm hyperechoic mobile mass attached to interventricular septum near the apex of the left ventricle. His blood cultures were sterile. Dilemma remained whether it was culture-negative IE, thrombus, or cardiac tumor. On the 3rd hospital day, he developed sudden respiratory distress which rapidly progressed to cardiopulmonary failure and he died within 3 h.

Case 7

A 15-month-old girl was admitted to the intensive care unit with severe respiratory distress due to pneumonia with empyema and congestive cardiac failure. She was a diagnosed case of large patent ductus arteriosus. There had been a failed attempt at device closure 3 months earlier. POCUS showed 11 mm × 10 mm vegetation over the tricuspid valve with severe tricuspid regurgitation and severe hyperkinetic pulmonary artery hypertension. She was started on LMWH considering thrombus and antibiotics for IE. Her blood culture was sterile but pleural fluid grew

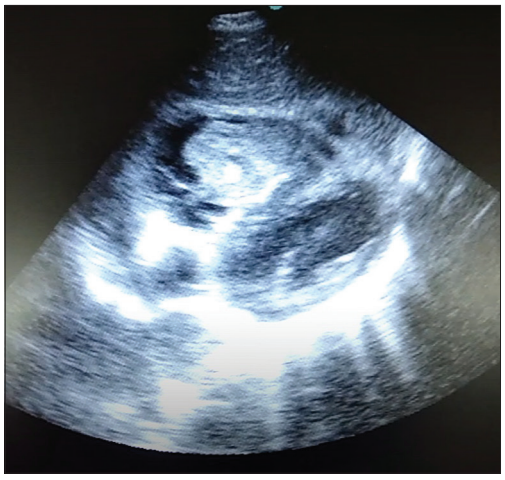

Figure 3: A 12-year-old child with acute myeloid leukemia and prolonged fever. Subcostal view: right ventricular mass

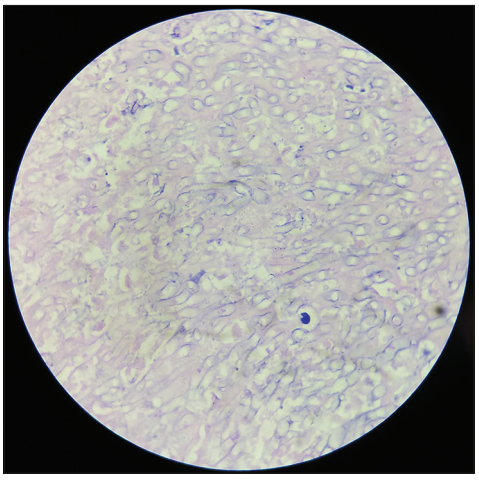

Figure 4: Histopathology of mass in the right ventricle from a 12-year-old boy with acute myeloid leukemia: mucormycosis

pseudomonas aeroginosa. The patient expired 22 days after admission.

Case 8

A 2-year-old male child was admitted with refractory shock. POCUS found mitral valve vegetations along with pyopericardium and small VSD. Here, the presence of pyopericardium with vegetations pointed toward the possibility of IE more than thrombus, so he was treated with ceftriaxone and vancomycin. However, had a fulminant course and died within 5 days of admission. His blood culture and pericardial fluid grew vancomycin-resistant *Staphylococcus aureus* (VRSA).

Case 9

A 9-year-old boy known case of dialysis-dependent chronic kidney disease was admitted with cardiogenic shock with multiorgan failure. POCUS showed a right ventricular mass of 1.4 mm × 1.2 cm mass attached to the right ventricle wall towardthe apex with an ejection fraction of 15%–20%. He was stabilized and discharged. His blood culture was negative and his cardiac mass responded to LMWH. He is listed for renal transplant.

DISCUSSION

In our case series we had one child with atrial myxoma, two with intracardiac thrombus, five with IE (of which four were culture positive) and dilemma remained in one patient whether it was thrombus or IE or cardiac tumor. POCUS helped in their timely detection of cardiac mass and had a significant impact on clinical decision-making such as choice of drug (LMWH or drugs for IE), site of the central line, and a further line of management like earlier involvement of cardiac surgeons. A recent retrospective study showed a similar utility of bedside echocardiography.[5] In this study out of 424 patients admitted in PICU 101 had a clinical indication for transthoracic echocardiograms and out of these 82 (81.8%) patients had new findings that significantly impacted the clinical decision of patient management, namely, alteration in drug therapy and procedure, whereas no difference in the management was yielded in the remaining 19 (17.8%) patients.

POCUS by definition is the use of ultrasound to diagnose problems at the place of treatment and it is usually done by the physician providing emergency care.[6] The concept of POCUS in children with suspected intracardiac pathologies is relatively new. While performing POCUS pediatric emergency care providers must distinguish abnormal masses (myxomas, vegetations, and thrombi) from normal cardiac structures (Eustachian valve, Chiari network, and moderator band) that may mimic a mass.[7] A sound knowledge of ultrasound artifacts and ways to overcome it (multiple acoustic windows) is essential for pediatricians doing POCUS.[5] Common ultrasound artifacts which may appear as pathological lesions include mirror artifacts, reverberation artifacts, and near field clutter. In addition to ultrasound artifacts and normal variants consideration must also be given to extracardiac pathologies (mediastinal tumors and hiatal hernias) which may cause compression over the heart and mimic intracardiac pathologies. The common pathologies which may be encountered by a pediatric intensivist during POCUS may include atrial myxomas, lipomas, papillary fibroelastosis, rhabdomyoma, fibromas, thrombus, vegetations, and congenital heart diseases.[8]

Cardiac thrombus in the pediatric age group is a rare occurrence. It may be seen in children with dilated cardiomyopathy, nephrotic syndrome, or postcardiac surgery (Fontan operation). John *et al*. in their study of 31 pediatric patients with intracardiac thrombi found that embolic events were uncommon and were seen in 4 out of 31 patients.[9] Most of the patients were either treated by heparin infusion, warfarin, or aspirin. In 19 out of 31 (63%) patients intracardiac thrombi resolved by medical management only. They further found that prognosis was poor for patients with left ventricular thrombus and the presence of coexistent ventricular dysfunction. Both our cases with thrombosis responded well to LMWH.

Most of our IE patients had predisposing factors with unusual organisms, namely, *Citrobacter freundii*, VRSA, Rapidly growing nontariff barrier, and mucormycosis with high mortality. The reason for unusual microorganisms can be contributed to antibiotic misuse along with increased invasive interventions such as device closure for congenital heart disease and central vascular catheters. Differentiating thrombus from vegetation may be challenging. Diagnosis is often perormed by a combination of clinical, laboratory, and echocardiographic findings. Vegetations usually have irregular margins; valvular vegetations are usually on the upstream side and have disordered motility. Occasionally, further imaging such as transesophageal ECHO, computed tomography or MRI scans may be needed to aid diagnosis. Where possible biopsy and culture of the mass should be performed.

POCUS has helped us in this case series early diagnosis of cardiac masses, to start appropriate therapy and surgical intervention whenever needed. Death is almost two-third of the patients in this series can be attributed to marked hemodynamic instability at admission and underlying

complex disease process in these patients. It is not possible to comment whether POCUS has changed the outcome of these patients from this case series, but it can help the intensivist in deciding initial treatment before a formal cardiology consultation is done. Application of POCUS in the detection and treatment of pediatric cardiac masses has tremendous potential. Further studies and standardization of educational curriculum are needed for its proper application in pediatric emergency care.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Clinical Update

Acute bronchiolitis in children

Kundan Mittal, Teena Bansal[1], Anupama Mittal[2]

Department of Pediatrics, [1]Department of Anaesthesia and Critical Care, Pt. B. D. Sharma, PGIMS, Rohtak, [2]Deputy Civil Surgeon, Rohatak, Haryana, India

Abstract

Bronchiolitis is the most common respiratory disease in children below 2 years of age. Primarily, the disease is caused by viral infection (respiratory syncytial virus), mainly in the month from November to April. Climate and environment both influence the season and severity of bronchiolitis. Forty percent infants are affected in 1st year of life. Diagnosis of the bronchiolitis is mainly clinical though various definitions have been suggested by different groups. Laboratory investigations including reverse transcription polymerase chain reaction, chest X-ray, and others do not contribute in diagnosing the disease. There is no effective treatment available and mortality is also low with bronchiolitis.

Keywords: Bronchiolitis, children, respiratory syncytial virus

Address for correspondence: Dr. Kundan Mittal, Department of Pediatrics, Pt. B. D. Sharma, PGIMS, Rohtak, Haryana, India.
E-mail: kundanmittal@hotmail.com

INTRODUCTION

Acute bronchiolitis is most important cause of hospital admission between November and April, in children below 2 years of age [Figure 1]. Although different peaks occur in tropical countries, it is a dynamic disease and its clinical features may change rapidly. In 1850, John Eberle published the first medical description of acute bronchiolitis "(a catarrhal effect in children <1 year, which was accompanied by breathing difficulty, coughing, and wheezing, similar to an asthma crisis)." Various definitions for bronchiolitis have been proposed since then. Bronchiolitis means inflammation of the small airways, the bronchioles and usually defined by its clinical and epidemiologic manifestations. "The American Academy of Paediatrics subcommittee defines bronchiolitis as a disorder in infants <24 months of age that is most commonly caused by a viral lower respiratory tract infection characterised by wheezing." The European guidelines define bronchiolitis "as a seasonal viral illness in infants <12 months of age characterised by nasal discharge, cough, tachypnoea, retractions, and bilateral crackles."

Common etiological agents causing acute bronchiolitis are; respiratory syncytial virus (RSV type A and B), rhinovirus, human bocavirus, metapneumovirus, enterovirus, adenovirus (also known to cause bronchiolitis obliterans and pneumonia), parainfluenza virus, coronavirus, mumps, picornavirus, echovirus, herpes simplex, mycoplasma pneumoniae, and chlamydia trachomatis [Figure 2]. Inflammation of lower respiratory tract is characterized by edema, necrosis of epithelial cells, replacement of ciliated epithelium with cuboidal epithelial cells, peribronchiolar infiltration, luminal obstruction, increased mucous production, bronchospasm, V/Q mismatch, hypoxia, hyperventilation, air trapping, and atelectasis. Epithelial

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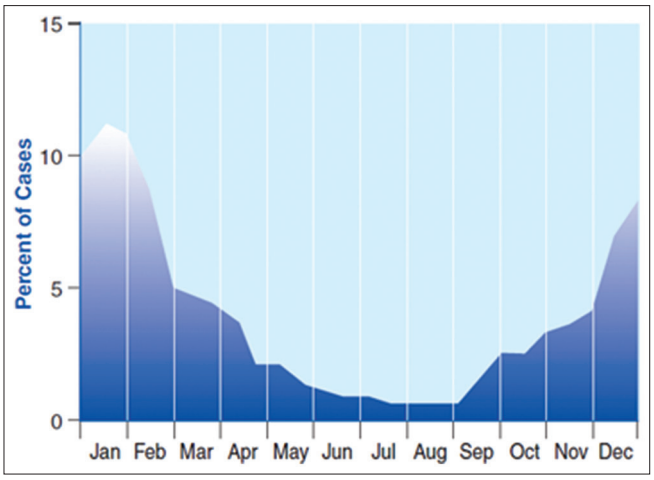

Figure 1: Seasonal occurrence of bronchiolitis

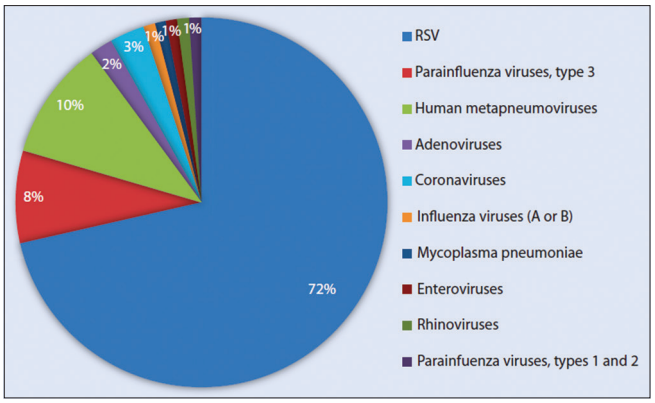

Figure 2: Viruses contribution in bronchiolitis

Table 1: Respiratory distress assessment instrument

Symptom	0	1	2	3	4	Maximum
Wheezing						
During expiration	None	End	½	¾	All	4
During inspiration	None	Part	All			2
Number of lung field involved	None	Segmental	Diffuse			2
Retractions						
Supraclavicular	None	Mild	Moderate	Marked		3
Intercostal	None	Mild	Moderate	Marked		3
Subcostal	None	Mild	Moderate	Marked		3
Total						17

More the score higher the severity

Table 2: Modified Tal scoring system

Score	Respiratory rate	Wheeze	SpO_2 (%)	Respiratory muscle utilization
0	30/min	None	>95	None
1	30-45/min	Terminal expiration only	94-95	Mild intercostal retraction
2	46-60/min	Entire expiration and inspiration with stethoscope	90-93	Moderate intercostal retraction
3	>60/min	Entire expiration and inspiration without stethoscope	<89	Marked intercostal with head bobbing or tracheal tug

cells start regenerating in 3–4 days and functional regeneration take 2 weeks. Risk factors for bronchiolitis are preterm child, low birth weight, age <3 months, cyanotic heart disease, chronic lung disease, neuromuscular disorders, airway abnormalities, male gender (1.5 times), overcrowding, exposure to tobacco, lack of breast feeding, and low-economic status. Various factors which contribute to severity of viral bronchiolitis are decreased airway diameter, collateral ventilation, lung recoil, chest wall stability, pulmonary and respiratory muscle reserve, direct cytopathic effect, and ciliary dysfunction.

CLINICAL FEATURES

Bronchiolitis is a clinical syndrome characterized by running nose, low-grade fever, increased respiratory rate and work of breathing, apnea ("red-flag sign"), hyperextended and hyper-resonant chest, polyphonic wheeze, crepitations on auscultation (diffuse, course, and sticky) at lung base. Liver and spleen may be palpable due to hyperinflation of chest. Extrapulmonary manifestations of RSV are seizures, encephalopathy, hypo or hyponatremia. Severity is usually assessed using following parameters: respiratory rate, work of breathing or use of accessory muscles, mental status, oxygen requirement, breath sounds, cough, apnea, and feeding. Clinical phenotype may be restrictive or obstructive type. Various scores have been developed to categorize severity [Tables 1 and 2] of bronchiolitis. Role of chest X-ray in diagnosis of disease is controversial and even may not be performed unless confusion in making the diagnosis is present. X-ray examination may reveal hyperinflation, atelectasis, increased interstitial marking, and peribronchial cuffing/enlargement. Clinical course of viral bronchiolitis is shown in Figure 3.

Differential diagnosis includes infantile asthma, cystic fibrosis, pneumonia, vascular rings, congenital heart diseases, congestive heart failure, gastroesophageal reflux, aspiration, retropharyngeal abscess, enlarged adenoids, pertussis, laryngo-tracheomalacia, and congenital lung diseases.

COMPLICATIONS

- Otitis media
- Apnea
- Dehydration
- Aspiration.

LABORATORY TESTING

- Pulse oximetry
- Arterial blood gas may show decreased PaO_2 and increased PCO_2 values

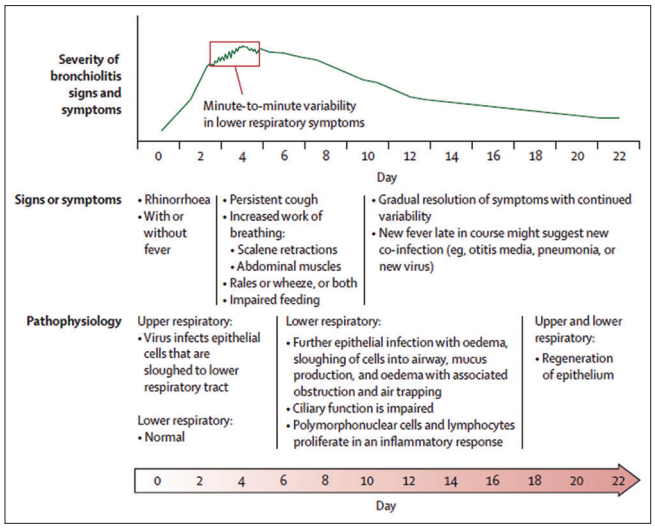

Figure 3: Clinical course of viral bronchiolitis

- RSV viral study, antigen testing of nasal washing, and viral cultures are routinely not recommended
- Reverse transcription polymerase chain reaction and other molecular diagnostic tests
- Biomarkers interleukin-33 (IL-33), IL-13, IL-15, cysteinyl leukotrienes, cathelicidin, caspase, lactate dehydrogenase, to assess severity of disease
- Antibody determination is not much useful
- Complete blood count and C-reactive protein if bacterial infection is suspected
- X-ray chest in child with suspected complications or course is not as expected.

MANAGEMENT

Bronchiolitis can be categorized mild (no respiratory distress, saturation normal, and feeding well), moderate (tachypnea, saturation <90%), and severe (severe tachypnea, not feeding well, increased work of breathing, signs of respiratory fatigue, hypoxia). Admission criteria include apnea, respiratory distress, tachypnea, oxygen requirement, poor feeding, underlying risk factor, and poor socioeconomic condition. Treatment is mainly supportive and careful monitoring.[1-16]

- Monitor the child for apnea, respiratory distress, hypoxemia/saturation, and dehydration
- Place the child in position of comfort to avoid laminar flow becoming turbulent (mother's lap), minimal handling, and prone position
- Maintain airway using simple methods. Nasopharyngeal suction (avoid deep suctioning) done if needed, since infants are obligatory nose breather
- Supplementary oxygen (used if SPO_2 <90% in absence of respiratory distress) targeting saturation >92%. Try to use oxygen in nonfrightening way. Oxygen support using face mask of oxygen hood is preferred
- Maintain hydration (100% fluid) since fast respiration and less oral intake may cause dehydration in infants. Keep a watch on serum electrolytes, serum, and urine osmolality since respiratory illness are known to develop Syndrome of inappropriate antidiuretic hormone secretion (SIADH). Restrict fluids to 70%–80% of normal in a child having features of SIADH. Continue breast feeding or oral feeding in milder case, if oral intake is <50% of normal intake start nasogastric feed or intravenous fluids (normal saline or DNS 100 mL/kg up to 10 kg)
- Inhaled β2-agonist has no role but in severe cases trial may be given (nebulized with salbutamol 2.5 mg or use metered dose inhaler (MDI) with spacer and mask). There is lack or immaturity of β2-receptors in infants
- Racemic epinephrine 0.05 mL/kg/dose diluted in 3–5 mL of saline may have some benefits in early stage of disease, i.e., decreasing need for hospitalization. Epinephrine acts on alpha-adrenergic receptors thus decreasing the edema and relaxation of bronchial muscles due to its action on β-receptors
- Role of 3% hypertonic saline (improves mucous viscosity and elasticity, enhancing mucus transport, and decreasing epithelial edema) is controversial and has shown to decrease hospital stay in moderate-to-severe cases. There is no role of inhaled normal saline
- Ipratropium bromide (minor improvement in oxygenation has been reported), theophylline and caffeine (prevention of apnea), montelukast, nebulized recombinant human DNAse (helps in liquefying mucus by cleaving the released DNA) and nasal phenylephrine have no proven roles in viral bronchiolitis
- Inhaled and systemic steroids (dexamethasone 0.15 mg/kg 6 h for 48 h showed benefit in one study) have no clinical benefit. Inhaled epinephrine combined with oral dexamethasone have shown some clinical benefits in one study but more studies are required
- Inhaled or intravenous magnesium sulfate has some improvement in clinical severity scores but still no recommended for use in bronchiolitis
- Nasal CPAP; 4–8 cmH_2O is indicated in severe respiratory distress, higher oxygen requirement, and apnea. It improves functional residual capacity (FRC), V/Q mismatch, and decreases work of breathing
- Noninvasive positive-pressure ventilation, usually applied in children above 1 year of age improves FRC, V/Q mismatch, recruitment of lung units, alveolar gas exchange, and lower oxygen requirement in some patients
- Heated-humidified-high flow nasal cannula have some beneficial effect in children with moderate-to-severe respiratory distress

- Heliox, a low-density gas has shown to play some role in decreasing resistance to gas flow thus allowing increase gas flow and decrease work of breathing. In addition, carbon dioxide diffuses four to five times more rapidly thus allowing improved ventilation. Data supporting heliox therapy are lacking. If the oxygen requirement is >40% this will not work. Heliox is delivered through simple face mask or nonrebreathing mask and also the flow should be kept higher than child peak inspiratory flow rate. Delivery of heliox by mechanical ventilator is difficult
- Surfactant therapy only decreases hospital stay but have no effect on gas exchange
- Inhaled nitric oxide known to enhance blood flow and ventilation-perfusion quotient but has no bronchodilator effect in bronchiolitis
- Chest physiotherapy (vibration, percussion, assisted autogenic drainage, and intrapulmonary percussive ventilation) in acute care is inconclusive
- Suspecting impending respiratory failure start invasive mechanical ventilation (worsening lung compliance, exhaustion, and apnea) volume or pressure controlled is choice. Variable positive end-expiratory pressure (PEEP) is used depending on lung status
- High frequency oscillatory ventilation and extracorporeal membrane oxygenation also have some place in children not responding to conventional therapy
- No active immunization against RSV is available. Children at risk (acyanotic congenital heart disease, immunodeficiency, chronic lung disease of prematurity, and preterm <29 weeks gestation) should receive passive immunization with palivizumab which is given monthly over five doses (15 mg/kg/dose) during winter. Motivzumab, a second-generation humanized monoclonal antibody is still not available for commercial use
- Hyperimmune RSV immunoglobulin intravenous (RSV 15 mL/kg) and monoclonal RSV monoclonal immunoglobulin have shown to reduce hospital admission rate
- Ribavirin used in immune-compromised children has some clinical benefit
- Antiviral drugs are not recommended
- Effective RSV vaccine is under research
- Anti-RSV pharmacological agents (presatovir, MDT-637, and lumicitabine) which inhibit replication of virus are under research
- Handwashing and contact precautions are important limiting factors in RSV transmission
- Discharge the child if clinically stable, feeding well, fully hydrated maintain saturation >92% in room air for the past 4 h
- Child with recurrent wheeze and persistent wheeze with clinical improvement are referred to higher center
- Child usually recovers symptomatically in 1–2 weeks and radiological clearance of atelectasis may take several weeks
- Bronchiolitis is associated with increased risk of bronchial asthma later in life or recurrent wheezing
- Lung function abnormalities (expiratory flow rate) may persist beyond 10 years of life
- Cough caused by RSV infection may last for 3 weeks
- Future apnea outcome is good.

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Conflicts of interest

There are no conflicts of interest.

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Letter to Editor

Carbamazepine poisoning: A narrow escape

In May–June 2020 issue of the *Journal of Pediatric Critical Care*, Kaiser *et al.*[1] reported a case of carbamazepine poisoning in a 1-year and 6-month-old Indian child. I have two comments on it.

First, though there was a history of ingestion of three tablets of carbamazepine (200 mg each), I wonder why Kaiser *et al.*[1] did not attempt to measure blood level of carbamazepine in their studied child at the initial presentation and serially. Actually, such measurement is pivotal to confirm diagnosis of poisoning with carbamazepine, plan certain therapeutic measures based on the carbamazepine level in blood, and help predict the outcome.[2]

Second, I do agree with Kaiser *et al.*,[1] in their statement that "the case is unique in its own way because of the extremely critical state in which this child presented and also the unfavorable neurodevelopmental outcome."[1] Another unique aspect in the case in question is that the poisoning occurred in a young child. Despite most of poisoning incidents in young children are due to their curiosity and exploration of the surroundings by mouth which could be importantly prevented by the close family supervision, poisoning in young children and infants could be one form of child abuse.[3] Interestingly, it has been reported that 6% of poisoning victims under the age of 6 years referred to the child protective services were due to concerns for intentional poisoning.[4] Although the poisoned child reported by Kaiser *et al.*[1] survived with neurodevelopmental sequelae, intentional poisoning with the carbamazepine induced by parents ought not to be overlooked. Hence, psychological evaluation of parents must be taken into consideration.

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Conflicts of interest

There are no conflicts of interest.

Mahmood Dhahir Al-Mendalawi

Department of Paediatrics, Al-Kindy College of Medicine, University of Baghdad, Baghdad, Iraq

Address for correspondence: Prof. Mahmood Dhahir Al-Mendalawi, P. O. Box 55302, Baghdad Post Office, Baghdad, Iraq.
E-mail: mdalmendalawi@yahoo.com

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PICU quiz

1. An 11-year-old child with newly diagnosed leukemia is admitted to the pediatric intensive care unit (PICU) in severe respiratory distress. Chest radiograph shows a widened mediastinum. Which one of the following measures is to be avoided during airway management in this child?
   A. Administration of muscle relaxants
   B. Endotracheal intubation
   C. Heliox administration
   D. Left lateral decubitus position.
2. Which of the following statements regarding near-fatal asthma is true?
   A. A ventilation strategy of low respiratory rates (<12 breaths/min), moderate-to-high tidal volumes (8–12 mL/kg), and permissive hypercapnia has been proved to be associated with increased mortality and a rate of pneumothorax approaching 100%
   B. Increasing positive end-expiratory pressure (PEEP) in mechanically ventilated asthma patients receiving neuromuscular blockade has been shown to have unfavorable effects on lung volumes, airway pressure, and hemodynamics
   C. Ketamine is contraindicated during intubation due to its slow onset of action and tendency to cause bronchoconstriction
   D. Nearly, all patients have a history of severe persistent asthma with frequent ICU admissions in the 1 year preceding the episode of near-fatal asthma.
3. What is the least accurate statement regarding the management of pulmonary arterial hypertension (PAH) in children?
   A. Co-administration of sildenafil with ketoconazole or rifampin should be avoided
   B. Due to the risk of hepatic toxicity, the Food and Drug Administration (FDA) requires that liver function tests is performed at least once in 3 months in patients on endothelial receptor antagonists such as bosentan
   C. Nitric oxide (NO) is currently the first-line drug in the acute management of PAH or in cases of postoperative PAH arising from congenital heart disease (CHD) repair
   D. There is a mutual pharmacokinetic interaction between bosentan and sildenafil that may influence the dosage of each drug in a combination treatment.
4. Which best describes the phase variables for pressure-support ventilation (PSV)?
   A. Patient triggered, flow limited, pressure cycled
   B. Patient triggered, pressure limited, flow cycled
   C. Pressure triggered, flow limited, patient cycled
   D. Pressure triggered, patient limited, flow cycled.
5. A 3-year-old child with a tracheostomy for 2½ years is being decannulated. Immediately following decannulation, he develops stridor and respiratory distress. Possible etiologies include all of the following except:
   A. Tracheal stenosis or granulation tissue
   B. An obstructing flap of the posterior tracheal wall
   C. Fusion of vocal cords
   D. Temporary laryngeal abductor failure.
6. Unilateral phrenic nerve paralysis is clinically more significant in infants and young children compared with adults because of all of the following except:
   A. Hemidiaphragmatic paralysis in this age group is equivalent to massive flail chest in an adult
   B. The excessively compliant chest wall of the young child
   C. The poor ability of intercostal muscles to stabilize the chest wall in the young infant
   D. Less compliant chest wall of the young child
   E. With inspiration, the ipsilateral intercostal muscles and the paralyzed diaphragm are sucked in.
7. The use of hyperbaric O_2 therapy for CO poisoning is probably the most common application of this technology. All of the following statements regarding this application are true except:
   A. The beneficial effect of hyperbaric O2 therapy is directly related to the associated increase in PaO_2
   B. The half-life of CO as measured by carboxyhemoglobin (HbCO) is decreased to 53 min at 3 atmospheric pressure (atm)
   C. Hyperbaric O_2 therapy helps reverse binding of carbon monoxide (CO) to cytochrome $\alpha 3$
   D. Hyperbaric O_2 therapy is indicated in patients who suffer unconsciousness or display signs of central nervous system (CNS) depression.
8. Wrong statement regarding technical errors during sampling of arterial blood gas is:
   A. A gas bubble in the syringe will falsely elevate $PaCO_2$
   B. The major blood gas error associated with excess heparin in the sample is a drop in $PaCO_2$

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C. When a sample that is obtained from a patient breathing room air is interfaced with a bubble, the PaO2 obtained will be close to 150 torr
D. In a patient on high FiO_2 with normal lungs, the presence of an air bubble in the syringe may spuriously lower PaO_2.

9. A 2½-year-old male child has a 2-day history of an upper respiratory tract infection and fever, now having mild stridor and dysphagia. His immunizations are up to date. Attending physician suspects retropharyngeal abscess. Which one of the following statements is incorrect regarding this patient?
   A. Age of the patient is somewhat atypical
   B. Inspiratory radiograph films are more informative than expiratory films
   C. A chest radiograph should be obtained to evaluate mediastinal extension
   D. The retropharyngeal space extends from the base of the skull to the level of the second thoracic vertebra
   E. The usual organisms are staphylococci, group A streptococci, and anerobes.
10. A 7-year-old child with status asthmaticus is undergoing treatment in your PICU with systemic corticosteroids, β2-agonists, ipratropium, and 60% FiO_2. He has moderate air entry, bilateral wheezes, no nasal flaring, and mild intercostal retractions. Her respiratory rate is 22/min. Her pulse oximetry saturations prior to and after initiation of therapy were 91% and 86%, respectively. Which of the following is the most likely explanation for this observed change in oxygen saturation?
    A. Excessive fatigue with hypoventilation and resultant hypoxemia
    B. Increase in airway secretion due to the institution of ipratropium
    C. Increase in ventilation/perfusion mismatch due to β2-agonist
    D. Mucus plugging of the airways due to institution of ipratropium.

PICU QUIZ ANSWERS

1. Answer A

   This child likely has an anterior mediastinal mass compressing the intrathoracic trachea. It can worsen dramatically over few days, hence it require rapid evaluation and aggressive therapy. Dyspnea on supine position often precedes other signs and symptoms (cough, tachypnea, and respiratory distress) of an anterior mediastinal mass. Obstruction by the mediastinal mass in the supine position is sometimes relieved by changing posture (lateral decubitus, prone, and sitting).

   Heliox (a mixture of 70% helium and 30% oxygen) administration may be beneficial in case there is severe narrowing of the trachea, because the characteristics of this mixture permit greater gas flow through areas of airway narrowing by streamline flow.

   Endotracheal intubation is indicated only if respiratory function becomes severely compromised. This measure, of course, is only of benefit if the tip of the endotracheal tube can be advanced distal to the site of tracheal compression, which often means that main stem intubation is necessary to bypass the lesion if it is at the level of the distal trachea or carina. If intubation is necessary, sedation/anesthesia before laryngoscopy should be carried out while maintaining spontaneous ventilation, as positive pressure ventilation might be impossible. Muscle relaxants in this situation should be avoided. As after muscle relaxant or deep sedation condition like cannot ventilate cannot intubate may occur and airway compression can be increased due to loss of tone.

2. Answer B

   Increasing PEEP in patients with airway obstruction who are receiving neuromuscular blockade is associated with hyperinflation, increased intrathoracic pressures and frequent decreases in systemic blood pressure. In our practice, we set minimal PEEP to mechanically ventilated asthmatic patients during neuromuscular blockade (less than auto-PEEP and not more than 8 cm H_2O).[1]

   Mortality from near-fatal asthma is approximately 4% in the United States. In a study by the Collaborative Pediatric Critical Care Research Network, 11 fatalities were observed out of 261 children with near-fatal asthma (4.2%). In that same publication1 the authors reported that 13% of subjects had no prior history of asthma (answer D) and that only 29% of patients had an admission for asthma in the preceding year. Similarly, among 51 patients who died from asthma in Australia, 32% of patients had never been admitted to the hospital because of asthma prior to their death.

   Ketamine is commonly employed when intubating a child with near-fatal asthma (answer C) due to its rapid onset, bronchodilatory effects, and beneficial hemodynamic outcomes. As described in the text, a ventilatory strategy that employs relatively low respiratory rates (6–12 breaths/min), tidal volumes of 8–12 mL/kg, and permissive hypercapnia (answer A). When a similar strategy was used in 26 individuals, all patients survived and pneumothorax was uncommon.

3. Answer B

   As sildenafil is metabolized by hepatic CYP450, co-administration of sildenafil with CYP3A inducers or inhibitors such as ketoconazole or rifampin should be avoided. There is a mutual pharmacokinetic interaction between bosentan and sildenafil that may influence the dosage of each drug in a combination treatment. Bosentan decreases the maximum plasma concentration of sildenafil (Cmax) by 55.4% on day 16, whereas sildenafil increased bosentan Cmax by 42%, hence close monitoring is advisable with co-administration. NO is currently the first-line drug in the acute management of PAH or in cases of postoperative PAH arising from CHD repair or other causes. Due to the risk of hepatic toxicity, the FDA requires that liver function tests be performed at least monthly and hematocrit every 3 months on patients on endothelial receptor antagonists such as bosentan. There is concern that the endothelin antagonists as a class may be capable of causing testicular atrophy and male infertility.

4. Answer B

   PSV is a form of assisted ventilation in which the ventilator assists the patient's own spontaneous effort with a mechanical breath with a preset pressure limit. As with any form of supported ventilation is designed to respond to the patient's effort, the inspiratory pressure assist of PSV requires a signal to trigger the demand valve to initiate flow. The patient's spontaneous breath creates a negative pressure (pressure triggering) or a change in flow through the circuit (flow triggering), which triggers the ventilator to deliver a breath. With initiation, the machine delivers high inspiratory flow to achieve a peak airway pressure level that is selected by the operator. The pressure limit stays constant as long as the patient's inspiratory effort is maintained with a variable gas flow rate from the ventilator. As inspiration continues, the inspiratory flow rate decreases. A threshold reduction in the flow rate is a signal to terminate the inspiratory support and opening of an expiratory valve, after which passive

exhalation occurs. The termination signal can be a predetermined percentage of the peak inspiratory flow (e.g., 10% or 25%) or a fixed flow (e.g., 5 L/min).

5. Answer B
   An anterior (and not a posterior) tracheal flap at the operation site for tracheostomy is one of the etiologies of obstruction following decannulation. Other etiologies include: fusion of vocal cords, granuloma, and temporary adductor failure.[2]
6. Answer D
   The more compliant chest wall of the young child contributes to the clinical manifestation of diaphragmatic paralysis.
7. Answer B
   CO poisoning is probably the most common application of hyperbaric O2 therapy. The half-life of CO is actually decreased to 23 min at 3.0 atmospheric pressure, as opposed to 180 min with 100% oxygen at the normal atmospheric pressure. From 60 to 90 min of hyperbaric oxygen at 2–2.5 atmospheric pressure seems to be safe, without significant CNS toxicity, although other side effects such as tympanic membrane perforation, pneumomediastinum, sinus damage, change in visual acuity (Myopia) are possible.
8. Answer A
   The presence of a gas bubble in a syringe will usually affect the PaO_2. The effect on the PaO_2 will depend on the amount of oxygen that is inspired by the patient. In patients on room air, this will lead to a false elevation of PaO_2 (atmospheric PO_2 is usually higher than alveolar PO_2). On the other hand, in patients who are receiving a high fraction of inspired oxygen and have normal lungs, the presence of an air bubble in a syringe may spuriously lower the PaO_2. Excess heparin does lead to a drop in $PaCO_2$, but usually, there are no changes in the pH level because it is neutralized by the acidity of heparin.
9. Answer A
   The typical age for retropharyngeal abscess is younger than 3 years. It is important to obtain inspiratory radiographs to evaluate the thickness of the retropharyngeal soft tissue. The measurement of this soft tissue is important in the diagnosis of the retropharyngeal abscess.
10. Answer C
    In persons with asthma, high inspired oxygen concentrations may prevent hypoxic pulmonary vasoconstriction and place low alveolar ventilation (V_A)/perfusion (Q) regions at risk for absorption atelectasis, and high doses of bronchodilators may enhance the perfusion of low V_A/Q areas, exacerbating V_A/Q mismatch. However, the beneficial effects of bronchodilators on airway resistance generally outweigh the worsening in V_A/Q mismatch. This child is not showing signs of excessive fatigue. There is no nasal flaring, and retractions are only mild. The air entry is moderate and wheezes are present, therefore option A is not correct. Ipratropium is an anticholinergic that causes a decrease in airway secretion (thus option B is incorrect), and there are no clinical signs that this child has a mucus plug in her airway.

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Conflicts of interest
There are no conflicts of interest.

Pradeep Kumar Sharma

Department of Pediatric Critical Care and Pulmonology, Sri Balaji Action Medical Institute, New Delhi, India

Address for correspondence: Dr. Pradeep Kumar Sharma, Department of Pediatric Critical Care and Pulmonology, Sri Balaji Action Medical Institute, New Delhi, India.
E-mail: drsharma025@gmail.com

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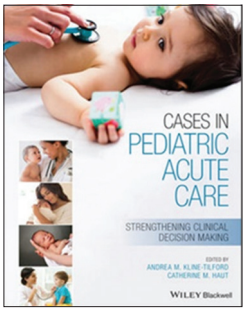
Book Review

Cases in Pediatric Acute Care: Strengthening Clinical Decision Making



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Cases in Pediatric Acute Care covers 116 cases (including trauma and newborn) starting from the history of present illness, presenting signs and symptoms, physical examination findings, approach to diagnosis and differential diagnosis, and management. It is important for pediatric health-care providers to have recent knowledge of evidence-based practice. It helps readers to provide answer to the questions about assessment, diagnosis, and management and interpret diagnostic studies. *Cases in Pediatric Acute Care* is an excellent resource material for physicians involved in the acute care of children.

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Conflicts of interest
There are no conflicts of interest.

Kundan Mittal

Department of Pediatrics, Pt. B D Sharma PGIMS, Rohtak, Haryana, India

Address for correspondence: Dr. Kundan Mittal, Department of Pediatrics, Pt. B D Sharma PGIMS, Rohtak, Haryana, India.
E-mail: kundanmittal@gmail.com

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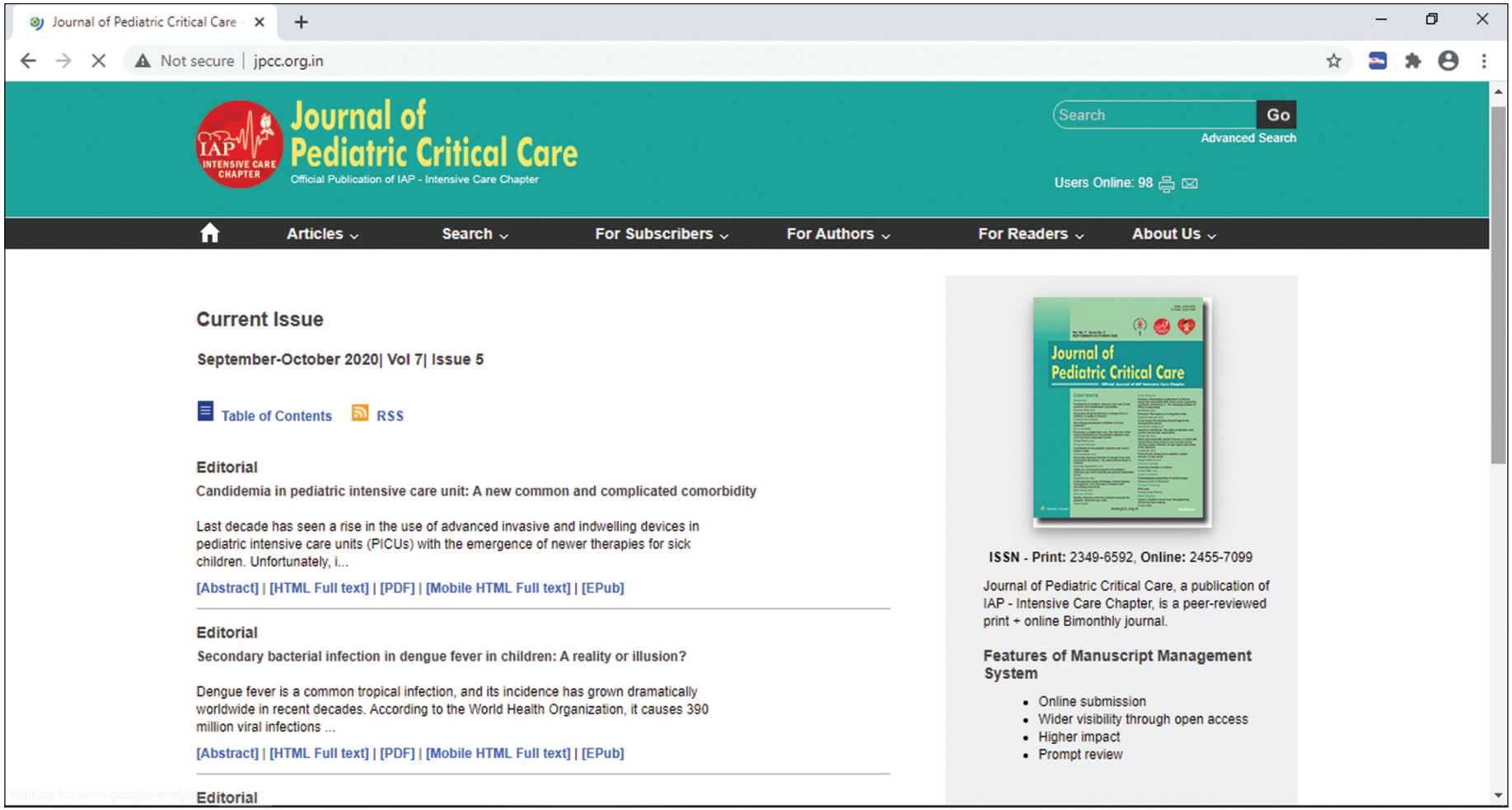
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