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BAKUL PAREKH AND RHIshIKESH THAKRE
From Indian Academy of Pediatrics, Mumbai, India.
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Patient safety and healthcare quality are high priorities to us clinicians. Quality in healthcare is defined as being safe, effective, patient centered, timely, efficient and equitable [1]. Thus patient safety and health care quality are interrelated. There is a gap between “what we do” and “what we can do” and successful outcome depends mostly on a range of factors, not just the competence of an individual healthcare provider [2]. If we wish to improve our patient health care, improvement methods must focus on understanding the steps (process) and improving the structure of systems where we work. It is thus imperative that we clinicians and staff must be competent in quality improvement (QI) skills. QI is the science of improvement using system based approach.

QI - SCIENCE OF IMPROVEMENT

QI is an intentional, structured approach to problem-solving in clinical practice. The goal is to make changes that lead to improvement. There are several frameworks to achieve this goal. A point of care quality improvement (POCQI) module [3] developed in India simplifies it using four steps – (i) Identifying the problem; (ii) Analyzing the cause of the problem and collecting data to measure the performance; (iii) Identifying, testing and analyzing ideas for change using Plan-Do-Study-Act (PDSA) cycle; and (iv) Sustaining the change.

Quality improvement is about changing behaviors, approaches and systems within the given infrastructure without any additional resources. Every unit has unique answers to similar problems because every system is unique in the challenges that it faces using the same QI tools. We need to move from individual-led care to team-based care which fosters openness, collaboration, communication, feedback and learning from mistakes from all care providers. Motivation, teamwork, data and leadership are keys to success in QI projects. To the pediatrician, involvement in successful and sustained QI project can be a very rewarding experience. Unlike clinical research which seeks to discover new knowledge in a prescribed population, QI science seeks to use and apply knowledge in real life scenarios. In short, QI is a common sense approach of planning your work and working your plan to find better ways of doing things in a consistent manner. It is all about closing the gap between actual practice and best known practice, be it clinical or operational [4].

QI AND PEDIATRIC CARE

QI science has the potential to improve coverage of evidence-based practices across the spectrum in pediatric care viz acute and chronic conditions (eg. asthma, epilepsy, diabetes, ADHD, gastroenteritis, sepsis, medication errors etc.), inpatient and outpatients, intensive care services (eg. effective central line care, decrease in nosocomial sepsis, improved hand hygiene, reducing use of antibiotics etc.), daily patient care (eg. triaging of OPD patients, reducing admission delays, reducing oxygen use, improving breast feeding rates, improve follow up rates etc.) across all sizes of hospitals [5-9]. This can led to strengthening of processes - adherence to guidelines, delivery of services in a consistent manner, reducing variations, decreasing delays, eliminating inefficient processes and improved outcomes - reduced patient costs, decreased hospital stay, improved survival and increased patient satisfaction. The standards for improving quality of maternal, newborn and adolescent care have been laid down by WHO [10,11]. There is need to have India specific indicators to monitor, compare and improve performance of practices across diverse settings which are of importance to patients, providers, payers and policy makers.

ROLE OF IAP: THE WAY FORWARD

Indian Academy of Pediatrics (IAP) is committed to develop nationwide standards for pediatric training and services. IAP advocates, supports and promotes the QI movement. The vision and mission is to identify a core set of pediatric quality indicators from five categories: prevention, acute care, chronic care, practice management...
and patient safety in primary care. The benchmarking of structures, processes and outcomes, could reveal opportunities for improving newborn, child and adolescent care across India. By embracing QI, IAP with collaboration with professional bodies (NNF, FOGSI, IMA etc) and organizations (WHO, UNICEF etc) plans to build a cadre of QI Coaches, Champions and Mentors who in turn shall educate, stimulate and motivate QI uptake. A combination of web based module, workshop learning and project implementation will engage the learner and help facilitate practice the art and science of QI. IAP realizes the value of QI in pre-service education and would strive to create a framework and essential competencies for quality, safety and systems level thinking to guide and support our future pediatricians. We are aware that QI work is not easy and can be particularly challenging given some of the barriers that exist within the existing system. We have a responsibility to our children and families to ensure universal right to high quality care. Let us join hands and apply the science of improvement to our clinical care and have zero tolerance to risks, errors and harm.

Acknowledgement: Dr Ashok Deorari, QI Guru, for his exemplary leadership in Quality care.

REFERENCES


Children of Incarcerated Parents

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Psychosocial health of children of incarcerated parents is a critical area of concern and yet acutely neglected in India. Despite Supreme court guidelines on ensuring age-appropriate care for children living along with their mothers in prison, there is variance in practice, which compounds the disadvantage of being a prisoner’s child. The children left behind at home due to parental incarceration also experience vulnerabilities that emanate from their pre-existing socio-economic disadvantages, the continued interface of the child with the criminal justice system, as well as societal perception towards them. This results in a pronounced effect on their health, and educational, social and emotional wellbeing. Conscious efforts are required for strengthening the factors that could mitigate the adverse consequences of parental incarceration coupled with a debate on penal populism and the social and economic costs associated with the same.

Keywords: Children of prisoners, Emotional consequences, Visitation, Women in prison.

Children of incarcerated parents continue to be a largely misunderstood and yet, a very vulnerable group. The extensive discourse on the possibility of their culpability without evidence to support the same, has driven attention away from the fact that their childhood needs to be protected and that their entitlements cannot be denied by virtue of their parent’s alleged involvement in offending behavior.

Children of incarcerated parents are broadly divided into two broad categories – those who can live along with their mother in the prison (up to the age of 6 years) and those that are left behind when their parent(s) is/are incarcerated. Children left behind could be living with the remaining parent, with other kin caregivers, in a child-care institution, or on their own as an only child household. Information with respect to the number of these children is missing except in the case of children living along with their mothers in the prison. Nonetheless, considering the fertility rate and the prison population within the reproductive age group [1], an extremely rough estimate of children of incarcerated parents could be more than 8 lakh in the country. The number of children living along with their mothers in prisons across India, was 1942 at the end of 2016 [1].

Research has been conducted in greater measure on children living with their mothers in the prison, largely due to their visibility and access within a single place. On the other hand, children living outside have been an invisible population.

CHILDREN LIVING IN THE PRISON

It is well established that the early childhood years are most critical for the physical, emotional, social and cognitive development [2]. The social and physical environment in interaction with biology exercise an influence on development beginning prenatally and continuing through infancy and childhood and even later [3]. Prisons do not offer the physical and social environment that is conducive for a child’s development. It is in this context that interventions are required if children (below the age of 6 years) are to stay along with their mother in the prison. The Honorable Supreme Court in its judgment in RD Upadhyay vs. State of Andhra Pradesh and Others [4] citing the recommendations made by the All India Committee on Jail Reforms[5] have laid down guidelines for care provision with respect to this category of children. They have emphasized that the child should not be treated as an undertrial or convict while in jail with his/her mother, is entitled to age-appropriate food, shelter, medical facilities and opportunities for education and recreation. Children’s physical growth must be monitored regularly along with provisions for vaccination within the prison. Every prison is required have a creche (for children aged 0-3 year) and nursery facility (for children aged 3-6 year), which should preferably be located outside the prison premises. Before sending a pregnant woman to jail, the competent authority must ensure that the jail has proper facilities for pre-natal and post-natal care. Lactating and pregnant women are
entitled to a special diet within the prison. Besides those considered to be high-risk prisoners, the jail authorities are to arrange temporary release for childbirth in a government hospital. Suspension of sentence can also be considered as an option in case of casual offenders. To protect the long-term interest of the child, the birth certificate is not expected to carry the place of birth as the prison but instead the locality within which the prison is located. In the absence of official data on the compliances with respect to these guidelines, reliance is being placed upon some state-specific studies in order to understand the situation of children living within prisons with their mothers.

Research has revealed that separate space is not earmarked for female inmates and their children in all prisons [6]. In cases where separate barracks have been earmarked, the challenge of overcrowding may remain [7]. Inadequacy of space pinches children’s development since prisons are locked up after sunset in most places.

The creche and nursery can offer an opportunity to the children to escape from the prison environment, for a few hours, besides being a space for education, recreation and supplementary nutrition. Notwithstanding the Supreme Court guidelines, the facility of a creche as well as nursery has been found to be available only in some jails [7-10]. Further, the quality of the nursery/creches, where available, has been found to be discrepant in terms of availability of teachers, play material, presence of a child-centered library and teacher-student ratio [6-9]. Recreational opportunities for children also vary from being provided with a few toys [9] to having few swings in a ground [7] which, at times, may be utilized for drying clothes [7]. Opportunity for using the swings is only available in the afternoon, which works as a disadvantage for children, particularly in summers [7]. The television sets were available in most prisons but were found to be largely used for viewing serials that cater to the interests of the women inmates rather than children. In a few prisons, children were reported to be occasionally taken for picnics, with the support of non-governmental organizations [10]. Quantity of food provided to the children has also been found to be inadequate and the mothers reported that no special diet was provided to the weak and unhealthy children [9]. There were also variations in respect of provision of age-appropriate diet for children. In some cases, specific efforts were made to provide diet to children in accordance with their nutritional requirements [10] but in other cases, female prison inmates had to share their food with their children [8]. A separate dietary plan in case of pregnant inmates was found to be missing in all the studies. Thus, variations are visible across prisons despite the incorporation of the court guidelines in the Model Prison Manual, 2016 [11].

In the absence of a pediatrician in the jail premises, the health concerns of children are not necessarily attended to adequately. Jail hospitals were not found to be properly equipped for providing treatment to small children [8]. In a more recent study undertaken in two prisons of Uttar Pradesh, mothers reported that in case of serious health-related concerns of children, the doctors from the district hospital were informed and requested to attend to the child, but the mothers were not satisfied with the medical facilities provided to their children [9]. Regarding the vaccination schedule, it was being largely followed [7-9] provided the children were available at the time that the vaccination was being administered and the vaccine was available [9].

While most of the researches have focused on the living, educational, health and recreational facilities available to children, there are very few studies that have tried to understand the physical, cognitive, social and language development amongst the children living with their mothers in prison. Reliance is thus being placed on two studies which are comparatively recent in nature and which were accessible. In one of the researches [7], which was done in a Delhi prison, the cognitive development of children was assessed through an observation checklist, (a brief recognition and naming test designed for the children by the researcher), as well as interactions with crèche staff, and language development was ascertained through interviews with the incarcerated mothers [7]. Due to the lack of a stimulating environment, children who were born in prison or had started living in the prison at a very early age, displayed difficulty in recognition of alphabets and numbers, in pronouncing words and understanding age appropriate instructions [7]. In another study also carried out in Delhi prisons [12], a school readiness instrument was used to assess the skills that help children (aged 3-6 year) to adjust better in school as well as acquire the literacy and numeracy skills. The researchers found that most of the children had been able to master lower order thinking skills such as pre-number concept, simple pattern thinking but found the tasks associated with higher order thinking skills such as sequential thinking, classification of objects, reading readiness, and relative comparison of numbers, challenging [12]. Significantly limited or no exposure to the outside world had an impact on the children’s conceptual understanding of the outside world. Children were often afraid of men, including even their male relatives. Furthermore, being inside the prison for a long time was seen to transform the meaning of ‘going outside’ for children, restricting it in many cases to a court visit in a van [7]. In another study, the mothers stated that the absence of family life was having an effect on the social
development of their children. The child misses out on playing with siblings, and the opportunity to understand and imbibe familial values and norms is denied to the child living in the prison [9]. Another major concern is the children’s exposure to profanities and violent fights in the barracks [13]. Such children were found to be more verbally abusive besides being engaged in violent fights and bullying [7].

CHILDREN LIVING OUTSIDE THE PRISON

Research on children left behind upon parental arrest has been limited. The absence of any database of these children coupled with the lack of any documentation at the time of parental arrest, makes any research on this group a challenging process. Notwithstanding this submission, some research has been carried out by Prayas (2002), a field action project of Tata Institute of Social Sciences on children of women under trials [14]. Additionally, the authors have also completed a study on children (aged 6-18 year) of convicted prisoners (unpublished data). Another study on children of women prisoners in Aligarh and Etah jails has also been published recently [9].

Children and caregivers experience extreme financial challenges consequent to parental incarceration due to the removal of the earning family member as well as expenditure incurred due to the interface with the criminal justice system [9, 14]. These challenges manifested in having to borrow money for meeting basic necessities or taking them on credit or managing without them, skipping meals, dropping out from school or entry of children into the labor force [14]. Abject poverty may also result in the child pilfering things so as to ensure food in the family [14]. Families are forced to sell off or mortgage their assets to meet the day-to-day expenses [14]. Retaining accommodation was seen to be a challenge in some of the cases where the families were living on rent [14]. In case of kutcha houses or semi-pucca houses, repair, even if required, slides down in the priority list resulting in the house crumbling down [14]. In cases of paternal incarceration, the mothers are caught off guard due to not having stepped into the world of employment prior to the incident and in some cases not having ventured out of the houses without their spouses. Visitation (mulaqat) to the prison can also be financially draining for most of the families who already find themselves on the edge [14].

These children experience health problems such as cough, cold, pneumonia, tuberculosis, typhoid, malaria, epilepsy, as well as skin and dental problems [9, 14]. Skin problems increased if there was no one to bathe the children or wash their clothes. Malnourishment was a serious concern due to food shortages or the absence of any elder person to cook in the family [14]. Children become dependent on others for the provision of a proper meal [9]. Treatment of children having an illness requiring prolonged medication were often stopped after the mother’s incarceration [14]. At times, even essential medication was not provided on account of lack of attention or limitation of resources. Minor health concerns got aggravated due to lack of required medical attention [9].

Children experience feelings of loneliness and sadness particularly during the initial period of their parent’s imprisonment. Caregivers report their inability to sleep for several days, not being able to eat, retracting into a shell, and excessively crying [14]. Self-care may also get affected due to the trauma of separation. There are feelings of fear which are related to having witnessed the crime scene, fear of leaving the mother alone in the prison, fear of the remaining parent, if he is abusive, or fear of the police (having witnessed the treatment that was meted out to the mother) [14].

On the other hand, there are also others who are angry and disappointed with the mother for having to bear the consequences of incarceration [14]. A few children may also hold feelings of resentment against the incarcerated parent particularly if they are responsible for the death of a loved one [14]. Disturbed or deviant behavior may also be seen in some of the children largely triggered by the consequences of parental incarceration. A feeling of hopelessness may result in suicidal behavior [14].

The emotional consequences on children are contingent on whether the child is able to understand the implications of imprisonment, the duration of imprisonment (with a shorter duration resulting in lesser consequences), pre-incarceration relationship with the caregiver, and single or repeated incarceration (with a first time incarceration of the mother having a serious effect on the child) [14].

In some families, children are not informed about parental incarceration due to the belief that the same may have an adverse consequence on them or at times in consideration of their young age. However, non-disclosure, over a period of time, can also result in a feeling of betrayal amongst the children.

The continued interface of the children with the criminal justice system also affects them in several ways. Even while the opportunity for visiting the parent is available in the prison, the procedures associated with the same can be extremely unpleasant for some. The repeated checking is viewed by some children as a violation of their body boundaries and some of them do
not like the look of suspicion that the police officers may hold for them. Prisons are not designed keeping in mind the effect that it may have on young children [13]. For many children, a prison visitation means long hours of travel followed by repeated security checks, and then finally a conversation with a parent across a glass barrier, with, most often, no opportunity for touching the parent. The court visits by the children also exposes them to the unethical practice of paying bribes to various functionaries in order to meet their parent, getting information for the case or making payments to the prosecutor [14].

Education stands a chance of being a major casualty. Continuance of children in schools can become challenging in the absence of means to pay school fees, for their uniform, books and other essential things or to even provide for supplementary academic support. Residential transitions due to parental imprisonment could also result in temporary educational cessation. When schools are located at a distance, discontinuation in case of adolescent girls due to the absence of anyone to accompany them and the perception of insecurity has also been seen [14]. At times, the need to take care of younger siblings can also cause drop-out [9].

Children of prison inmates may also be living in child care institutions, registered under the Juvenile Justice legislation or even in hostels, but by and large they feel discomforted with this provision. They were found to long for their parents as well as their siblings who were at times separated from them because of institutionalization [14]. For children living in hostels, the absence of visitors made them the subject of ridicule by others by being referred to as ‘orphans’ [7].

The effect of parental incarceration on children living outside is, to a certain extent, determined by the quality of caregiving available. However, caregiver’s own abilities are governed by various factors including their age, their physical abilities, the support available to them by their own families, as well as their financial wherewithal [14]. In cases where children have to assume the role of caregivers, they are overstretched and find it challenging to cope with the situation if other forms of support are not available over a prolonged period of time [14]. In the presence of other co-occurring adversities such as death of a caregiver in close proximity of incarceration or disability of a child, the effects of parental incarceration become more pronounced.

CONCLUSION

Internationally, children of incarcerated parents are recognized as ‘orphans of justice’ but this recognition does not always translate into the desired attention that needs to be given to this group, as is evident through this review. This population, on their own, feel under-empowered to advocate for their entitlements. Concomitantly, adherence to the colonial legacy of law without any significant changes has also resulted in penal populism without necessarily examining alternative forms of sentencing which could serve the dual purpose of ‘repairing the harm’ and mitigating the effect of parental offending on children. More attention to the concerns of these children, and research in their social, emotional and health needs would definitely be helpful in improving their status.

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Childhood Status Epilepticus: Current Status and Future Directions

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Status epilepticus (SE) is a common neurological emergency of childhood with a high prevalence. Childhood status is unique in having a greater frequency of febrile status (35%), recurrent status, and 30% risk of subsequent epilepsy [1]. SE has significant morbidity and mortality (29%), which is influenced majorly by the etiology and the management. Given the lack of information on etiology and outcome of SE in children from India, the study by Chetan, et al. [2] in this issue of Indian Pediatrics is a welcome addition to the literature on the topic [3,4].

Status epilepticus (SE) is a condition resulting from a failure of mechanisms that terminate a seizure or from strong seizure predisposition or irritative mechanisms which may be inflammatory, genetic, and cellular or sub-cellular, that perpetuate the seizure cycle. SE is often recurrent in epileptic children with structural malformations, resistant epilepsies, certain genotypes, recurrent inter-current illnesses and drug compliance issues.

The earlier definition of SE i.e., seizures persisting for 30 minutes with continuous motor activity or non-gain of consciousness between seizures has undergone significant changes. SE has now been stratified into Evolving SE, Established SE, Refractory SE, Super refractory SE, NORSE and FIRES, based on duration of seizures, response to one benzodiazepines and other anti-seizure drugs [5]. This has resulted in clinical development of treatment guidelines and logical algorithms for domiciliary, community/hospital and tertiary level of care [6].

Benzodiazepines are the frontline agents for SE. They have a variety of routes of administration and quick onset of action – either of the rectal, oral, buccal, nasal, intramuscular and intravenous routes are possible. Rectal diazepam, buccal midazolam and oral lorazepam have now been superseded by intranasal midazolam. Intranasal midazolam exhibited best efficacy for non-venous treatment of SE in a recent meta-analysis [7,8]. Early treatment of SE is the cornerstone of effective control and better outcomes [9]. Domiciliary therapy at seizure onset with intranasal midazolam is of supreme importance in halting the evolution of status and preventing established status, thus reducing cost of hospitalization and morbidity. This window of opportunity should not be missed. Empowerment of the family of a child with frequent seizures and of school health personnel with information regarding appropriate dose, route, technique and frequency of use of benzodiazepine is crucial. Its power is still not adequately harnessed in the community.

At the hospital level, intravenous anti-seizure drugs are the mainstay [6]. The choice has really widened in the past decade from benzodiazepines, phenobarbitone, phenytoin and valproate to fosphenytoin, levetiracetam, lacosamide, steroids and immuno-suppressants. Multi-centric studies are desired for comparative trials between the various conventional ASDs and the new anti-seizure drugs and to allocate their appropriate place. Two studies in this issue of Indian Pediatrics address this research need. Srivastava, et al. [10] report on the efficacy, serum levels achieved and side-effects after intravenous forphenytoin loading dose, and Vignesh, et al. [11] report on a randomized-control trial comparing phenytoin, valproate and levetiracetam in pediatric convulsive status epilepticus. At hospital level, every triage area and emergency should display the desired algorithm of use with doses, route of ASDs and the logical step-wise upgradation of therapy [12].

For refractory status and beyond, a clear guideline for ICU care in a tertiary setting is recommended. Patients must be referred on time. Patients with refractory status have multiple challenges and they merit monitoring of EEG, cardio-respiratory status, blood gas and recognition of cerebral edema. Familiarization with use of pentobarbitone, propofol, ketamine, and anesthetic agents is essential for their care in an ICU setting. The exhaustive review by Arya, et al. [13] in this issue of the journal shall definitely add to the pediatrician’s and the intensivist’s knowledge on the management of this
vexing problem. Intravenous immunoglobulins for specific situations and ketogenic diet have found a unique place in SE management.

Novel researches in SE are now addressing the mechanisms of seizure initiation/persistence and will pave way for possible interventions [14,15]. This challenging research revealed the role of hypothermia in preventing neuronal death and hippocampal injury. Evidence of brain dynamics indicated reset after successful anti-seizure treatment of SE utilising stereo electrographic data (SEEG). In autoimmune SE, morphological alterations in microglia resulted in epileptogenesis. Studies in a kainite-induced SE model showed that neuronal loss does not necessarily correlate with higher seizure rate. Phytoalexins have shown efficacy in easing neurodegeneration, neuro-inflammation, and aberrant neurogenesis, minimalizing ensuing chronic epileptic state. Ketogenic diet initiation in SE can help smoothen the withdrawal of aggressive therapy within 7-10 days, and is a useful adjunct in refractory SE.

Future research to reduce refractoriness of status and neuro-morbidity is warranted. The need to update management guidelines for pediatric SE for use in India, after incorporating recent evidence, is also highlighted. I look forward to translation of cutting edge research into clinical practice for the betterment of children with SE.

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Clinical Profile and Short-term Outcome of Pediatric Status Epilepticus

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Status epilepticus (SE) is a common pediatric emergency, yet understanding of contemporary care practices remains incomplete, particularly for children in developing countries. The clinical profile and outcome of SE in children from developing countries is bound to be different than those from the developed countries. But, there are very few studies on pediatric SE from India, especially in the last decade after the new definition of SE was proposed, and many of the published studies have been retrospective studies. The current operational definition of SE is any active seizure of ≥5 minutes duration or recurrent episodes of seizures without gaining consciousness in between that last for more than 5 minutes [1,2]. In this issue of Indian Pediatrics, Chetan, et al. [3] provide some useful prospectively collected data on pediatric SE presenting to a tertiary-care center in India. Using the current operational definition of SE and an objective outcome measure, Pediatric Overall Performance Category, they have described the clinical profile and short-come outcome of 109 children with pediatric SE from January 2017 to April 2018. Their findings provide important information about the etiological profile of SE, the current protocol for management of SE, the response to various anti-epileptic drugs and short-term outcome.

Amongst the various prognostic factors in SE, the duration of convulsive SE is the only modifiable one with proper management. Prolonged seizures are associated with increased risk of mortality and morbidity [4]. Unfortunately, due to lack of public awareness, absence of prompt availability of medical care, and lack of infrastructure to transport to appropriate centers there is significant delay in children reaching the tertiary care centers in developing countries. In the study by Chetan, et al. [3] the average (range) duration of seizure was 17.5 (7-60) min. A shorter interval between onset and initiation of treatment is important for rapid control. However, studies from developing countries have shown that despite significant delay in initiating SE management, the incidence of RSE and case fatality is comparable with other cohorts [5]. Prolonged SE or treatment delay should not always be considered a hopeless situation and all cases should be managed aggressively.

The cause of SE is the most important factor that determines morbidity and mortality. Failure to treat the underlying cause promptly and correctly will preclude seizure control regardless of which anti-epileptic drug one chooses. Seizures and brain injury will ensue if we fail to address the underlying hypoglycemia/hypocalcemia or CNS bacterial infection in a patient presenting with refractory seizures and acute encephalopathy [6]. In the current study, 60.6% children had acute symptomatic etiology and measures to treat the underlying cause need to be instituted along with the management of SE to get good outcome. This fact needs to be stressed in the protocol for management of SE. Infectious etiology for both SE and RSE is common in developing countries like India [5,7].

In the current study, the second dose of midazolam was not effective in any of the children it was administered. It resulted in further delay in administering the second line anti-epileptic drugs. So, this may be taken as evidence for skipping this step in the protocol. Due to rapid internalization of GABA-A receptors, benzodiazepines become rapidly ineffective in management of SE with time [8]. After the first benzodiazepine dose, currently there is insufficient evidence to suggest that one antiepileptic drug is better than the other. Choice can be made based on the cost, availability, past use of that drug and the details of the type of seizures. Intravenous midazolam is the preferred anesthetic agent for management of refractory SE in view of its safety and ease of administration, as was the case in the present study. There is little evidence to choose between midazolam, propofol, and thiopentone, and all have shown comparable efficacy [5].

There is a need for continuous video-EEG monitoring to identify and treat subclinical seizures/SE and to avoid administering potentially harmful anti-seizure medica-
tions (i.e. barbiturate infusions) to treat clinical paroxysms mimicking seizure [6]. In the current study, EEG monitoring was not done, and this is one of the limitations of the study. Though non convulsive SE is a poor prognostic indicator, whether aggressive treatment of this translates into better outcome is not clear and this is fraught with complications like prolongation of ventilation, hypotension and other medical complications [5].

In the present study [3], non-administration of anti-epileptic drugs (AED) prior to presentation to the hospital was found to predict an unfavorable outcome. Pre-existing epilepsy was present in around 30% children. These children are always at a risk of having seizure recurrence. It is important to stress on the drug compliance and prescribe them intranasal/buccal midazolam and train parents how to administer them. A clear plan of treatment depending on the cause of seizures should be given to parents, so that in case of recurrence, appropriate steps can be taken to control the seizures quickly.

In summary, Chetan, et al. [3] provide a much needed insight into current care practices for pediatric SE. Their findings demonstrate the benefits of auditing data to better understand current treatment practices and identify potential areas for refinement. This process helps in the design of both local quality improvement initiatives and future clinical investigations.

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Fosphenytoin in Status Epilepticus: The Ice Needs to be Broken

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Status epilepticus (SE) is the most common neurological emergency encountered by pediatricians and the incidence is significantly higher in children compared to adults. North London Status Epilepticus in Childhood Surveillance Studies (NLSTEPSS), amongst the largest prospective population-based studies of convulsive SE in children, reported an annual incidence of 18-20 convulsive SE episodes per 100000 population as opposed to 4-6 per 100000 in the adult population [1].

Most pediatric SE guidelines recommend intravenous phenytoin (PHT) as the antiepileptic of choice after benzodiazepines [2,3]. However, various adverse effects have been reported with parenteral PHT, which include fluid incompatibilities, patient discomfort, patient irritation, tissue damage, muscle necrosis and cardiac toxicity [4]. The local adverse effects are related to the poor water solubility of phenytoin. This has led to the emergence of fosphenytoin (fPHT), a phosphate ester of PHT, to obviate the local complications of PHT [5]. fPHT was first approved in USA in 1996 and subsequently in Japan in 2011, and then other countries followed suit [6].

Fosphenytoin is a water soluble prodrug of phenytoin, which rapidly and entirely converts to PHT. Increased solubility of fPHT allows rapid infusion in status epilepticus, which compensates for the delay in the conversion of the prodrug to active metabolite. The mechanism of action and drug interactions are similar to PHT. Till date, no interaction has been reported in terms of the conversion of fPHT to PHT. The recommended loading dose for fPHT is 18-20 mg/kg of phenytoin equivalent at an infusion rate of 100-150 mg/minute [6].

The largest randomized trial evaluating fPHT in status epilepticus, the ESETT trial [7], compared the efficacy of levetiracetam, fPHT and valproate in 384 patients, of which around 40% were children and adolescents. There was no significant difference in terms of seizure control, regaining consciousness at 60 minutes, and frequency of adverse effects. In an Indian pediatric study [8], intravenous fPHT was compared with levetiracetam in status epilepticus. Time to stop seizure was significantly lesser in the fPHT group. However, seizure control, seizure recurrence, seizure-free duration and intensive care unit and hospital stay were similar in both the groups [8]. In a pediatric study [9] comparing intravenous fPHT with midazolam infusion as a second line agent in febrile status, efficacy of both was found to be similar and the latter was found to be relatively safe. The proportion of patients requiring barbiturate coma, mechanical ventilation and inotropic support and having incomplete recovery from consciousness was also not significantly different between the groups [9].

In the current issue of Indian Pediatrics, Srivastava, et al. [10] found that of the 51 children who presented with convulsive SE, 92% got controlled with fPHT, reinforcing the fact that it is a highly efficacious drug in convulsive SE, particularly in children. The study by Senthilkumar, et al. [8] showed control in 84% which could be explained by the fact that it was conducted on a pure pediatric population. In ESETT trial [7] only 45% showed initial control, which may be because this was predominantly in an adult population with a different etiological spectrum. Srivastava, et al. [10] reported a weak correlation of serum PHT levels with the original dose of fPHT received, and poor association with control of seizures; however, the serum PHT levels were estimated at 90-100 minutes post fPHT loading dose [10]. These findings could be explained by the fact that PHT follows nonlinear kinetics and early estimation of serum PHT levels may reveal a different picture, when it is following first order kinetics. The maximum serum PHT levels after fPHT administration are achieved at 10-20 minutes [6]. None of the children in the current study showed any adverse effects, highlighting the safety of fPHT in pediatric age group. Although, the chances of local complications are less with fPHT compared to PHT, the incidence of cardiac systemic complications like hypotension and arrhythmia are similar to PHT [6]. Under ideal circumstances, electrocardiogram, blood pressure and respiration should be monitored during fPHT administration. The most notable local complication of
fPHT is purple glove syndrome, which is seen to the tune of up to 45%. This rate is higher with PHT [6].

The existing literature reinforces the fact that fPHT is a safe drug with reasonable efficacy for convulsive SE. However, except for decreased chances of local complications, it does not provide any obvious superiority to PHT. Studies like the present one will go a long way in breaking the ice for fPHT. More studies, including head-to-head comparative trials with PHT, should be planned, particularly in the pediatric population, to establish safety and efficacy.

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Pediatric Convulsive Status Epilepticus: Act Fast, No matter With What!

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Convulsive status epilepticus (SE) is associated with considerable mortality and morbidity [1], and irreversible brain damage may occur if timely treatment is not given [2]. The International League Against Epilepsy (ILAE) has included two time frames in its definition of SE viz, time to intervene (T1=5min) and time of occurrence of permanent brain damage (T2>30min) [2]. So early and effective treatment that can achieve the above goal is searched for by many researchers, and the last decade has witnessed many studies that have compared various drugs and different routes. Many protocols also have incorporated those new drugs arbitrarily [3,4].

Though for the acute (first stage) seizure control benzodiazepines are the main treatment, superiority of lorazepam is challenged by many studies and current conclusion is that intramuscular midazolam and intravenous diazepam are as effective as intravenous lorazepam [5]. However, a consensus has not yet been achieved regarding which is the best antiepileptic in the armamentarium for the rapid control of the seizures once the benzodiazepines fail (stage 2). Levetiracetam, sodium valproate, phenytoin/fosphenytoin, lacosamide, and phenobarbital are being widely used and extensively studied for this indication [4]. A third stage is recognized as refractory SE, defined as SE persisting despite sufficient dose of benzodiazepines and at least one antiepileptic drug (AED), irrespective of time. Midazolam, propofol, and thiopental are used in an ICU setting to manage this stage but with limited support of evidence from well-controlled trials. Finally, a fourth stage is also recognized—super refractory SE defined as SE, that continues for 24 hours or more after the use of anesthetic therapy. Management of this stage is still hazier, with anecdotal treatment modalities like ketamine, IV immunoglobulin, ketogenic diet, and surgical measures [6].

Since standardized management of second stage can bring about realistic positive outcomes, evidence-based recommendations are required for drug-selection. Extrapolation of results from Western studies to the Indian context may not be appropriate given the differences in the body constitution and the genetic diversity, which may affect both drug dosages and drug metabolism. In this issue of Indian Pediatrics, Vignesh, et al.[7] report on their well-designed study comparing the efficacy of phenytoin, valproate and levetiracetam for the management of pediatric CSE. They showed a better seizure control with levetiracetam (94%), phenytoin (89%), and valproate (83%) when compared to other studies that had used much higher dosages. Three facts are highlighted by this study [7]. Firstly, there is equal efficacy of all drugs, meaning thereby that we need not confine ourselves to phenytoin as the sole second line drug. Moreover, a lower dose is enough for seizure control, and such a lower dose is associated with lesser chances of adverse reactions.

In a randomized multicentric trial (ESSET trial), Kapur, et al. [8] found that the same three AEDs (fosphenytoin instead of phenytoin) were effective in approximately half the patients with benzodiazepine-refractory convulsive SE, and they did not differ significantly with regard to safety. However, that study used a higher dosage of levetiracetam (60 mg/kg) and valproate (40 mg/kg) instead of uniform 20 mg/kg used by the present study [7]. Similarly, EcLiPSE trial [9] showed that levetiracetam had comparative efficacy to phenytoin and suggested that former could be an appropriate alternative to phenytoin. But, the ConSEPT trial concluded that levetiracetam is not superior to phenytoin for second-line management of pediatric convulsive SE [10]. It may be noted that all the three trials showed an effectiveness of only 50% in children as compared to >80% response in the present study [7]. However, the uniform infusion time (20 min) taken for binding by Vignesh, et al. [7] compared to 10 min and 5 min infusion by other trials might have impacted the time for seizure control by valproate and levetiracetam, which are safer to be infused faster. As the rapid control of seizure will bring a better outcome, this advantage could have been better utilized by modifying the binding technique. Another
EDITORIAL

meta-analysis by Yaziry, et al. [11] concluded that valproate, levetiracetam and phenobarbital can all be used as first line therapy in benzodiazepine-resistant SE but did not support the use of phenytoin.

The fact that the dose used in this study for levetiracetam(20mg/kg) and sodium valproate (20mg/kg) was well below the internationally recommended dose but with better outcome suggests that regional variation in dose will improve the outcome and reduce adverse effects while using these options. The methodology of random sequence generation and allocation concealment increases the power of this study but at the same time points to the fact that the three drugs have different infusion rates which have important implications for seizure control. Levetiracetam can be administered more rapidly (5–10min) than phenytoin (20min), which could potentially terminate convulsive status epilepticus faster with levetiracetam than phenytoin. This factor would not be taken into account during allocation concealment thus affecting the good outcome in both levetiracetam and valproate arm as they would be infused slowly at the same rate as phenytoin. Moreover, the ease of drug preparation and administration favours the newer antiepileptics rather than phenytoin. This study; however, has not provided the important epidemiological insights that could help in making the AED choice, as the seizure control and outcome may depend more on the etiology than the drug used.

We feel that this study has clearly established the equal effectiveness and safety of the three drugs. We need to generate more evidence and experiment with dosing and act quickly with the effective medications we have, so as to bring out region-based guidelines taking into consideration the epidemiological and socio-economic aspects.

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REFERENCES

Clinical Profile and Short-term Outcome of Pediatric Status Epilepticus at a Tertiary-care Center in Northern India

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Objective: To assess clinical profile and short term treatment outcomes of pediatric status epilepticus (SE) at a tertiary-care center in northern India.

Methods: Prospective cohort study enrolled children aged 1 month to 18 years presenting with SE to the emergency department. Enrolled children (109) were treated as per hospital protocols. Clinical features during hospitalization were noted. Pediatric overall performance category (POPC) scale was used for classification of outcome at the time of discharge.

Results: Acute symptomatic etiology was identified in 66 (60.6%) cases (CNS infections were predominant). Previous diagnosis of epilepsy was found in 32 (29.4%) children; and benzodiazepine responsive SE were seen in 65 (59.6%) children. Predictors of unfavorable outcome were acute symptomatic etiology (adjusted OR 4.50; 95% CI 1.49, 13.62) and no treatment administered prior to hospital (adjusted OR 3.97; 95% CI 1.06, 14.81).

Conclusions: Acute symptomatic etiology, mainly acute CNS infections, is the leading cause of SE in this region. Early and pre-hospital management with benzodiazepines may improve SE outcome.

Keywords: Epilepsy, Etiology, Seizures, Treatment.

Status epilepticus (SE) can present with varied clinical manifestations, and have different etiologies, which vary with age and geographical areas. It is well known that the duration of SE positively correlates with the refractoriness to treatment, and the prognosis is poor in children who have prolonged uncontrolled seizures [1-3]. Due to poor access to healthcare facilities in developing countries, there is higher likelihood of prolongation of seizures and delay in initiation of treatment. There is paucity of data regarding the etiology and treatment outcomes of SE in Indian children [4]. Therefore, the objective of the present study was to understand the clinical profile and short term treatment outcome in children with SE.

METHODS

This prospective cohort study was undertaken at a teaching government hospital in New Delhi, India from January 2017 to April 2018. Institutional ethics committee approval was obtained. Consecutive children aged 1 month to 18 years presenting in convulsive SE were enrolled. SE was defined as active seizures of ≥5 minutes duration or recurrent episodes of seizures without gaining consciousness in between [5]. Psychogenic non-epileptic seizures were excluded. Written informed consent was taken from the caregivers after initial stabilization of the child.

The enrolled children were treated as per the hospital SE protocol in accordance with the current guidelines in India [4]. The anti-epileptic drug (AED) was considered effective if there was clinical cessation of seizures within 10 minutes of the initial dose of medication and if there was no recurrence of seizures for 30 minutes [6]. A patient was classified to have benzodiazepine - responsive SE if the SE responded with first or second dose of benzodiazepine (BZD). Established SE was defined as SE which persisted despite two BZD doses and required 2nd line AED. Refractory SE was defined as SE persisting despite the administration of two appropriate anticonvulsants at acceptable doses and responding only to 3rd line AED or midazolam infusion [7]. Super-refractory SE was defined as SE that continued 24 hours or more even after the onset of anesthesia, including those cases in which the SE recurred on the reduction or withdrawal of anesthesia [8].
Detailed history, examination and investigations were documented in a predesigned form. Neuroimaging was done in all children with SE, except in hypocalcemic seizures, typical febrile seizures, and known cases of epilepsy without any new neurological deficits. The etiology of SE was determined according to the history, examination and the investigations done. The patients were followed till discharge or death during the hospital admission. The patients with pre-morbid developmental delay were evaluated for return to their baseline functional status. Neurologically normal patients were classified using the pediatric overall performance category (POPC) scale at the time of discharge [9]. POPC scale scores of 1-2 were considered as a favorable outcome and scores of ≥3 were considered as an unfavorable outcome.

Statistical analysis: This was performed using IBM SPSS software version 21. Continuous data was represented as mean with standard deviation or median with interquartile range. Qualitative data was represented as proportions or percentages. Multivariate logistic regression model was used to predict unfavorable outcome at discharge. A P-value of <0.05 was considered statistically significant.

RESULTS

A total of 115 children presenting as SE were assessed for eligibility during the study period and 109 were enrolled (3 declined to participate, and 3 children had psychogenic non-epileptic seizures) The median age at presentation was 2 (IQR 1-6) years. Generalized tonic-clonic seizures were seen in 70 (64.2%) children. The clinico-etiological characteristics of the study population are presented in Table I.

Sixty five (59.6%) children responded to first line AED (midazolam). Second dose midazolam was given in 29 patients (15 patients received one pre-hospital dose) but with no added benefit as seizures persisted in all. Out of the 44 cases who did not respond to midazolam (established SE), 28 responded to 2nd line AEDs. In the remaining 16 patients (refractory SE), 12 responded to 3rd line AEDs or midazolam infusion and 4 were classified into super-refractory SE. The response to medications in the study population is summarized in Fig. 1. In 44 children who did not respond to phenytoin, 37 were given valproate and 7 were given valproate as second line AED. Valproate was used based on history of compliant maintenance therapy with high normal dose phenytoin or past history of adverse reaction to phenytoin. Twenty two (59.5%) responded after phenytoin and 6 (85.7%) responded after valproate. Out of the 15 who did not respond to phenytoin, valproate was used in 12 children, out of which 4 (33.3%) responded. In 12 children, where valproate was either ineffective or was not used as third line AED, phenobarbitone or levetiracetam was used. Levetiracetam was effective in 4 out of 10 children (40%), whereas phenobarbitone was effective in 2 out of 7 children (28.6%).

Six children were initiated on midazolam infusion. The seizures subsided within 24 hours of midazolam infusion in one child and did not recur on stopping the infusion (refractory SE). One child died within 24 hours of midazolam infusion. Four children had super-refractory SE; of these three received phenobarbitone infusion and one received thiopentone infusion.

TABLE I Clinico-etiological Characteristics of Children with Status Epilepticus (N=109)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age , y</td>
<td>2 (1-6)</td>
</tr>
<tr>
<td>Males</td>
<td>64 (58.7)</td>
</tr>
<tr>
<td>Pre-existing epilepsy</td>
<td>32 (29.4)</td>
</tr>
<tr>
<td>Seizure duration, min</td>
<td>17.5 (7-60)</td>
</tr>
<tr>
<td>Type of seizures</td>
<td></td>
</tr>
<tr>
<td>Generalized tonic-clonic</td>
<td>70 (64.2)</td>
</tr>
<tr>
<td>Focal, impaired awareness</td>
<td>20 (18.3)</td>
</tr>
<tr>
<td>Focal evolving to bilateral tonic-clonic</td>
<td>10 (9.2)</td>
</tr>
<tr>
<td>Generalized tonic</td>
<td>9 (8.3)</td>
</tr>
<tr>
<td>Etiology of status epileptic</td>
<td></td>
</tr>
<tr>
<td>Acute symptomatic</td>
<td>66 (60.6)</td>
</tr>
<tr>
<td>Acute CNS infections</td>
<td>27 (24.8)</td>
</tr>
<tr>
<td>Febrile status epileptic</td>
<td>16 (14.7)</td>
</tr>
<tr>
<td>Neurocysticercosis</td>
<td>14 (12.8)</td>
</tr>
<tr>
<td>Hypocalcemic seizures</td>
<td>7 (6.4)</td>
</tr>
<tr>
<td>ADEM</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>CSVT</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Remote symptomatic seizures</td>
<td>27 (24.8)</td>
</tr>
<tr>
<td>Perinatal insult</td>
<td>18 (16.5)</td>
</tr>
<tr>
<td>Mesial temporal sclerosis</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Focal cortical dysplasia</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Congenital intrauterine infections</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Hippocampal atrophy*</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>4 (3.7)</td>
</tr>
<tr>
<td>Unknown etiology</td>
<td>16 (14.7)</td>
</tr>
</tbody>
</table>

All values in n (%) except median (IQR); *One case each of late infantile neuronal ceroid lipofuscinosis type 2, Dravet syndrome, suspected case of IEM, and Wolcott Rallison syndrome; †Only 15 of these were receiving antiepileptic drugs; CNS: Central nervous system ADEM: Acute disseminated encephalomyelitis, CSVT: Cerebral sinus venous thrombosis.
Multivariate logistic regression showed that presence of an acute symptomatic etiology (adjusted OR 4.50, 95% CI 1.5, 13.6) and no AED administered prior to hospitalization (adjusted OR 3.97, 95% CI 1.1, 14.8) predicted unfavorable outcome at discharge. The age, sex, presence of pre-existing epilepsy, duration of seizures prior to reaching the hospital, and response to the first line BZD were not found to be significant.

DISCUSSION

This prospective cohort study explored the clinical profile and treatment outcomes of pediatric SE, in the setting of a developing country. Acute symptomatic etiology was identified in a majority of the cases. BZD-responsive SE was seen in more than half of the children. Predictors of unfavorable outcome were found to be acute symptomatic etiology, and absence of an AED administered prior to reaching the hospital.
We used the second dose of midazolam in children who continued to have seizures after 10 minutes of the first dose. However, none of these children responded. The reason for this may be the inherent pharmacokinetics of BZDs; with higher doses of these drugs, proportionate increase in clinical effect may not be seen. We could not find any literature providing data on the use of second dose of intravenous (IV) midazolam. The response to IV midazolam noted in more than half of the patients in our study is similar to another study which observed an efficacy of around 70% in children given lorazepam or diazepam [6]. In another study, midazolam was reported to be effective in 90.3% children [10]. The reason for such a high response rate was that they considered it effective even if it failed as initial injection, but was effective as infusion. In a Cochrane review of studies including patients of all age groups, IV lorazepam was found to be more efficacious than diazepam; however, no difference was seen between IV midazolam, diazepam or lorazepam [11]. A few studies done in the pediatric age group have not shown superiority of any particular BZD over the others [6,12]. In a retrospective analysis of patients with SE [13], 31% of the patients required midazolam infusion [13], as compared to 5% in this study. This difference could be attributed to possible delays in reaching the centre/initiation of treatment as the study center is a busy referral centre in Northern India. Further, the retrospective collection of data might also have influenced the results.

The causes for SE differ greatly in developed and developing countries. In contrast to developing countries where CNS infections are the predominant cause of SE in children, febrile SE and idiopathic (unknown etiology) cause form the majority in developed countries [10,14]. Due to the wider age range of children in our study, we probably had a large spectrum of causes of SE. In the studies from developed countries, though the acute symptomatic cause is less common, but still CNS infections constitute the majority in the acute symptomatic group [10,14,15].

In our study, children with acute symptomatic etiology and non-administration of AED prior to the hospital were found to predict unfavorable outcome. Children with refractory SE and super refractory SE, had a significantly unfavorable outcome. In previous studies, younger age group, longer duration of SE, poor response to initial anticonvulsants, acute symptomatic group and refractoriness to the overall treatment have been shown to be associated with higher mortality [1-3,16,17].

In conclusion, CNS infections are the single leading cause of SE in children in this region. Absence of pre-hospital AED treatment predicts an unfavorable outcome for the children. However, more than half of the children have BZD responsive SE. Increasing the awareness of parents and primary health care providers about the appropriate use of BZDs may decrease the morbidity and poor outcome of SE.

Contributors: SS, SA: conceived the study; CC,SS,SBM,SA: provided clinical care to the patients; CC,SS,PJ: did the data analysis and interpretation; CC, SBM: wrote the first draft which was the read, revised and approved by all the authors. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.

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REFERENCES


**Efficacy, Tolerability and Serum Phenytoin Levels after Intravenous Fosphenytoin Loading Dose in Children with Status Epilepticus**

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**Objective:** To evaluate the efficacy and tolerability of intravenous fosphenytoin in children with status epilepticus, and resulting serum total phenytoin levels.

**Methods:** In this prospective study, 51 children aged less than 18 years received intravenous loading dose of fosphenytoin (18-20 mg/kg). Serum total phenytoin levels were estimated at 90-100 minutes. Outcomes studied were (i) seizure control and local and/or systemic adverse effects in next 24 hours and (ii) phenytoin levels and its correlation with dose received, seizure control and adverse effects.

**Results:** The actual dose of fosphenytoin received varied from 15.1 to 25 mg/kg. Seizures were controlled in 45 (88%) children and, two required additional dose of 10 mg/kg. None of the children showed any local or systemic adverse effects. Serum total phenytoin levels were in the therapeutic range (10-20 µg/mL) in 12 (23.5%), sub-therapeutic in 16 (31.3%) and supra-therapeutic in 25 (49%) children. There was weak correlation of the phenytoin levels with dose of fosphenytoin received, seizure control, or adverse effects.

**Conclusion:** Intravenous fosphenytoin loading dose of 20 mg/kg is effective in controlling seizures in 88% of children with status epilepticus, with a good safety profile. Seizure control and adverse effects appear to be independent of serum total phenytoin levels achieved.

**Keywords:** Anticonvulsant, Management, Seizure control, Therapeutic levels.

Intravenous Phenytoin (PHT) is the first long-acting drug (after benzodiazepines) recommended for the treatment of status epilepticus [1,2]. Fosphenytoin (FOS) is a pro-drug which is rapidly converted to PHT and preferred due to less incidence of thrombophlebitis and cardiotoxicity [3,4]. PHT follows non-linear kinetics, causing unpredictable blood levels, with higher levels associated with cardiac arrhythmias and hypotension. PHT concentrations may be influenced by ethnicity due to its hepatic metabolism through cytochrome P450 enzymes [5,6].

While it is recommended to maintain serum total PHT levels in the therapeutic range of 10 to 20 µg/mL, monitoring is not done routinely in India, possibly due to cost or feasibility issues. Efficacy and safety of FOS have been stressed by few authors, and others have evaluated the pharmacokinetics in status epilepticus [7-11]. Hence this study was done to evaluate the efficacy and tolerability of loading dose of 20 mg/kg of intravenous FOS in children admitted for status epilepticus and to correlate the serum PHT levels after 90-100 minutes of loading with actual dose received, seizure control and adverse effects.

**METHODS**

This was an observational study conducted in emergency ward and pediatric intensive care unit (PICU) of a medical college affiliated hospital over 10 months (December, 2016 to September, 2017). Institutional Ethics Committee approval was taken, and written informed consent from parents was obtained to participate in the study.

Children aged one month to 18 years with status epilepticus were enrolled in the study. Status epilepticus was defined as seizure duration of more than 30 minutes or two or more seizures without regaining consciousness. Those who were already on oral PHT or loaded with any other antiepileptic drug outside the hospital were excluded.

All patients received a standard protocol for securing airway, oxygenation, and circulation. IV Lorazepam 0.1 mg/kg followed by IV FOS [(Brand Fosolin, Zydus Cadilla), content: 50 mg/mL of phenytoin equivalents (PE)] at a dose of 20 mg/kg for estimated weight (or actual weight, if known) was administered.
Blood sample (5 mL) was obtained at 90 to 100 minutes (after loading dose) to determine the serum total PHT levels, serum albumin, and creatinine. The PHT levels were estimated using CLIA (Chemiluminescence immunoassay) method by Immulite 1000 machine (Siemens, Los Angeles CA 90045 USA). If there was a breakthrough seizure, a second dose of 10 mg/kg of IV FOS was administered.

A detailed history of perinatal events, development, family history, and etiology of seizures were recorded, along with physical and neurological examination. Seizure control was defined as cessation of any clinical seizure activity. The total duration of seizure, need of additional dose/ other anti-epileptic drugs, and any adverse effects were recorded for the next 24 hours. The patients were followed till discharge/death, and final outcome noted.

Accurate weight was obtained after recovery and the actual dose received in mg/Kg was recalculated. Optimal dose was defined as 18-20 mg/kg of PE, subnormal if less than 18 mg/kg and supra-normal if more than 20 mg/kg. PHT levels were considered to be in the therapeutic range between 10-20 µg/mL, below 10 µg/mL as sub-therapeutic, above 20 µg/mL as supra-therapeutic and more than 40 µg/mL to be in toxic range. The outcome studied for efficacy was the number of patients with clinical control of seizures in next 24 hours. For tolerability, number of patients with local (cording of vein, erythema, and swelling at IV site) and systemic adverse effects (e.g. vomiting, nystagmus, ataxia etc.) was recorded.

Statistical analysis: Linear regression of serum PHT levels with actual loading dose received was plotted, and Pearson correlation coefficient was computed. PHT levels were further analyzed to see whether they correlated with seizure control and adverse effects.

RESULTS
Fifty-one children (54.9% males) were prospectively enrolled. Age distribution was as follows: below one year (n=9), 1-5 years (n=19), 5-10 years (n=14) and more than ten years (n=9). The seizure types were generalized tonic-clonic seizure (n=40), focal seizure with impaired awareness (n=8), or evolving into bilateral convulsive seizure (n=3). Among the fifteen children who were already diagnosed with epilepsy, 11 were on antiepileptic medications: valproate (n=2), topiramate (n=2), oxcarbazepine (n=2), levetiracetam (n=2) and nitrazepam (n=2). One child was on both valproate and levetiracetam. Etiologies were febrile status epilepticus (n=10), prior brain insult (n=7) meningitis (n=6), traumatic brain injury (n=4), sepsis (n=2), subdural hematoma (n=1), neurocysticercosis (n=1), metabolic disorder (n=1) and unknown (n=19).

Among the 51 children, 32 (62.7%) received optimal dose of 18-20 mg/kg, 16 (31.3%) received supra-normal, and rest three received sub-normal doses. The dose varied from 15.1 to 25 mg/kg (mean dose 20.22 mg/kg) Serum albumin and creatinine were within normal range in all children.

Forty-five out of 51 (88%) patients achieved seizure control after the first dose. All children with febrile status epilepticus (n=10) were controlled after a single dose. Two patients (with unknown etiology) had breakthrough seizures (after 3 and 12 hours of loading dose), which were subsequently controlled after second dose of 10 mg/kg. Thus overall, 47 (92%) children achieved seizure control on FOS alone.

None of the children showed any local or systemic adverse effects, even with PHT levels in the supratherapeutic or toxic range. Two patients with meningitis showed local cording of vein, attributed to vancomycin.

### Table I Serum Total Phenytoin Levels and Seizure Control in Children and Loading Dose of Fosphenytoin (N=51)

<table>
<thead>
<tr>
<th>Dose received</th>
<th>Sub-normal dose (n=3)</th>
<th>Optimal dose (n=32)</th>
<th>Supra-normal dose (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin levels (µg/mL)</td>
<td>Very low &lt;2.5</td>
<td>Low 2.5-10</td>
<td>In range 10-20</td>
</tr>
<tr>
<td>Patients, n</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Seizure control achieved</td>
<td>Yes</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>-</td>
<td>0</td>
</tr>
</tbody>
</table>

Sub-normal dose: <18 mg/kg; Optimal dose: 18-20 mg/kg; Supra-normal dose: >20 mg/kg; *Needed second dose; #Needed continuous midazolam infusion.
events, including ten deaths were reported between 1997 to 2003, although many of these patients had pre-existing cardiac pathology [14].

In our study, only 35 patients (68.62%) achieved PHT levels in therapeutic or supratherapeutic range. Single-dose is shown to achieve and maintain therapeutic levels up to 24 hours after loading dose, irrespective of body mass index [8,15-17]. One study suggested 22.5 mg/kg may be a better dose to achieve therapeutic levels in children [18]. Ogutu, et al [9] showed comparable serum levels when intravenous FOS and PHT were given (dose 18 mg/kg) and FOS achieved peak levels faster (mean 0.08 hours) as compared to 0.37 hours for PHT.

We found a weak correlation between the FOS dose and PHT levels achieved. Selioutski, et al [19] also found similar results, 63% of those receiving 15-20 mg/kg dose and 51% of those receiving 20-55 mg/kg dose did not achieve levels of 20 µg/mL or more within the first 6 hours; while some patients achieved levels of >20 µg/mL despite receiving low doses.

Therapeutic drug monitoring of PHT levels is considered necessary to ensure non-toxic levels, and should preferably be done at least one hour after loading [6]. In our study, seizure control did not depend on serum PHT levels. Also, a low incidence of adverse effects even with blood levels in toxic range is reassuring. Thus, we did not find any additional benefit of monitoring PHT levels, though numbers are small. Seizure control (without adverse effects) may be a better measure of clinical efficacy as compared to blood levels, which indicate pharmacokinetic efficacy.

Due to limited funding, our sample size was small, and PHT levels could not be repeated at later time intervals to ascertain whether they remain in the therapeutic range. We did not exclude patients who were already on other anti-epileptic drugs before admission, which can influence PHT levels.

In future studies, serum PHT levels can be serially measured at different time/points after the loading dose. Efficacy, tolerability, and pharmacokinetics of

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**WHAT IS ALREADY KNOWN?**

- Fosphenytoin shows good efficacy in control of seizures, with less risk of adverse effects.

**WHAT THIS STUDY ADDS?**

- Fosphenytoin showed good efficacy in children with status epilepticus, with good safety profile.
- Serum total phenytoin levels at 90-100 minutes showed poor correlation with the dose of fosphenytoin received.

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**DISCUSSION**

The present study revealed good efficacy of IV FOS (with a dose of 18-20 mg/kg) in controlling status epilepticus in children, similar to findings of other studies [7,8,10,11]. However, in an African study, seizures were controlled in only 36% and 44% patients who received PHT and FOS, respectively each in the dose of 18 mg/kg [9].

In our study, intravenous FOS demonstrated an excellent safety profile, even among those with PHT levels in supratherapeutic or toxic range in 23 (45%) patients. As compared to PHT, IV FOS has lesser rates of venous irritation, mechanical ventilation and use of inotropic agents [11-13]. However, in adults, 29 cardiac

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**Fig. 1** Correlation of serum phenytoin levels with the actual dose of intravenous fosphenytoin received (R²=0.038).
intramuscular loading dose of FOS should also be studied, along with a detailed pharmaco-economic assessment.

A single loading dose of intravenous FOS (18-20 mg/kg) is effective in controlling status epilepticus in 88% of children with very low risk of adverse events. It should be preferred over PHT as second-line drug for status epilepticus. Serum PHT levels were in therapeutic and supratherapeutic range in only 68.6% at 90-100 minutes of loading, and appear to be independent of dose received.

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Contributors: KS: conceptualized and planned the study, along with manuscript writing; SB, VG, RP: carried out the data collection and analysis. SR: revised the manuscript.

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Competing interest: None stated.

REFERENCES
Comparison of Phenytoin, Valproate and Levetiracetam in Pediatric Convulsive Status Epilepticus: A Randomized Double-blind Controlled Clinical Trial

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Objective: To compare the efficacy of phenytoin, valproate, and levetiracetam in the management of pediatric convulsive status epilepticus.

Design: Randomized double-blind controlled clinical trial.

Setting: Pediatric critical care division in a tertiary care institute from June, 2016 to December, 2018.

Participants: 110 children aged three month to 12 year with convulsive status epilepticus.

Intervention: Patients not responding to 0.1 mg/kg intravenous lorazepam were randomly assigned (1:1:1) to receive 20 mg/kg of phenytoin (n=35) or valproate (n=35) or levetiracetam (n=32) over 20 minutes. Patients with nonconvulsive status epilepticus, recent hemorrhage, platelet count less than 50,000 or International normalized ratio (INR) more than 2, head injury or neurosurgery in the past one-month, liver or kidney disease, suspected or known neurometabolic or mitochondrial disorders or structural malformations, and allergy to study drugs; and those who were already on any one of the study drugs for more than one month or had received one of the study drugs for current episode, were excluded.

Outcome measure: The primary outcome was the proportion of patients that achieved control of convulsive status epilepticus at the end of 15 minutes after completion of the study drug infusion. Secondary outcomes were time to control of seizure, rate of adverse events, and the requirement of additional drugs to control seizure, length of ventilation, hospital stay, and functional status after three months (Glasgow Outcome Scale).

Results: The study was stopped after the planned mid-interim analysis for futility. Intention to treat analysis was done. There was no difference in primary outcome in phenytoin (31/35, 89%), valproate (29/35, 83%), and levetiracetam (30/32, 94%) (P=0.38) groups. There were no differences between the groups for secondary outcomes. One patient in the phenytoin group had a fluid-responsive shock, and one patient in the valproate group died due to encephalopathy and refractory shock.

Conclusions: Phenytoin, valproate, and levetiracetam were equally effective in controlling pediatric convulsive status epilepticus.

Keywords: Anti-epileptic drugs, Management, Outcome Seizure.

Trial Registration: CTRI/2016/05/006908.

METHODS

This randomized, double blinded-controlled clinical trial was conducted in the Division of pediatric critical care of a tertiary-care academic institution between June, 2016 to...
December, 2018. The institutional ethics committee approved the study and written informed consent was obtained from parents/legal guardians. Children aged 3 month to 12 years with convulsive status epilepticus (clonic, tonic, tonic-clonic, and myoclonic, focal or generalized) were enrolled. Children with either of the following conditions were excluded (i) non-convulsive status epileptics, (ii) active or recent hemorrhage (less than one week) from any site, (iii) documented platelet count less than 50,000, or international normalized ratio more than two, (iv) head injury or neurosurgery in the past one month, (v) acute or chronic liver or kidney disease, (vi) suspected or known neurometabolic or mitochondrial disorders or structural malformations, (vii) known or suspected allergy to any of the study drugs, (viii) patient with epilepsy already on levetiracetam (more than 20 mg per kg per day) or valproate (more than 20 mg per kg per day) or phenytoin (more than 5 mg per kg per day) for more than one month, and (ix) patients who have received the appropriate dose of study drug(s) for the current episode of convulsive status epilepticus. Convulsive status epilepticus was defined as continuous seizure activity or recurrent seizure activity without regaining consciousness, lasting more than five minutes [6,7]. Status epilepticus and its etiology were classified as per International League Against Epilepsy guidelines [6].

A computer-generated and unstratified block randomization with variable block sizes of three, six, and nine were used. A person not involved in the study performed the random number allocation. Individual assignments were placed in sequentially numbered opaque sealed envelopes (SNOSE) with a three-component alphanumerical code. The envelope contained an instruction slip about the preparation of the study drug. Nursing personnel, who was not part of the research team, opened the envelope and prepared the study drug concentration of 5 mg/mL in 0.9% normal saline dilution in the syringe. Each syringe was labeled with the same alphanumerical code, and study drug dose (4 mL per kg over 20 minute). The person who prepared the study drug was blinded to the patient’s identity. Injection phenytoin sodium (Ciroton, 2 mL per 100 mg, Ciron Pharmaceuticals, India), injection sodium valproate (Valprol, 5 mL per 500 mg, Intas Pharmaceuticals, India) and injection levetiracetam (Levesam, 5 mL per 500 mg, Abbott Ind. Ltd, India) were used in this study. The Institute’s central pharmacy supplied the study drugs. The participants, treating doctors and nurses administering the drugs, as well as the investigators and research personnel, were unaware of the treatment assignments until control of seizure. Later, the study drug was unblinded to the treating team to continue maintenance therapy. The person who collected the data and entered it into the datasheet, and the study statistician were unaware of the treatment assignments until final analyses. At the time of analysis, another person not involved in the study and SNOSE preparation decoded the treatment assignment by using the code from the online stored datasheet.

Enrolled patients were managed by stabilizing the airway, breathing and circulation, and using intravenous lorazepam 0.1 mg/kg in the pediatric emergency room. Patients not responding to intravenous lorazepam received the study drug at the dose of 20 mg kg over 20 minutes as an intravenous infusion. If convulsions were not controlled with the study drug or there was recurrence of seizure after control by study drug, additional antiepileptic drugs were administered as per the treating team’s discretion. The patients were shifted to the pediatric intensive care unit or ward for further management and etiological workup, as per unit protocol. Survivors were followed for three months post-discharge. The functional status was assessed using Glasgow outcome scale score, which ranges from one to five (higher the score better the neurological function).

The primary outcome was the proportion of patients who achieved control of convulsive status epilepticus at the end of 15 minutes after completion of study drug infusion (i.e., 35 minutes after starting the study drug infusion). The secondary outcomes were (i) time (minutes) taken to control seizure from the initiation of study drug infusion, (ii) proportion of patients who required additional drug to abort clinical seizures, (iii) rate of adverse events, (iv) length of mechanical ventilation if ventilated; (v) hospital stays including pediatric intensive care stay, (vi) in-hospital mortality; and (vii) functional status at three months of follow-up by Glasgow Outcome Scale.

Based on a study by Mundlamuri, et al. [8], control of convulsive status epilepticus by phenytoin and valproate was found to be at 68%. We, therefore, assumed that levetiracetam might increase the control rate to 88%. With a two-sided alpha of 5% and 80% power, 68 patients were needed in each group (nQuery + nTerim3.0 version software). Interim analysis was planned at the end of 50% enrollment. The trial progress was reviewed yearly by the institute’s ethics and data and safety monitoring committee, including an independent statistician who was also a physician. The trial had to be stopped prematurely after the planned interim analysis contended that it was futile to continue the study further.

Statistical analyses: Data of all the patients were analyzed according to their assigned groups (Intention to treat). The normality of data was checked with the Kolmogorov-Smirnov Z test. Continuous data were compared by one-way analysis of variance (ANOVA) if normally distributed.
RESULTS

The study flow is depicted in Fig. 1. The baseline characteristics and investigations were comparable in the study groups (Table I). The median duration of seizure, before enrollment, was 10 minutes in each group. Seven (7%) of patients received normal saline bolus and six (6%) patients received vasoactive therapy. Five patients in each group received osmotherapy for cerebral edema. Antibiotics and antivirals were given in 40 (39.2%) and 16 (16%) patients, respectively (Table I). Computerized tomography was done in 55 (54%) patients, and magnetic resonance imaging was done in 41 (40%) patients. Abnormalities were found in 18 studies, with tubercular involvement in two children and multiple neurocysticercosis in one child. Control of convulsive status epilepticus was higher in the levetiracetam group (94%) as compared to the phenytoin group (89%) and valproate group (83%), though statistically no difference was found ($P=0.38$). The mean time to control of seizure was three minutes ($P=0.42$). Additional drug to control the seizure after control of seizure by study drug was higher in the phenytoin group (26%) as compared to the valproate (14%) and levetiracetam (13%) groups. Twenty-eight patients (27.5%) were shifted to the pediatric intensive care unit; mean stay was significantly lower in the phenytoin group (Table II). One patient died in the valproate group due to encephalopathy and refractory shock; this death was not thought to be due to the study drug. No intervention-related serious adverse event was noted, except for one patient in the phenytoin group who had a fluid responsive shock.

DISCUSSION

The present randomized controlled study found that phenytoin, valproate, and levetiracetam are safe and equally efficacious in the management of pediatric status epilepticus. Our study findings are consistent with recent controlled studies. A study in adults [8], compared phenytoin (20 mg per kg), valproate (30 mg per kg) and levetiracetam (40 mg per kg) after 0.1 mg per kg of lorazepam found that there was no difference in the control of generalized convulsive status epilepticus (68% vs. 68% vs. 78%) and 6% of levetiracetam group patients had post-ictal psychosis. A more recent study [9] in both children and adults, comparing fosphenytoin (20 mg of phenytoin...
TABLE I Baseline Characteristics of Children With Convulsive Status Epilepticus in the Three Treatment Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Phenytoin group (n=35)</th>
<th>Valproate group (n=35)</th>
<th>Levetiracetam group (n=32)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Age (mo)</td>
<td>44 (43)</td>
<td>59 (44)</td>
<td>58 (50)</td>
<td>0.32</td>
</tr>
<tr>
<td>Male</td>
<td>19 (54.3)</td>
<td>21 (60)</td>
<td>18 (56.2)</td>
<td>0.89</td>
</tr>
<tr>
<td>*Body Mass Index, z score (cm)</td>
<td>-1.7 (2)</td>
<td>-1.1 (1.9)</td>
<td>-1.6 (2)</td>
<td>0.32</td>
</tr>
<tr>
<td>*(cm) Head circumference</td>
<td>46.4 (4.2)</td>
<td>48.3 (3.5)</td>
<td>47 (4.8)</td>
<td>0.16</td>
</tr>
<tr>
<td>#PRISM-III</td>
<td>5 (3 - 8)</td>
<td>4 (2 - 7)</td>
<td>3 (0 - 5)</td>
<td>0.17</td>
</tr>
<tr>
<td>#Duration of seizure, prior to enrollment (min)</td>
<td>10 (10 - 23)</td>
<td>10 (10-15)</td>
<td>10 (10-18)</td>
<td>0.57</td>
</tr>
<tr>
<td>Fever history</td>
<td>23 (66)</td>
<td>15 (43)</td>
<td>15 (47)</td>
<td>0.13</td>
</tr>
<tr>
<td>Classification of status epilepticus, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.44</td>
</tr>
<tr>
<td>Generalized convulsive</td>
<td>26 (74)</td>
<td>31 (88)</td>
<td>24 (75)</td>
<td></td>
</tr>
<tr>
<td>Focal motor</td>
<td>5 (14)</td>
<td>2 (6)</td>
<td>6 (19)</td>
<td></td>
</tr>
<tr>
<td>Focal onset evolving into bilateral convulsive SE</td>
<td>4 (11)</td>
<td>2 (6)</td>
<td>2 (6)</td>
<td></td>
</tr>
<tr>
<td>Family history of seizure disorder</td>
<td>4 (11)</td>
<td>2 (6)</td>
<td>1 (3)</td>
<td>0.38</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>5 (14)</td>
<td>8 (23)</td>
<td>5 (16)</td>
<td>0.60</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>4 (11)</td>
<td>3 (9)</td>
<td>2 (6)</td>
<td>0.76</td>
</tr>
<tr>
<td>Abnormal CT head (n=55)</td>
<td>4/23 (17)</td>
<td>3/16 (19)</td>
<td>1/16 (6)</td>
<td>0.37</td>
</tr>
<tr>
<td>‡MRI Brain* (n=41)</td>
<td>5/12 (42)</td>
<td>2/13 (15)</td>
<td>5/16 (31)</td>
<td>0.43</td>
</tr>
<tr>
<td>‡Electroencephalographic abnormality</td>
<td>15/27 (56)</td>
<td>17/29 (59)</td>
<td>12/21 (57)</td>
<td>0.97</td>
</tr>
<tr>
<td>Cerebrospinal fluid pleocytosis</td>
<td>10 (29)</td>
<td>7 (20)</td>
<td>4 (13)</td>
<td>0.27</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
<td></td>
<td>0.28</td>
</tr>
<tr>
<td>Acute</td>
<td>16 (46)</td>
<td>7 (20)</td>
<td>14 (44)</td>
<td></td>
</tr>
<tr>
<td>Remote</td>
<td>9 (25)</td>
<td>7 (20)</td>
<td>5 (16)</td>
<td></td>
</tr>
<tr>
<td>Acute on remote</td>
<td>1 (3)</td>
<td>2 (6)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Febrile status epiletics</td>
<td>2 (6)</td>
<td>2 (6)</td>
<td>2 (6)</td>
<td></td>
</tr>
<tr>
<td>Unknown (ie, cryptogenic)</td>
<td>7 (20)</td>
<td>17 (48)</td>
<td>11 (34)</td>
<td></td>
</tr>
</tbody>
</table>

All values in no. (%) except *mean (SD) or #median (IQR); Hypocalcemia defined as ionized calcium less than one mmol/L or total serum calcium less than 8.5 mg/dL; PRISM: *Pediatric risk mortality score; CT: Computer tomography; MRI: Magnetic resonance imaging; ‡done during the follow-up.

equivalent per kg), valproate (40 mg per kg) and levetiracetam (60 mg per kg), found that cessation of status epilepticus and improvement in the level of consciousness at 60 minutes of starting study drug infusion was similar in all three groups (45%, 46%, and 47%, respectively). The ConSEPT study [10] and the EcLiPSE study [1] compared 20 mg per kg phenytoin and 40 mg per kg levetiracetam. Clinical cessation of seizure activity in children with status epilepticus refractory to benzodiazepine was similar in both studies (60% vs 50% and 64% vs 70%, respectively) [1,10].

Isguder, et al. [11] reported that control of status epilepticus in pediatric patients was 71.8% with valproate and levetiracetam. The lower rate of seizure control could be due to a longer median duration of status epilepticus of 75 minutes, as compared to 10 minutes in our study.

A meta-analysis in pediatric status epilepticus found that valproate had a higher efficacy of 75.7% as compared to levetiracetam (68.5%) and phenytoin (50.2%) after administration of benzodiazepine [12]. Another meta-analysis of five randomized studies, which included one pediatric study (valproate vs. phenytoin), with insufficient information about random sequence generation and allocation concealment, found that there was no difference in clinical seizure control in both direct (valproate vs. phenytoin; 77% vs. 76% and levetiracetam vs. phenytoin; 72% vs. 68%) and indirect (levetiracetam vs. valproate; 72% vs. 77%) comparison [13]. Our study found a relatively higher control rate of seizure; as compared to other published studies [1,8-13], possibly due to shorter duration of seizures before treatment in our study.

We found that the proportion of patients shifted to the pediatric intensive care unit was significantly higher in the phenytoin group. This could be due to the underlying illness in addition to the drug effects on neurological
TABLE II Outcome in Children With Convulsive Status Epilepticus in the Three Treatment Groups (N=102)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Phenytoin group (n=35)</th>
<th>Valproate group (n=35)</th>
<th>Levetiracetam group (n=32)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome, n (%)</td>
<td>31 (89)</td>
<td>29 (83)</td>
<td>30 (94)</td>
<td>0.38</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to control seizure (min), mean (SD)</td>
<td>3 (1.2)</td>
<td>3.2 (1.4)</td>
<td>3.1 (1.3)</td>
<td>0.42</td>
</tr>
<tr>
<td>Additional drug to control the seizure, n (%)</td>
<td>4 (11.4)</td>
<td>6 (17)</td>
<td>2 (6)</td>
<td>0.38</td>
</tr>
<tr>
<td>Mechanical ventilation, n (%)</td>
<td>7 (20)</td>
<td>5 (14)</td>
<td>3 (9)</td>
<td>0.47</td>
</tr>
<tr>
<td>Length of mechanical ventilation (d), mean (SD)</td>
<td>2 (1.2)</td>
<td>7 (5.5)</td>
<td>3 (1.7)</td>
<td>0.08</td>
</tr>
<tr>
<td>PICU shifting, n (%)</td>
<td>15 (43)</td>
<td>7 (20)</td>
<td>6 (19)</td>
<td>0.04</td>
</tr>
<tr>
<td>Hospital stay (d), mean (SD)</td>
<td>6.1 (4.1)</td>
<td>5.5 (5.4)</td>
<td>7 (7.4)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

Functional status (at discharge), n (%): 0.46

- GOS score-1
- GOS score-3
- GOS score-4
- GOS score-5
- #Functional status (at 3 mo), n (%): 0.06
- GOS score-3
- GOS score-4
- GOS score-5
- Mortality, n (%)
- Adverse event, n (%)

PICU: Pediatric Intensive Care Unit; GOS: Glasgow Outcome Scale; *fluid responsive shock, †n=34 for valproate group, ‡after control of seizure by study drug; †no response to study drug.

function. Valproate is reported to have a lower risk of cardiorespiratory compromise and a lack of sedative effect [14,15].

Our study had certain methodological differences from other similar studies. We assessed the absence of seizure 15 minutes after completion of study drug infusion, i.e. 35 minutes after starting the infusion, and the mean time taken to control of seizure was three minutes. We randomized the patients who did not respond to the benzodiazepine and used intention to treat analysis. This finding differs from the EcLiPSE study, which found that median time from randomization to the cessation of convulsive status epilepticus was similar in phenytoin and levetiracetam group (45-minute vs. 35-minute) and ConSEPT study assessed the clinical cessation of seizure activity five minutes after completion of infusion of the study drug with a different infusion time used for administration of study drugs (over five minutes and over 20 minutes) [1,10]. Another controlled study by Kapur, et al. [9] assessed the absence of seizure and recovery of consciousness after 60 minutes of starting the study drug infusion, and emergency unblinding before 60 minutes was considered a protocol deviation. Hence, the time limit followed for assessment of primary endpoint in our study is in line with the International League Against Epilepsy operational time point (t1 and t2) of status epilepticus [6].

Apart from the duration of seizure, age and underlying etiologies have a different impact on the prognosis of neurological outcome, even if assuming a similar seizure type [6]. In our study, these prognostic factors were not analyzed. Though it is difficult to differentiate the role of each of the prognostic factors, data from larger studies could allow for redefining of the risk of long-term neuromorbidity. Another strength of our study was that the neurological outcome at three-month was assessed. This is in contrast to six previous open-labeled controlled studies with valproate and two with levetiracetam, no follow-up details were provided [5]. Our study did not include the recovery of postictal consciousness, long term drug-related adverse effects, and behavioral assessment. Future studies with large sample size, preferably multicentric, should focus on children with different etiologies,
including liver and hematological diseases, with stratification of the duration of seizure and convulsive versus non-convulsive seizures.

In conclusion, our study shows that phenytoin, valproate, and levetiracetam are equally effective in controlling seizure in the management of pediatric convulsive status epilepticus with a similar neurological outcome at three-month follow-up.

Acknowledgments: S Raja Deepa, JIPMER Campus, Puducherry, India for review and editing of the manuscript; Mr Rakesh Mohindra, Punjab University, Chandigarh, India. Mrs Thenmozhi M for helping with statistical analysis and Mrs. Harpreet Kaur, Punjab University, Chandigarh, India, Mrs. Neelima Chadha (Tulsi Das Library, PGIMER, Chandigarh, India) for helping with medical literature search.

Contributors: VV, RR, SM: Management of the patients and study supervision. VV: collected the data, reviewed the literature and drafted the first manuscript: SM: contributed for protocol development, review of literature and manuscript. RR: conceptualized the study, reviewed the literature and critically reviewed the manuscript. All authors approved the final version of the manuscript. RR: is the guarantor of the paper.

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WHAT THIS STUDY ADD?

- Phenytoin, valproate, and levetiracetam at a dose of 20 mg/kg infusion over 20 minute were equally efficacious in the management of pediatric convulsive status epilepticus not responding to single dose of lorazepam, and patients had similar neurological outcome at three-month follow-up.
Clinical Profile of Critical Pertussis in Children at a Pediatric Intensive Care Unit in Northern India

TK Kavitha1, Madhusudan Sampath1, Muralidharan Jayashree1, Vikas Gautam2 and Lucky Sangal3

From 1Pediatric Emergency and Intensive Care Units, 2Medical Microbiology, Post Graduate Institute of Medical Education and Research, Chandigarh, India; and 3NPO-VPD laboratories, WHO Country Office for India.

Objective: To delineate the clinical profile, complications, intensive care needs, and predictors of mortality in children with critical pertussis. Methods: Retrospective analysis of case records of children in the pediatric intensive care unit of a tertiary-care hospital, with a diagnosis of critical pertussis over 3 years. Diagnostic criteria included CDC case definition and confirmation by polymerase chain reaction (PCR), when available. Survivors and non-survivors were compared to identify predictors of mortality. Results: 36 records were analysed, most cases were infants (31, 86.1%). 10 (27.7%) were (below 6 weeks of age). In the rest, 16 (61.5%) were partially immunized or unimmunized against pertussis. Rapid breathing (88.9%), paroxysmal cough (86.1%) and apnea (41.7%) were common presenting complaints. Hypoxemia (97.2%), hyperleukocytosis (61.1%) and encephalopathy (52.8%) were common complications. Intensive care needs were mechanical ventilation in 11 (30.6%), vasoactive support in 7 (19.4%) and exchange transfusion in 3 (8.3%). Female gender, apnea, hyperleukocytosis, encephalopathy, need for vasoactive support, and mechanical ventilation predicted mortality. Conclusion: Pertussis demands attention due to its varied presentation, increased complications and higher mortality.

Key words: Apnea, DPT vaccine, Immunization, Outcome.

Pertussis has shown an alarming increase in global incidence recently [1]. Disease burden is high despite vaccination coverage of almost 85% among children [2]. Precise data from low- and middle-income countries (LMICs) are unavailable due to variable case definitions, limited awareness, inadequate infrastructure and weak surveillance systems. The exact cause of resurgence is unclear. Multiple factors like antigenic shifts in bacteria, waning vaccine immunity and reduced duration of protection by acellular pertussis vaccine have been implicated [1]. Studies suggest that source of infection may be identifiable only in about 27-43% of infant pertussis, and the most common source is usually mothers or siblings [3-5]. Critical pertussis is defined as pertussis requiring admission to an intensive care unit (ICU) or resulting in death [6]. It can lead to life-threatening complications like pulmonary arterial hypertension (PAH), respiratory failure and shock. Mortality rate ranges from 4.8-55% [7-13]. Data on critical pertussis is scarce, with very few reports from LMICs like India [13,14]. In this case series we describe the clinical profile, complications, intensive care needs and predictors of mortality in children with critical pertussis.

METHODS

This was a retrospective study in the Pediatric Intensive Care Unit of a tertiary-level teaching and referral hospital in Northern India. Cases were identified from the electronic database of the unit over a period of 3 years (2016-18), and those fulfilling the clinical and critical pertussis criteria as per WHO case definition were included. Clinical pertussis was defined as “any patient with cough lasting ≥2 weeks with at least one of the following symptoms – paroxysmal cough, inspiratory whoop or post-tussive vomiting” [2]. Critical pertussis was defined as pertussis requiring admission to an ICU or resulting in death. A total of 36 children with critical pertussis were retrieved for final analysis. No children were excluded. Demographic details (age, immunization status), presenting complaints, intensive care needs, complications, laboratory parameters and treatment modalities were recorded on a pre-designed performa. Hyperleukocytosis was defined as total leukocyte count (TLC) >50,000/µL [15]. Real time polymerase chain reaction (PCR) targeting IS481 and Ptxs1 was done in 28 children. Serology using IgM ELISA antipertussis toxin was also done in 21 children. All children received
azithromycin 10 mg/kg/day for 5 days and other supportive measures, which included respiratory and vasoactive support, and exchange transfusion depending on clinical need.

Statistical analysis: Chi-square and Fisher’s exact tests were used to compare proportions while Student t test and Mann Whitney test were used for means. Survivors and non-survivors were compared by univariate analysis to identify predictors of mortality. SPSS version 21 was used for statistical analysis.

RESULTS

Thirty-six cases (58.5% boys) of critical pertussis were enrolled. Median (IQR) age was 3.5 (1.5, 7) months. Most children were infants (n=31, 86.1%), with 10 (27.7%) being below six weeks and too young to be immunized against pertussis. The rest 16 (41.5%) were partially immunized or unimmunized against pertussis. Contact history with respiratory illness was evident in only two children. The major presenting symptoms were rapid breathing in 32 (88.9%), typical paroxysmal cough in 31 (86.1%) and apnea in 15 (41.7%) children. Most patients (35, 97.2%) had hypoxemia (SPO2<94% in room air) at admission.

Hyperleukocytosis and thrombocytosis were noted in 22 (61.1%) and 26 (72.2%) patients, respectively. Median (IQR) total leukocyte count (TLC) (per µL) was 64,000 (23050, 100037). Out of 28 children tested for pertussis RT-PCR, 19 (52.8%) were positive. Of the 8 children in whom PCR was not done, 1 was positive, 4 showed intermediate positivity and 3 were negative by ELISA. When tested for co-infections with other viruses, two children were positive for RSV, and all were negative for H1N1.

Hypoxemia (35, 97.2%) was the commonest complication, followed by hyperleukocytosis, encephalo-pathy (19, 52.8%), seizures (17, 47.2%), and acute kidney injury (6, 16.6%). Out of 11 children who under-went neuroimaging, multiple CNS infarcts were seen in 3 children and 8 were normal. Pulmonary arterial hyper-tension (PAH) was seen in 5 of 15 children who under-went echocardiography (33.3%). Intensive care needs were mechanical ventilation in 11 (30.6%), vasoactive support in 7 (19.4%) and exchange transfusion (ET) in 3 (8.3%). The most common indication for intubation was apneic spells in 9 children, out of which 4 were emergent during spells, and remaining 5 were elective for recurrent spells and hypoxemic events. Two children were intubated for encephalopathy. In majority (n=6), the intubation was done within 24 hours. The problems faced during ventilation were recurrent apnea (n=9), paroxysms of cough (n=9), air leaks (n=2), and ventilator associated pneumonia (n=1). Of the 7 ventilated children who underwent echocardiography, 4 had pulmonary arterial hypertension (PAH). Persistent hypoxemia and failure of conventional ventilation was seen in four children who required high frequency ventilation. Healthcare associated infections were seen in four children; ventilator-associated pneumonia in one child and blood stream infections in three children.

An increasing trend of hospital incidence (2 cases in 2016, 7 in 2017 and 27 in 2018), and mortality (no mortality in 2016, 1 in 2017 and 7 in 2018) of critical pertussis was observed over the 3 year study period. Eight patients (22.2%) with median (IQR) age of 3.5 (1.1, 5.5) months died; all were unimmunised including three who being <6 weeks old had yet to begin primary immunisation. All non survivors except one required mechanical ventilation. Major causes of death were hypoxemia and refractory shock (4), massive brain infarcts (2), secondary infection (1), and acute kidney injury and hyperkalemia (n=1 each). Female gender (P=0.04), apnea (P=0.01), hyperleukocytosis (P=0.01), encephalopathy (Glasgow coma score <14) (P=0.04), need for vasoactive support (P<0.001) and mechanical ventilation (P<0.001) were significantly associated with mortality on univariate analysis. PAH and need for ET did not determine mortality (Table I).

DISCUSSION

Our study has shown an increased hospital incidence of critical pertussis in young infants before completion of their primary vaccination. Major complications noted were hypoxemia, hyperleukocytosis, encephalopathy and seizures. PAH was present in few children. Intensive care needs were ventilation, vasoactive support and exchange transfusion. Female gender, apnea, hyperleukocytosis, encephalopathy, need for vasoactive support and mechanical ventilation were predictors of mortality.

The study: however, suffers from the inherent drawbacks of a retrospective analysis. Diagnostic tests like PCR could not be done in all. Details of maternal immunization status were unavailable and leukocyte count threshold for initiating exchange transfusion was not clearly defined.

Incidence of pertussis is increasing globally with periodic outbreaks being reported from different parts of the world including India [16-19]. Resurgence of a vaccine preventable disease like pertussis causing increasing hospitalization, costs and mortality is a
wrnisome trend, and has led to calls for relook of immunization schedules [16,20]. However, our patients were mostly young infants similar to previously published reports [8,13]. Over half of the patients were unimunized against pertussis. Critical pertussis occurring before primary immunization highlights the importance of maternal immunization against pertussis. Pertussis masquerading as any other acute respiratory infection often runs the risk of under-diagnosis and under-reporting. None of our patients were suspected to have pertussis nor received macrolide antibiotics before referral. Delayed diagnosis can make ‘benign’ pertussis ‘critical’ due to evolving complications. The prevalence of seizures, encephalopathy, hyperleukocytosis in this cohort was significantly higher compared to earlier studies on critical pertussis which have reported seizures in 9-16%, encephalopathy in nearly 20% and hyperleukocytosis in 21-35% of children [8-13]. One-third of the screened patients had PAH. Increased pulmonary vascular resistance is postulated to be secondary to obstruction of pulmonary vasculature by lymphocytes accumulation resulting from hyperleukocytosis [21]. Leucocytosis, especially in young infants, was shown to be associated with PAH, encephalopathy, greater risk of PICU admission and mortality but a causal link is yet to be proven [10,15]. Therefore screening of all patients of critical pertussis for PAH is essential. Children with critical pertussis often require mechanical ventilation and inotropic support for hypoxemia, apnoea, shock, PAH and encephalopathy [13]. Exchange transfusion for hyperleukocytosis especially if done before organ failure or immediately at the onset of shock was found to be associated with improved hemodynamics, hypoxemia and mortality in few case series and reports; the clear cut indications and mortality benefits are yet to be conclusively proven on a larger scale [14,22,23]. Mortality in critical pertussis varies between 4.8-55% [7-13]. Recognized predictors of mortality include younger age, comorbidities, need for ventilation, vasoactive use, PAH and a rapid course, similar to those identified in this study [7-13].

We have highlighted the important complications; intensive care needs and our limited experience with exchange transfusion in patients with hyperleukocytosis. To conclude, resurgence of pertussis demands attention due to its varied presentation, increased complications and higher mortality. The importance of clinical recognition and empirical treatment in such a setting cannot be overemphasised. Prospective studies on critical pertussis, its complications and the utility of various therapies are the need of the hour.

**Contributors:** TKK, MS: collected and analysed the data and prepared the initial draft of the manuscript; MJ designed the study, finalized the manuscript; VG and LS provided the laboratory support and gave critical inputs for the manuscript. All authors approved the final version.

**Funding:** None; **Competing interests:** None stated.

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Association of Early-Onset Sepsis and Vitamin D Deficiency in Term Neonates

POONAM SINGH AND VAISHALI CHAUDHARI
From Department of Pediatrics, Surat Municipal Institute of Medical Education and Research, Surat, India.

Objective: To determine if vitamin D status is affected in term neonates with early onset sepsis and its association with outcome. Methods: Study was done at a level 3 neonatal unit on 140 neonates. Term neonates with early onset sepsis (study group, 70 patients) and without sepsis (control group, 70 patients) were enrolled. Results: Mean neonatal vitamin D level in the study group was 16.00 (10.49) ng/mL and in the control group, was 29.07(8.36) ng/mL (P =0.061). In the study group 80% (n=56) babies had low vitamin D levels (<32 ng/mL) among whom 51.7% (n=29) had severe vitamin D deficiency (<11ng/mL). In the control group, 58.5% (n=41) had low vitamin D levels of whom, 9.8% (n=4) had severe vitamin D deficiency (P<0.001 and P<0.001, respectively). Mortality and highly probable sepsis were more common with vitamin D levels <11ng/mL in the study group (P= 0.005 and P=0.006, respectively). Conclusion: Vitamin D is deficient in neonates with early onset sepsis and is associated with increased sepsis severity and mortality.

Keywords: 25-OHD, Deficiency state, Sepsis severity.

Neonatal sepsis is an important cause of morbidity and mortality. It has been suggested that vitamin D might have a role in the optimal functioning of the innate immune system by inducing antimicrobial peptides in epithelial cells, neutrophils and macrophages [1,2]. Some studies suggest that vitamin D concentration in cord blood is associated with increased susceptibility to infections in newborns [3,4]. Some studies report a link between vitamin D deficiency and neonatal sepsis in term infants [5-8]. The present study was designed to assess the association of vitamin D deficiency and early onset sepsis in term babies.

METHODS
This prospective study was carried out in the NICU of a tertiary-care hospital between October, 2015 and September, 2016. Term neonates presenting within first 3 days of life with one or more of the following clinical features suggestive of sepsis were eligible for inclusion: temperature instability, apnea, need for supplemented oxygen, need for ventilation, tachycardia/bradycardia, hypotension, feeding intolerance, abdominal distension, and necrotizing enterocolitis. Neonates with history of maternal clinical chorioamnionitis, premature rupture of membranes, and major congenital abnormalities were excluded. In all enrolled neonates, serum C-reactive protein (CRP), white blood cell count, absolute neutrophil count, platelet count and blood culture were done. Highly probable sepsis was defined as at least three sepsis-related clinical signs, CRP >1mg/dL, alteration in at least two other blood tests listed above, irrespective of any isolates in blood culture. Probable sepsis was defined as less than 3 sepsis-related clinical signs, CRP>1 mg/dL, at least two other altered serum parameters in addition to CRP, and blood culture negative. Possible sepsis was defined as less than 3 sepsis-related clinical signs, CRP <1 mg/dL, alteration in less than two blood tests listed earlier and no isolates in blood culture. Neonates not fulfilling any of the above criteria were considered as no sepsis (Control group). Informed consent was obtained from the parents/guardians prior to enrolment. All data was recorded in pre-designed structured proforma. The study was approved by the institutional ethics committee. Blood samples were also taken for measurement of 25-hydroxyvitamin D (25-OHD) levels. Blood samples were separated and stored at -80 °C. Levels of 25-OHD were determined using ECLIA 411 Model with chemiluminescence system attached with ultraviolet detector. Vitamin D status was classified into three groups: Serum 25-OHD level <11ng/mL was severe deficiency, 11-32 ng/mL was insufficiency, and >32-100 ng/mL was adequate [10]. Complete blood count was performed using an automatic counter Sysmax. CRP was determined by CRP Kit by latex slide method with a detection limit of 0.6 mg/dL.

Statistical analysis: Data were analysed using . (SPSS,
version 20.0). The differences between groups were evaluated using chi-square test for qualitative data and t-test for independent sample for continuous data with normal distribution. ANOVA and Post Hoc test were other tests used. Values of $P < 0.05$ were considered statistically significant.

RESULTS

During the study period, 1431 neonates were admitted to the neonatal care unit, the final study group had 70 with sepsis, while 70 neonates without sepsis formed the control group. The baseline neonatal profile, mean weight, gender and Apgar scores were comparable in both groups. Neonatal vitamin D level was lower in all seasons (winter, summer and monsoon) in the study group ($P=0.02$, $0.03$ and $0.04$, respectively). This level was lowest in monsoon season. In the study group, 56 (80%) babies had low vitamin D levels (<32ng/mL) and in the control group only 41 (58.5%) had low vitamin D levels ($P<0.001$) (Table I). In the study group, mortality was higher in babies with vitamin D deficiency 15 (51.7%) as compared to babies with adequate level 1 (7%) ($P=0.005$) (Table II). Most common pathogens found in blood culture of patients with neonatal sepsis were Coagulase negative Staphylococcus Aureus (21.42%), Klebsiella (12.86%), and Acinetobacter (10%).

DISCUSSION

This observational study showed that neonatal vitamin D (25-OHD) levels were significantly lower in term infants with early onset sepsis in comparison to babies without sepsis. Severity of vitamin D deficiency was also associated with increased mortality and degree of sepsis. An important limitation of the study was that the maternal vitamin D status was not evaluated.

In our study, mean vitamin D levels were lower in the sepsis group as compared to the control group. Cetinkaya, et al. [6] and Kanth, et al. [7] also found low vitamin D levels in neonates with sepsis. Some other studies also support the observation that lower maternal and neonatal vitamin D levels are associated with early onset sepsis [6-8]. Similar to our results, Cetinkaya, et al. [6] found larger proportion of neonates in sepsis group having severe deficiency as compared to the control group [7]. As reported by previous researchers [6,7], we found that severe neonatal vitamin D deficiency was associated with higher severity of sepsis, higher mortality and culture positivity.

We conclude that vitamin D is deficient in neonates with early onset sepsis and is associated with increased sepsis severity and mortality.

Acknowledgements: We acknowledge the contribution in statistics to Dr Prakash Patel and Ms Swati Patel and to Dr Ajay Sethi for his inputs during the study.

Contributors: PS: conceived the study, conceptualized study design, supervised data collection and analysis, and reviewed the intellectual outcome: drafted and critically revised the manuscript; VC: prepared study design, carried out the study, enrolled patients, collected

---

Table I Profile of Neonates in the Study

<table>
<thead>
<tr>
<th>Variables</th>
<th>Study group (n=70)</th>
<th>Control group (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthweight, g *</td>
<td>2640 (480)</td>
<td>2580 (370)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>43 (61)</td>
<td>40 (57)</td>
</tr>
<tr>
<td>Apgar 1 min #</td>
<td>9 (9-10)</td>
<td>9 (9-10)</td>
</tr>
<tr>
<td>Apgar 5 min #</td>
<td>9 (9-10)</td>
<td>10 (9-10)</td>
</tr>
<tr>
<td>Vitamin D level (ng/mL)*</td>
<td>16.0 (10.5)</td>
<td>29.07 (8.4)</td>
</tr>
<tr>
<td>#Vitamin D‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;32 ng/mL, n (%)</td>
<td>56 (80)</td>
<td>41 (58.5)</td>
</tr>
<tr>
<td>&lt;11 ng/mL, n (%)</td>
<td>29 (51.7)</td>
<td>4 (9.8)</td>
</tr>
</tbody>
</table>

*mean (SD), # median (IQR); ‡P<0.001.

---

Table II Association Between Vitamin D Status and Outcome Among Neonates in the Study Group (N=70)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Deficiency n=29 (%)</th>
<th>Insufficiency n=27 (%)</th>
<th>Adequate n=14 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Death</td>
<td>15 (51.7)</td>
<td>1 (3.7)</td>
<td>1 (07)</td>
</tr>
<tr>
<td>Culture positive</td>
<td>19 (65.5)</td>
<td>8 (29.6)</td>
<td>5 (35.7)</td>
</tr>
<tr>
<td>*Sepsis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possible</td>
<td>07 (24.1)</td>
<td>10 (37)</td>
<td>7 (50)</td>
</tr>
<tr>
<td>Probable</td>
<td>04 (13.8)</td>
<td>12 (44.4)</td>
<td>3 (21.4)</td>
</tr>
<tr>
<td>Highly probable</td>
<td>18 (62.1)</td>
<td>5 (18.6)</td>
<td>4 (28.6)</td>
</tr>
</tbody>
</table>

*P<0.01; All values in No. (%); deficiency and insufficiency defined as serum vitamin D levels <11 ng/mL and 11-32 ng/mL, respectively.

WHAT THIS STUDY ADDS?

- Low vitamin D levels were found in term babies with early onset sepsis.
- Vitamin D-deficiency was associated with higher mortality in neonates with early onset sepsis.
data and prepared result: collected data, data analysis and drafted the manuscript. All authors have reviewed and approved of the final draft of the paper. Dr Poonam Singh will act as guarantor for the paper.

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**Competing Interest:** None stated.

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Wheezing in Preschool Children and Total IgE Levels: A Birth Cohort Study

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Objectives: To evaluate association between total IgE levels and wheezing in preschool children from India. Methods: Data were collected in a prospective birth cohort study related to wheezing till three years of age. Total IgE was measured at enrolment, at one year and two years of age and correlated with wheezing episodes. Results: A total of 310 (167 boys) children were enrolled. Total IgE levels increased with age ($P<0.001$). Overall, 101 (32.6%) children had 182 episodes of wheezing. The median (IQR) total IgE levels in children with wheezing and without wheezing were similar at one year [42.1 (12.7, 93.5) vs 41.9 (17.1, 96.7) kU/L; $P=0.39$] and two years of age [62.8 (32.4, 212.0) vs 75 (25.8, 173.0) kU/L, $P=0.92$]. Conclusion: Total IgE levels increased with age and were not different in preschool children with and without wheezing.

Keywords: Immunoglobin E, Rhonchi, Under-five wheezer.

About 50% children report at least one episode of wheezing by six years of age [1]. It is postulated that events including viral infections in first few years of life determine the occurrence of wheezing and asthma later in life [2,3]. There is a strong correlation of IgE levels and asthma at least in older children, but limited information about association of IgE levels and wheezing in preschool children viral respiratory tract infections are common. Studies from developed countries show variable association show between IgE levels and wheezing in young children [4-8]. Similar data are lacking from developing countries where atopy is not so common. The aim of our study was to evaluate association between total IgE levels and wheezing in preschool children from a birth cohort in India.

METHODS

This study was a part of a prospective birth cohort study where term appropriate for gestational age babies without adverse perinatal events were enrolled at birth. Baseline data (demographic profile, gestational age, anthropometry, physical findings, family history of asthma or allergy etc.) were collected. Acute respiratory infection (ARI) was defined as presence of cold or cough with or without fever, fast breathing or breathing difficulty. Children were followed-up at the hospital every 6 months. Parents were additionally asked to report to the hospital whenever they had ARI (breakthrough visit). Parents were contacted telephonically for any respiratory symptoms monthly. Each episode of respiratory symptoms was evaluated for presence of wheezing and for etiology. The primary objectives of the birth cohort study were to evaluate development of asthma at five years of age following ARI during infancy, to assess effect of ARI on pulmonary function, to generate normative data for infant pulmonary fuction test (PFT), and to study etiology of ARI. The data on etiology have been already published [9]. For index study, total IgE levels and episodes of wheezing were evaluated to assess for association. Total IgE levels were measured at enrolment, at one year of age, and at two year of age using ImmunoCAP Phadiatop (by Thermo Scientific, Sweden). Secondary outcomes were: total IgE levels in children with no, single or multiple episodes of wheezing; demographic characteristic in children with and without wheezing; and total IgE levels by onset of age of wheezing.

The episodes of illness when child had wheezing were recorded in follow-up till three years of age and were correlated with total IgE levels at different ages. Each wheezing episode was confirmed by a pediatrician and was managed as per unit’s policy. Blood samples were collected within two weeks of schedule time. If there was wheezing on the scheduled date of sampling, blood sample was collected after recovery. Elevated value of total IgE at birth, one year of age and two years of age was defined as values of more than 1.28 kU/L, 15.3 kU/L and 29.5 kU/L, respectively [10].
The study was approved by the ethics committee of our institute, and parents’ consent was taken before enrolment in the study.

**Statistical analysis:** Continuous data were reported as mean (SD) if normally distributed otherwise as median (IQR) and were compared using parametric and non-parametric tests as appropriate. Categorical data were presented as percentage and were compared using chi-square test. Total serum IgE levels at different age were compared in children with and without wheezing. STATA 12 software was used to analyze the data.

**RESULTS**

A total of 310 (169 male) children with mean (SD) gestational age of 267.9 (22.6) days and mean (SD) birth weight of 2648.2 (689.2) g were enrolled. One infant died of an unrelated cause. One hundred one (32.6%) children had 182 episodes of wheezing up to three years of follow up, of which 50 children had a single episode of wheezing. Majority (139, 76.4%) of wheezing episodes were detected during breakthrough visit and 43 (23.6%) episodes were detected during six monthly visits. The frequency of wheezing was not different in boys and girls.

Total IgE levels were available for 288, 255, and 219 children at baseline, one year, and two years of age, respectively and at all three time points for 189 children. A total of (9.0%), 191 (74.9%), and 159 (72.6%) children had abnormal total IgE levels at baseline, one year, and at two years of age, respectively. The median (IQR) total IgE values were significantly higher at two year than one year of age [72.7 (26.3, 184.0) and 42.1 (15.2, 94.8), respectively; \( P < 0.001 \)]. The total IgE levels were not different in boys and girls. The serum IgE levels in children with and without wheezing are shown in **Table I**.

The risk factors for wheezing, total IgE levels and the proportion of children having abnormally high IgE at birth, one year of age, and two years of age was not different among children with or without wheezing (Table II). The total IgE levels at one and two years of age were not different among children with or without history of asthma and other atopy in any family members (data not shown).

Total median (IQR) IgE levels were not different between no or one episode of wheezing \((n=259)\) versus more than one episode of wheezing \((n=51)\) at one year \([41.1 (16.7, 96.4) \text{ vs. } 42.5 (10.2, 75.6); \ P=0.34]\) and two years of age \([77.4 (26.3, 184.0) \text{ vs. } 54.3 (21.9, 147.0); \ P=0.43]\).

Out of total 182 wheezing episodes, 89 (48.9%) wheezing episodes occurred in 60 children below one years of age, 66 (36.3%) wheezing episodes occurred in 53 children in second year of life, and 27 (14.8%) wheezing episodes occurred in 20 children in third year of life. Total IgE levels were not different among children with and without wheezing by age of wheezing episodes (data not shown). Total IgE levels were above 100 kU/L in 58 (22.8%) and 90 (41.1%) children at one and two years of age respectively. There was no difference in wheezing in children having total IgE above 100 kU/L and less than 100 kU/L \((P=0.84)\).

**DISCUSSION**

In this cohort study, about one-third children had at least one episode of wheezing by three years of age, most of

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Wheezing ((n=101))</th>
<th>No wheezing ((n=310))</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>57 (56.4)</td>
<td>112 (53.6)</td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>15 (14.9)</td>
<td>21 (10.0)</td>
<td></td>
</tr>
<tr>
<td>Smoking at home</td>
<td>33 (32.7)</td>
<td>64 (30.8)</td>
<td></td>
</tr>
<tr>
<td>*Pet at home</td>
<td>12 (12.6)</td>
<td>25 (13.9)</td>
<td></td>
</tr>
<tr>
<td>‡Family history</td>
<td>48 (47.5)</td>
<td>96 (45.9)</td>
<td></td>
</tr>
<tr>
<td>*Birthweight (g)</td>
<td>2793.9 (314.1)</td>
<td>2778.1 (401.6)</td>
<td></td>
</tr>
</tbody>
</table>

*Data shown for total 95 and 180 children, respectively; †Data expressed as mean (SD); all \(P>0.05\); ‡History of asthma or atopy.

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**Table I Serum IgE Levels in Children With and Without Wheezing \((N=310)\)**

<table>
<thead>
<tr>
<th>Total IgE levels (kU/L), median (IQR)</th>
<th>No.</th>
<th>With wheezing</th>
<th>No.</th>
<th>Without wheezing</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 1 y of age</td>
<td>95</td>
<td>42.1 (12.7, 93.5)</td>
<td>160</td>
<td>41.9 (17.1, 96.7)</td>
<td>0.39</td>
</tr>
<tr>
<td>At 2 y of age</td>
<td>82</td>
<td>62.8 (32.4, 212.0)</td>
<td>137</td>
<td>75.0 (25.8, 173.0)</td>
<td>0.92</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Elevated IgE, n (%)</th>
<th>No.</th>
<th>With wheezing</th>
<th>No.</th>
<th>Without wheezing</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At birth</td>
<td>101</td>
<td>10 (10.5)</td>
<td>209</td>
<td>16 (8.3)</td>
<td>0.53</td>
</tr>
<tr>
<td>At 1 y of age</td>
<td>95</td>
<td>65 (68.4)</td>
<td>160</td>
<td>126 (78.8)</td>
<td>0.07</td>
</tr>
<tr>
<td>At 2 y of age</td>
<td>82</td>
<td>63 (76.8)</td>
<td>137</td>
<td>96 (70.1)</td>
<td>0.28</td>
</tr>
</tbody>
</table>
which were associated with ARI. There was no difference in total IgE levels in children with wheezing and without wheezing suggesting that all wheezing may not be IgE-mediated.

A limitation of the study was that allergen-specific IgE levels and skin prick test to look for presence of atopy were not done. It is reported that pollen-specific IgE or mite allergen-specific IgE contribute most to total IgE [6]. Details of allergic rhinitis, atopic dermatitis, allergic conjunctivitis or food allergy, exertion precipitated cough/dyspnea and frequency of use of paracetamol were not collected.

The association between total IgE levels and wheezing is not uniform. A few studies reported association between total IgE levels and wheezing [4,8,11-13] unlike other studies which reported no association [5,14-16]. Latter studies suggest that chronic airway inflammation triggered by a viral infection in early life may be risk factor for recurrent wheezing in young children. The absence of association between total IgE levels and wheezing in preschool children suggests that wheezing was a benign transient condition associated with viral respiratory tract infection and not related to asthma.

In the present study, the total IgE levels increased significantly with age unlike an earlier study [11]. In developing countries antibodies against parasitic infections like Ascaris have also been associated with wheezing and atopy in preschool children [17]. In the same study, active Trichuris trichiura infection was also associated with wheezing in preschool children [17]. Cross reactivity of IgE against Ascaris and mite has been described [18]. It is difficult to say if parasitic infections might have contributed to high total IgE levels in the present study as we did not look for helminthic infection and parasite specific IgE in this study.

Total IgE levels were high at birth possibly related to maternal factors, though maternal IgE levels were not measured.

Therefore, to conclude, wheezing in young children may not be IgE-mediated and it may be triggered by viral infections in congenitally small airways. It will be interesting to see whether development of asthma in this cohort at 5 years of age has any association with total IgE levels at birth, one and two years of age.

Contributors: KRJ: analyzed data, reviewed literature, and prepared initial draft of the manuscript; PK, SR, and BJ: enrolled patients, collected and analyzed data, and reviewed literature; AM: analyzed data, and reviewed literature; KM: analyzed data; SKK and RL: conceptualized and designed the study, and developed protocol. All authors had critically revised and approved the final version of the manuscript.

Funding: Department of Biotechnology (DBT), Government of India.

Competing interest: None stated.

REFERENCES

10. Kjellman NM, Johansson SG, Roth A. Serum IgE levels in healthy children quantified by a sandwich technique.

WHAT THIS STUDY ADDS?

• The total IgE levels were not different in young children with or without wheeze suggesting that wheezing in preschool children may not be IgE-mediated.
17. Alcántara-Neves NM, Badaró SJ, dos Santos MCA, Pontes-de-Carvalho L, Barreto ML. The presence of serum anti-Ascaris lumbricoides IgE antibodies and of Trichuris trichiura infection are risk factors for wheezing and/or atopy in preschool-aged Brazilian children. Respir Res. 2010;11:114.

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Refractory and Super-refractory Status Epilepticus

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Context: Refractory status epilepticus (RSE) and super-refractory status epilepticus (SRSE) are neurological emergencies with considerable mortality and morbidity. In this paper, we provide an overview of causes, evaluation, treatment, and consequences of RSE and SRSE, reflecting the lack of high-quality evidence to inform therapeutic approach. Sources: This is a narrative review based on personal practice and experience. Nevertheless, we searched MEDLINE (using PubMed and OvidSP vendors) and Cochrane central register of controlled trials, using appropriate keywords to incorporate recent evidence. Results: Refractory status epilepticus is commonly defined as an acute convulsive seizure that fails to respond to two or more anti-seizure medications including at least one non-benzodiazepine drug. Super-refractory status epilepticus is a status epilepticus that continues for ≥24 hours despite anesthetic treatment, or recurs on an attempted wean of the anesthetic regimen. Both can occur in patients known to have epilepsy or de novo, with increasing recognition of autoimmune and genetic causes. Electroencephalography monitoring is essential to monitor treatment response in refractory/super-refractory status epilepticus, and to diagnose non-convulsive status epilepticus. The mainstay of treatment for these disorders includes anesthetic infusions, primarily midazolam, ketamine, and pentobarbital. Dietary, immunological, and surgical treatments are viable in selected patients. Management is challenging due to multiple acute complications and long-term adverse consequences. Conclusions: We have provided a synopsis of best practices for diagnosis and management of refractory/super-refractory status epilepticus and highlighted the lack of sufficient high-quality evidence to drive decision making, ending with a brief foray into avenues for future research.

Keywords: Convulsive status epilepticus, Epilepsy, Management, Outcome.

Status epilepticus (SE) is a common pediatric neurological emergency. The definition of SE has evolved over time, to reconcile the likelihood of spontaneous seizure cessation based on pathophysiology, versus the operational urgency to achieve seizure termination and avoid adverse consequences. We have summarized some of the key definitions in Box 1. The temporal evolution of SE is conventionally divided into early (5-30 min), established (30-60 min), and refractory (≥60 min) phases [1].

There are two common definitions of refractory SE (RSE), which may operationally converge. These include a convulsive seizure lasting longer than 60 minutes, which may be continuous or intermittent without return to baseline mental status; and an acute convulsive seizure that fails to respond to ≥2 anti-seizure medications (ASMs) including at least one non-benzodiazepine ASM. In our experience, the latter criteria is more commonly used in practice. At present, there is a dearth of sufficient high-quality evidence to formulate a uniform management strategy for RSE, resulting in variability in treatment approaches and the choice of therapeutic endpoint(s).

Partly because of this, about 15%-35% of RSE patients fail to achieve desired treatment response, and progress to super-refractory SE (SRSE), which is defined as an SE that continues for 24 hours or more despite anesthetic treatment, or recurs on an attempted wean of the anesthetic regimen [2,3].

We, herein, provide an overview of RSE and SRSE. However, we have not reviewed the epidemiology of RSE/SRSE, because of insufficient data for these entities separate from SE. We have also not discussed the pathophysiology of drug-resistance in SE, because the relative importance of different molecular mechanisms remains uncertain at present, and does not inform treatment approach. Finally, our discussion is focused on RSE/SRSE evolving from a convulsive seizure with impaired awareness, and does not address epilepsy partialis continua.

CAUSES AND RISK FACTORS

The underlying causes of RSE/SRSE in a patient with no previous history of seizures, or possible triggers which may precipitate RSE/SRSE in a patient known to have
epilepsy, are similar to those responsible for the more common convulsive SE. In general, any pathology which can trigger an acute symptomatic seizure can cause an SE which may progress to an RSE/SRSE. This includes neurological and systemic infections, acute vascular events, traumatic brain injury, and immune, metabolic, or toxic encephalopathies.

Febrile SE: Lessons from FEBSTAT

In the pediatric population, prolonged febrile seizures constitute the most common subgroup and account for up to 35% of all episodes of SE [4]. The importance of recognizing and promptly managing febrile SE has been underscored by the FEBSTAT study. In this study, 71% of
patients with acute changes on brain magnetic resonance imaging (MRI) after febrile SE, were found to have obvious hippocampal sclerosis 1 year later [5,6]. Given the importance of hippocampal sclerosis as a substrate for drug-resistant temporal lobe epilepsy, this finding emphasizes the direct association between the two. Another important finding from FEBSTAT study was the association of seizure duration with the time to initial treatment with benzodiazepines (BDZs), where every 2.7 min delay in the initial treatment was associated with 1.3 min increase in seizure duration [6,7]. Another study which found shorter median duration of febrile SE (35 min) compared to FEBSTAT (68 min), potentially attributed it to shorter time to access emergency medical services and initial treatment [8].

**Infectious Causes**

The etiology of RSE/SRSE varies geographically, and studies from India have noted a predominance of infectious causes [9-11]. In a series of 148 adults with encephalitis, 18 were diagnosed with SE, predominantly in those with herpes simplex virus (HSV) infection or Japanese encephalitis [12]. Children were noted to be more susceptible to have encephalitis-related SE in this cohort. The diagnosis of HSV is important in SE/RSE patients, as treatment with acyclovir within 24 hours of onset has been shown to be associated with better prognosis [13]. A recent study reported convulsive SE in 41 patients with neurocysticercosis, although they did not progress to RSE/SRSE [14]. The duration of SE was found to be shorter in patients with single calcific lesion compared to those with degenerating cysts. In another study including 141 children presenting emergently with acute convulsive seizures, 49% were found to have neurocysticercosis, though again the progression to RSE was not reported [11]. There is a paucity of data on epidemiology of RSE/SRSE from India in other common infections including acute bacterial meningoencephalitis, cerebral malaria, and dengue. Differentiating acute symptomatic SE in a young child with a neurological infection, from a febrile SE, is a challenging and important consideration.

**Autoimmune and Genetic Etiologies**

Regarding RSE/SRSE, it is important to recognize two particular groups of diseases, which may prompt an etiology-specific treatment or prognostication early in the course of management. The first group includes autoimmune encephalitis. In children and adolescents, the leading autoimmune entity is anti-NMDA-receptor encephalitis, which can present with non-specific manifestations, such as, fever or headache in the prodromal stage. The next stage, involving the cerebral cortex, is the one which can present with RSE/SRSE in additional to behavioral symptoms. In children, these behavioral symptoms can take the form of new-onset temper tantrums in an otherwise well-adjusted child, unexplained episodes of aggression, and speech disturbances. Compared to the predominant temporal localization for seizures in adults with anti-NMDAR encephalitis, extra-temporal seizures, and sometimes even diffuse bilateral ictal onset can be seen in children, and should not exclude this consideration [15,16]. The other limbic encephalitis are also being increasingly recognized in children, and may often not occur as a para-neoplastic syndrome. In addition to seizures, which can progress to SE/RSE, other manifestations of limbic encephalitis can be relatively non-specific in children. The behavioral phenotype of limbic encephalitis in adults often consists of disturbances in recent memory, and affective symptoms including irritability, depression, or hallucinations. However, in children, non-specific disturbances of executive function (attention control, social inhibition, regulation of purposeful behavior) are often seen, and should be evaluated in a developmental context [17]. The second important etiologic subgroup of RSE/SRSE, which should be evaluated promptly, comprises of certain genetic epilepsies. These include, but are not limited to, Dravet syndrome and other sodium channelopathies, ring chromosome 20, pathogenic variants in polymerase-G or amino-acyl-tRNA synthetase genes affecting mitochondrial function, and Angelman syndrome [18].

**Seizure Triggers**

About 16-38% SE episodes occur in children with a prior diagnosis of epilepsy, with low anti-seizure medication levels being the most common risk factor [4]. Low levels of regular anti-seizure medicines can, in turn, result from lack of adherence, scheduled withdrawal, insufficient dose, interaction with other concurrent medications, or growth spurt, etc. Other common precipitants of SE include inter-current illness, exposure to a known trigger (e.g. sleep deprivation in some idiopathic generalized epilepsy syndromes), or metabolic decompensation.

**DIAGNOSTIC EVALUATION**

The goals of evaluation in RSE/SRSE include diagnostic verification, particularly in patients with subtle and non-convulsive SE (NCSE); monitoring for therapeutic efficacy; diagnosis of the underlying etiology and/or risk factors; and early recognition of multisystem complications. We have summarized these in Table I, and briefly discuss the role of electroencephalography (EEG) and neuroimaging below.

**EEG Monitoring**

The foremost utility of EEG monitoring is to detect
Table I  Selected Investigations Useful in Management of Refractory and Super-refractory Status Epilepticus

<table>
<thead>
<tr>
<th>Objective</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial stabilization</td>
<td>ABG, glucose, electrolytes, CBC, liver and renal function tests</td>
</tr>
<tr>
<td>Monitoring of seizure activity, and titration for treatment response</td>
<td>Electroencephalography</td>
</tr>
<tr>
<td>Etiology of RSE/SRSE</td>
<td></td>
</tr>
<tr>
<td>• Toxin screen</td>
<td></td>
</tr>
<tr>
<td>• Levels of anti-seizure medication</td>
<td></td>
</tr>
<tr>
<td>• Brain MRI (cerebrovascular diseases, tumors, malformations of cortical development, TBI, HIE, autoimmune encephalitis)</td>
<td></td>
</tr>
<tr>
<td>• Acquire MRS with MRI, plasma ammonia, lactate, pyruvate, acylcarnitine profile, plasma amino acids, urine organic acids (IEMs)</td>
<td></td>
</tr>
<tr>
<td>• CSF biochemistry, microscopy, culture, viral studies, neurotransmitter levels (CNS infections, neurotransmitter disorders, certain IEMs)</td>
<td></td>
</tr>
<tr>
<td>• Autoimmune encephalitis panel, CRP, ANA and other antibodies (Ro/SSA, La/SSB, Sm, RNP, dsDNA, anti-phospholipid, ANCA), C3, C4, serum cryoglobulins, serum immune electrophoresis, quantitative Ig levels, MR angiography (autoimmune encephalitis, vasculitis)</td>
<td></td>
</tr>
<tr>
<td>• Specialized muscle or liver tissue studies (suspected mitochondrial disorders)</td>
<td></td>
</tr>
<tr>
<td>• Chromosomal microarray and epilepsy next-generation sequencing panel (genetic causes)</td>
<td></td>
</tr>
<tr>
<td>• Brain biopsy (unknown cause)</td>
<td></td>
</tr>
<tr>
<td>Monitoring for treatment related complications</td>
<td>Related to ASMs: ASM levels, serum albumin</td>
</tr>
<tr>
<td>Monitoring for complications related to intensive care</td>
<td>Related to ketogenic diet: ABG, CBC, lipid profile, carnitine, ECG, gastro-intestinal motility studies, calcium, alkaline phosphatase, 25-OH-D levels, liver and renal function tests, levels of magnesium, selenium, copper, and zinc, coagulation screen, and serum beta-hydroxybutyrate levels for ketosis</td>
</tr>
<tr>
<td>Monitoring for complications related to intensive care</td>
<td>CXR (pulmonary edema, embolism, aspiration or ventilator-associated pneumonia)</td>
</tr>
<tr>
<td>• Brain MRI (hypoxic or vascular injury, cerebral edema)</td>
<td></td>
</tr>
<tr>
<td>• Biochemistry to monitor liver, kidney, and pancreatic function, and electrolyte levels</td>
<td></td>
</tr>
<tr>
<td>• Monitoring for disseminated coagulopathy, thrombophlebitis, rhabdomyolysis</td>
<td></td>
</tr>
<tr>
<td>• NCS/EMG (critical illness neuropathy)</td>
<td></td>
</tr>
<tr>
<td>• CBC, appropriate cultures (iatrogenic infections/sepsis)</td>
<td></td>
</tr>
<tr>
<td>• Calcium, alkaline phosphatase, x-rays, DEXA (bone health and fractures)</td>
<td></td>
</tr>
</tbody>
</table>


Etiologies or complications related to a particular investigation are provided in parenthesis. This list is not exhaustive, and should be guided by clinical judgement.

ongoing subclinical seizure or NCSE after the convulsive seizure has apparently terminated. Hence, professional societies have recommended continuous EEG monitoring to be initiated within 1 hour of SE, and continued for at least 24-48 hours, often longer in the presence of altered consciousness [19-21]. Although the EEG diagnosis of NCSE has been fraught with disagreement, recent studies have shown good diagnostic validity and inter-rater agreement for the Salzburg criteria [22,23]. In patients without known epileptic encephalopathy, occurrence of ≤2.5 Hz, or the ictal pattern limited to rhythmic slow waves, it is important to evaluate for electroencephalographic improvement with a bolus of intravenous BDZ; associated subclinical clinical manifestations; and typical spatiotemporal evolution in the morphology, frequency, or locus of the electroencephalographic pattern. The availability of synchronized video monitoring, allowing simultaneous review of video-EEG is important in such situations. The diagnosis of NCSE becomes more challenging in patients with a known epileptic encephalopathy. In such patients, diagnosis of NCSE requires evidence of a distinct increase in the locus, field,
or frequency of epileptiform discharges, and an obvious change in clinical state, or response to an intravenous BDZ bolus [23]. Hence, in these patients, it is important to have a good understanding of the baseline EEG pattern prior to the onset of RSE, based on a personal review of previous EEGs.

Other periodic and rhythmic EEG patterns, which do not meet the criteria for NCSE, are often labelled as lying on an interictal-ictal continuum. Although, this terminology is an useful EEG descriptor, its clinical significance remains uncertain. However, recognition of periodic patterns including lateralized periodic discharges (LPDs) or generalized periodic discharges (GPDs) may be important because of some association with the risk of seizure recurrence and certain specific conditions, such as, LPDs with stroke and herpes encephalitis [24]. Rarely, other EEG patterns may suggest a specific etiology, for example, extreme delta brushes in anti-NMDAR encephalitis.

The second most important role of EEG monitoring in the management of RSE/SRSE is to establish the therapeutic target. In these children, clinical evaluation for continued seizure activity is often non-informative, and becomes more so as the anesthetic infusions are increased, or neuromuscular blockers are used to facilitate airway control. At this point, the EEG usually shows electrographic bursts interrupted by periods of relative diffuse amplitude suppression. The optimal EEG target for treatment of RSE/SRSE is not strictly defined, and have included, suppression of seizures, varying degrees of suppression-burst pattern, and nearly complete EEG suppression [26]. Our practice is to aim for complete suppression of seizures, and achieve 50%-70% suppression ratio. Once this therapeutic goal is achieved, EEG monitoring is continued for 24-48 hours, when attempts are first made to wean off the infusions. EEG monitoring is important at this point to recognize the occurrence of emergence seizures or bursts with epileptiform elements, though these are not always treated individually.

**Neuroimaging**

The primary goal of neuroimaging in RSE/SRSE is to help identify the etiology, which in some cases, may lead to a specific urgent intervention. Secondly, identification of a potentially epileptogenic lesion may prompt consideration of emergency epilepsy surgery for RSE/SRSE in centers where such expertise is available. However, the interpretation of MRI studies early in the course of an RSE/SRSE can be challenging due to seizure-related or treatment-related changes. Specifically, it may be worthwhile to distinguish vasogenic edema reflected by T2/FLAIR hyper-intensities, from cytotoxic edema predominantly manifested as diffusion restriction. This is because vasogenic edema can sometimes point to an underlying etiology, whereas cytotoxic edema often represents compromised neuronal integrity from RSE/SRSE. In many patients there is an overlap between the two, and it is helpful to follow their neuroimaging over time. It is also important to look for confounding factors, for example, vigabatrin can be associated with both T2 hyper-intensities and restricted diffusion, predominantly in corpus callosum and deep gray structures [27,28]. In the FEBSTAT study, about 10% of children with a single febrile SE episode were found to have altered signal in the hippocampal region. After one year, 86% of them showed hippocampal volume loss and 71% had evidence of hippocampal sclerosis [5], emphasizing the need for longitudinal neuroimaging to ascertain neuronal injury in patients with RSE/SRSE.

**TREATMENT**

The primary goal of treatment is the termination of clinical and electrographic SE. However, the objectives of treatment in RSE/SRSE are somewhat different from those in early/established SE. In patients with early/established SE, the treatment efforts are focused on rapid seizure control to avoid neuronal injury. However, by definition, RSE represents a situation where pathophysiological mechanisms that support drug-response in established SE have been overwhelmed or altered, and hence, conventional treatment approaches are unlikely to be successful. Further, in SRSE, it is very likely that excitotoxic and other processes which compromise neuronal survival,
have already been activated. Hence, the goal of treatment in RSE/SRSE is to limit or reverse these processes, prevent their downstream consequences, and salvage end-organ function to the maximum possible extent [29]. Clinically, this means that the treatment plan should encompass not only seizure control, but to also avoid, anticipate, and manage multisystem dysfunction resulting from ongoing seizure activity, from medications, and from prolonged unconsciousness and immobility [30]. While the intensive care related to RSE/SRSE is outside the scope of this paper, we have briefly summarized the first and second line treatment for SE, and then discussed specific therapeutic approaches to RSE/SRSE in more detail.

First- and Second-line Drug Treatments

The American Epilepsy Society guidelines published in 2016, have synthesized available evidence for drug-treatment of early and established SE [31]. There is consensus that BDZs represent the initial treatment of choice for SE, with equipoise among intramuscular midazolam (MDZ), intravenous lorazepam (LZP), and intravenous diazepam (DZP). This equipoise is based on three class I randomized controlled trials, which are summarized below. The Veterans Affairs study compared four interventions including DZP followed by phenytoin (PHT), LZP, phenobarbital (PHB), and PHT alone [32]. There were no significant differences among these 4 interventions on intention-to-treat (ITT) analysis. However, on pairwise comparisons in patients with generalized convulsive SE, LZP was superior to PHT, for cessation of all motor and EEG seizure activity within 20 min of starting drug infusion and no recurrence of seizure activity during the next 40 min. The Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART), showed equivalence between intramuscular MDZ and intravenous LZP for the proportion of patients who achieved seizure termination without need for additional rescue [33]. However, the auto-injectors used in RAMPART are not available commercially, and whether conventional intramuscular MDZ injection will have similar efficacy is open to question. The third class I trial, showed equivalence between intravenous LZP and DZP for the proportions of patients with seizure termination, need for assisted ventilation, recurrence within 1 hour, and time to SE termination [34].

Only when these three options are not available, or not feasible due to challenges in achieving intravenous access in a convulsing child, other treatments may be considered, including rectal DZP, intranasal MDZ, and buccal MDZ. A network meta-analysis of 16 studies, specifically looking at non-venous treatments for acute convulsive seizures, found intramuscular and intranasal MDZ to be superior to other comparators for clinically relevant outcomes [35]. Specifically, this meta-analysis excluded data from RAMPART in their quantitative synthesis, thus independently supporting the efficacy of conventional intramuscular MDZ and encouraging the use of intranasal MDZ. From a practical standpoint, MDZ has the advantage of not needing refrigeration for storage. In US, MDZ nasal spray has been recently approved to treat seizure clusters and acute repetitive seizures [36]. Intranasal formulations of DZP and rapid systemic delivery of alprazolam (staccato alprazolam) by inhalation of thermally generated aerosol from a single-use hand-held device, are currently undergoing evaluation [37,38].

Appropriate first-line drug-treatment results in seizure termination in about 65% of patients. However, the subsequent choice of treatment is not driven by rigorous evidence. Traditionally, intravenous PHT has been the most commonly used 2nd line treatment for SE. Fosphenytoin (FOS) has been preferred over PHT, due to the ability for faster infusion, less risk of cardiac arrhythmias, and decreased incidence of local tissue reaction. However, a meta-analysis of 22 studies has found the efficacy of PHT to be below, though not significantly, to that of valproate (VPA), PHB, and levetiracetam (LEV) [39]. This meta-analysis also concluded that there is insufficient data for the use of lacosamide (LAC) in the treatment of SE. Recently, two different open-label trials: ConSEPT study from Australia and New Zealand, and EcLiPSE study from United Kingdom, have compared LEV and PHT in children with BDZ-refractory SE [40,41]. Clinical cessation of seizure activity 5 min after infusions were not statistically different between the two groups. Overall, 50%-70% of participants achieved primary efficacy endpoint. An ongoing trial in US, Established Status Epilepticus Treatment Trial (ESETT), is also comparing LEV, FOS, and VPA [42]. Given the lack of class I trials, decisions about 2nd line treatment are often based on local availability, cost, and most importantly patient-specific factors.

In addition to medical stabilization, the treatment of early/established SE proceeds concurrently with attempts to ascertain the etiology of SE. The specific treatments are driven by presumptive or definite etiology, often determined by local epidemiology, and investigative resources. A few suggestions are offered in Table II.

Third-line Treatment: Drug Therapy for RSE

There is a further paucity of clinical trials for drug treatment of RSE. Designing comparative effectiveness trials in this population has been challenging due to several reasons, including heterogeneity of 1st and 2nd line treatment choices, concurrent use of multiple other
medications affecting the nervous system, variability in the time course of administration of different medications, and the level of supportive intensive care. This is exemplified by a multicenter trial which was terminated inconclusively, because only 14 patients could be recruited over 3 years, against an estimated sample size of 150 [43]. Another trial of brexanolone (an aqueous formulation of the neuroactive steroid allopregnanolone) in 25 patients with SRSE was also inconclusive regarding efficacy end point, though it showed reasonable tolerability [44].

Conventionally, the three most commonly used anesthetic agents for the treatment of RSE include MDZ, short-acting barbiturates (pentobarbital/thiopentone), and propofol (Table III). Currently, MDZ is perhaps the most commonly used drug for RSE due to faster onset of action and short duration of effect [45]. However, use of MDZ in RSE/SRSE is fraught with several issues including development of tolerance, prolonged half-life with continued use, and potential for interactions with other drugs, nephrotoxicity, hepatotoxicity, and cardio-respiratory depression [45,46]. Several studies have reported on the use of MDZ for RSE/SRSE, using different doses and treatment targets, as reviewed elsewhere [45]. A meta-analysis including 111 children showed that MDZ was as effective as other coma inducing medications, but had a lower mortality [47]. However, another study that compared MDZ and DZP in 40 children and found a similar efficacy (86% and 89%, respectively), reported MDZ to be associated with a higher recurrence (57% vs 16%) and higher mortality (38% vs 10.5%) [48]. Seizure control has been reported as occurring within 0.3-1.1 hours [45]. Breakthrough seizures have been reported in 47-57% of patients [49].

To compare, barbiturates have been used for the longest period, and believed to have higher efficacy. A meta-analysis including 193 adults with RSE compared pentobarbital, MDZ, and propofol. Although pentobarbital was associated with a significantly lower incidence of short-term treatment failure, breakthrough seizures, and the need to change to a different medication, it was also associated with a significantly higher frequency

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Suggested treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic disturbances</td>
<td>Hypoglycemia, hyponatremia, hypocalcemia, hypomagnesemia, other electrolyte disturbances</td>
</tr>
<tr>
<td>Inborn errors of metabolism or genetic causes</td>
<td>Alper’s syndrome (POLG and ARS variants)</td>
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<td></td>
<td>Dravet’s syndrome</td>
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<td></td>
<td>Presumptive suspicion</td>
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<tr>
<td>Traumatic brain injury</td>
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<tr>
<td>Febrile status epilepticus</td>
<td></td>
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<tr>
<td>Infections</td>
<td>Herpes simplex virus encephalitis</td>
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<td></td>
<td>Neurocysticercosis</td>
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<tr>
<td></td>
<td>Cerebral malaria</td>
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<tr>
<td></td>
<td>Acute bacterial meningitis</td>
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<tr>
<td></td>
<td>Bartonella encephalitis</td>
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<tr>
<td>Autoimmune encephalitis</td>
<td></td>
</tr>
<tr>
<td>Psychogenic status epilepticus</td>
<td></td>
</tr>
<tr>
<td>Toxic</td>
<td>Theophylline ingestion</td>
</tr>
</tbody>
</table>

This list is not exhaustive and should be modified according to local epidemiology and available resources.
of hypotension [50]. One of the important confounding factors in this study was that the target of treatment in patients receiving pentobarbital tended to be burst-suppression, while it was limited to seizure suppression in those treated with MDZ and propofol. In pediatric RSE/SRSE the efficacy of pentobarbital has been reported to be 74-100% in heterogeneous studies [47,51]. Some experts believe that barbiturates have a neuroprotective effect and have an additional anti-seizure efficacy from their ability to lower core body temperature [52]. However, barbiturates have more potent cardiorespiratory suppression, immunosuppression, longer half-life with storage in the lipid compartment resulting in slow recovery, and problems of auto-induction and zero-order kinetics. Intravenous formulations of pentobarbital also contain propylene glycol, which at the high cumulative doses necessary to achieve burst suppression, may cause hyperosmolality and lactic acidosis that can progress to cardiac arrhythmias, refractory hypotension, renal dysfunction, and multi-organ failure [53]. It is possible that advances in intensive care, and the increasing practice for pre-emptive control of ventilation and perfusion, may help mitigate some of these challenges.

In adults, propofol is used for management of RSE/SRSE due to its quick onset of action and prompt recovery on withdrawal. Studies in adults have shown that propofol infusion terminates RSE/SRSE in 67% of patients [54]. Although propofol induces burst-suppression within 35 minutes of initiation, frequent titration may be needed to maintain adequate suppression [55]. A retrospective study of 33 children aged 4 months to 15 years with RSE reported that propofol was more effective than thiopental in terminating seizures (64% vs 55%). However, adverse effects including rhabdomyolysis and hypertriglyceridemia, prompted discontinuation in 18% of patients, with recovery after discontinuation of propofol [56]. Use of propofol has been restricted in children due to the risk of

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism of action</th>
<th>Initial dose</th>
<th>Titration</th>
<th>Usual dose</th>
<th>Absolute maximum rate or concentration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>GABA receptor agonist</td>
<td>0.2 mg/kg bolus, then 0.05-0.2 mg/kg/h</td>
<td>Bolus 0.2 mg/kg up to 10 mg and increase by 0.2 mg/kg every 15-20 min until burst suppression</td>
<td>0.05-0.2 mg/kg/h</td>
<td>3.3 mg/kg/h to max total dose of 100 mg/h</td>
<td>Monitor for respiratory depression, hypotension, rhabdomyolysis, metabolic acidosis, withdraw slowly</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>GABA receptor agonist</td>
<td>5 mg/kg bolus, then 0.5-1 mg/kg/h</td>
<td>Bolus 5 mg/kg and increase by 0.5 mg/kg/h every 15-20 min until burst suppression</td>
<td>0.5-3 mg/kg/h</td>
<td>10 mg/kg/h (brief duration only)</td>
<td>Monitor for propylene glycol toxicity - dose and duration dependent (serum Osm and Osm gap, pH, lactic acid, BUN, SCr and EKG)</td>
</tr>
<tr>
<td>Propofol</td>
<td>GABA receptor agonist</td>
<td>2.5-3.5 mg/kg bolus, then 25-100 mcg/kg/min</td>
<td>Bolus 3 mg/kg and increase by 25 mcg/kg/min every 15-20 min until burst suppression</td>
<td>15-200 mcg/kg/min Max dose 4 mcg/kg/h per package insert</td>
<td>300 mcg/kg/min</td>
<td>Requires propofol consent before use, Monitor BP, Monitor triglycerides, pancreatitis, PRIS; Calculate lipid load from propofol into nutrition calculations; Arterial line and central access strongly recommended – will get hypotensive</td>
</tr>
<tr>
<td>Ketamine</td>
<td>NMDA receptor antagonist</td>
<td>0.5-1 mg/kg/h</td>
<td>Bolus 0.5 mg/kg and increase dose by 0.5 mg/kg/h every 15-20 min until burst suppression</td>
<td>2-3 mg/kg/h</td>
<td>7.5 mg/kg/h</td>
<td>Co-administer with benzodiazepine (or barbiturate) to prevent dissociative syndrome; Monitor BP; HR (typically see increases on initiation)</td>
</tr>
</tbody>
</table>
propofol infusion syndrome (cardiac failure, rhabdomyolysis, metabolic acidosis, renal failure, and sometimes death) and propensity to induce dyskinesias which can mimic breakthrough seizures [57]. Risk factors reported to be associated with a higher likelihood of the infusion syndrome include high doses, prolonged use, concurrent use of catecholamines and corticosteroids, and possibly malnutrition. However, there have been some concerns that this syndrome may not be limited to propofol, and could in fact, result from drug-induced cerebral suppression [58]. Also relevant to pediatric practice are the reported fatalities on concurrent use of propofol and ketogenic diet (KD) [59].

Ketamine

Acceptance for the use of ketamine in RSE/SRSE has been steadily increasing due to favorable hemodynamics and a different mechanism of action than conventional anesthetics. Given the GABA receptor endocytosis in RSE/SRSE, and the NMDA glutamate receptor antagonism of ketamine, there is a theoretical advantage for its use instead of, or more commonly in addition to, other anesthetic agents. A systematic review of 25 class IV studies analyzed 244 SE episodes (37 in children) treated with ketamine [60]. Although authors reported 73% of children to “respond”, the heterogeneity in the definition of response was not addressed. Our practice is to start with MDZ infusion, and optimize it to achieve seizure suppression and >50% burst suppression. In non-responders, we then consider ketamine concurrent to MDZ. In patients who do not respond, we finally start pentobarbital and wean off MDZ and ketamine (Fig. 1). This is different from published multicenter experience from US, where ketamine was typically used after pentobarbital [61]. Salient pharmacological aspects of these drugs are summarized in Table III.

Therapeutic Target for RSE

As we have already alluded, there is a lack of consensus regarding optimal target for treatment of RSE/SRSE. Different therapeutic endpoints have included seizure suppression, burst suppression, or electro-cerebral silence. Moreover, the extent of burst-suppression that is associated with best outcomes, remains undefined [62]. This results in variability in clinical practice as shown by a study including 35 adult RSE patients, which reported that patients remained within the target suppression range (defined as 65-95%) only 0-29% (median 8%) of the total time under treatment [63]. Our practice is to increase infusions rapidly to achieve a suppression ratio of 50-70% and complete seizure control, as soon as possible after failure of 2nd line treatment, and to frequently review EEG to ensure that this degree of suppression is maintained.

We try to wean off anesthetic infusions once this treatment target is maintained for 24-48 hours. However, this duration is not based on rigorous evidence, and a shorter duration of burst suppression may be beneficial in some patients, whereas several cycles may be needed in patients with SRSE. Longer pharmacological coma of up to 5-7 days may have to be tolerated in particularly challenging cases. Simultaneously, additional ASMs preferably with complimentary mechanisms of action, short half-life, and low incidence of drug inter-actions, should be added to facilitate ongoing seizure suppression and smooth weaning of infusions. Topira-mate, LEV, LAC, and more recently, brivaracetam and perampanel have been used for this purpose [26].

The effectiveness of this empirical practice was recently assessed in a cohort of 111 RSE patients recruited prospectively over two years in an observational study. MDZ was the most frequently used initial anesthetic agent (78%), and pentobarbital was most frequently used agent after MDZ failure (82%) [64]. Treating physicians used up to four cycles of serial anesthetic therapy in these patients, and seizure termination was achieved in 94% patients by the second cycle. However, other studies have shown regional differences in the use of therapeutic coma for RSE treatment, lack of effect on overall mortality, and increased length of hospital stay, related costs, and adverse effects [65,66].

A suggested protocol for management of RSE/SRSE, based on the practice at authors’ institutions is provided as Fig. 1. This protocol is applicable only to patients >29 days of age. Given the lack of class I evidence, modifications to this protocol driven by local epidemiology and resources are strongly encouraged. Treatments other than anesthetic infusions may be considered earlier based on suspected/proven etiology of status epilepticus.

Additional Treatment Options

Patients with RSE, particularly after failure of first anesthetic infusion, or those with SRSE, represent a desperate situation for the clinical team. Hence, myriad approaches are brought upon to control the RSE/SRSE, often based on limited experience. These diverse treatments have been discussed elsewhere [67]. The relative position of these modalities in the treatment of SRSE has to be individualized according to the patient and the clinical resources.

Ketogenic Diet

Among these approaches, the most promising appears to be ketogenic diet (KD), partly due to its potential for undermining pathophysiology of RSE/SRSE [68,69]. A
IV midazolam:
- Give 0.2 mg/kg bolus (maximum 10 mg), then start infusion at 0.2 mg/kg/h (maximum 10 mg/h)
- Increase infusion rate by 0.2 mg/kg/h (maximum 10 mg/h) every 10 minutes until target burst suppression or reach a dose of 2 mg/kg/h (maximum 100 mg/h)
- Prepare to add IV ketamine when midazolam infusion reaches 1.6 mg/kg/h
- Perform endotracheal intubation if not already done
- Start continuous EEG monitoring
- Transfer to pediatric ICU

Therapeutic target not achieved

Add IV ketamine:
- Start infusion at 0.5 mg/kg/h
- Increase infusion rate by 0.5 mg/kg/h every 15-20 minutes until target burst suppression or maximum dose of 7.5 mg/kg/h
- Prepare to add IV pentobarbital infusion when IV ketamine infusion reaches 6 mg/kg/h

Therapeutic target not achieved

IV pentobarbital:
- Give 5 mg/kg bolus, then start infusion at 1 mg/kg/h
- Increase infusion rate by 0.5 mg/kg/h every 15-20 minutes until target burst suppression or maximum dose of 3 mg/kg/h
- Decrease midazolam infusion rate to 1 mg/kg/h at the start of pentobarbital infusion, stop MDZ after first increase of pentobarbital infusion to 1.5 mg/kg/h
- Consider decreasing ketamine infusion rate also at this point

Therapeutic target not achieved

Consider other therapies (see text for details):
- Ketogenic diet
- Immunotherapy (corticosteroids, IVIg, plasmapheresis)
- Pyridoxine (if not already tried)
- Epilepsy surgery consultation

Therapeutic target achieved

Target of treatment:
- Complete suppression of seizures
- EEG burst suppression around 70% (never <50%)

Maintain burst suppression:
- Initial: 24-48 hours
- Repeated: 48-72 hours

Weaning continuous infusions:
- ≤48 hours duration: wean over 6-12 hours, decrease rate by 15-30% every 2 hours
- >48 hours duration: slow wean, decrease rate by 15-30% every 6-12 hours
- Consider adding scheduled benzodiazepines or barbiturates for withdrawal for infusions >5 days

Add maintenance anti-seizure medications:
- Use doses at high end of therapeutic range
- Consider combinations with multiple different mechanisms

Fig. 1 A suggested protocol for management of refractory/super-refractory status epilepticus.
study including 14 pediatric patients reported electrographic seizure resolution and ≥50% suppression in 10 patients within 7 days of starting KD [70]. In 11/14 patients, continuous infusions could be weaned off within two weeks of starting KD. However, the authors noted under-utilization of and delay in starting KD. Other series with 8–17 patients have also reported seizure resolution within 7 days of starting KD in 20–90% patients [67,70]. KD is typically administered via enteral route, though ketogenic parenteral nutrition has been used in some cases, both in 4:1 ratio. However, keto- 

tis may sometimes be difficult to achieve with concomitant barbiturate infusions which contain propylene glycol that is metabolized to lctaldehyde and then to lactic acid. Common reported adverse effects of KD have included metabolic derangements like hypoglycemia; and gastrointestinal symptoms like emesis.

Surgery
In patients with a potentially epileptogenic brain lesion and concordant neurophysiology, an urgent epilepsy surgery may be considered, if such expertise is readily available. However, such decisions also incorporate the location, size, and nature of MRI lesion(s); and functional significance of surrounding cortex, which may require intracranial EEG evaluation and electrical stimulation mapping. Surgical decision-making becomes more challenging in MRI-negative RSE/SRSE or discordant neurophysiological data. Functional imaging is often confounded in such cases by ongoing ictal activity and concurrent anesthetic infusions. In some cases, palliative options like vagus nerve stimulation, or corpus callosotomy may be considered. Non-invasive neuro-stimulation, particularly with transcranial magnetic stimulation, are emerging modalities for interrupting RSE/SRSE, which may be useful in future.

Other Approaches
Among other modalities, therapeutic hypothermia is the only intervention tested in a randomized controlled trial for RSE/SRSE management. However, such trials, including the HYBERNATUS study, found the efficacy of hypothermia to be no better than placebo for RSE/SRSE, and raised concerns about its safety [67,71]. Immunotherapy (including any combination of steroids, intravenous immunoglobulins, or plasma exchange) may be helpful in known autoimmune epilepsies or entities with presumed immunological basis, such as febrile-infection related epilepsy syndrome (FIRES). At present, there is insufficient evidence for or against the use of immunotherapy in other RSE/SRSE patients. Similarly, there is no evidence for use of magnesium and pyridoxine outside of specific indications. These specific scenarios include using magnesium for acute convulsive seizures in eclampsia, and pyridoxine for suspected functional antiquitin deficiency or isoniazid toxicity.

Inhalational Anesthetics
There is limited experience for the use of inhaled anesthetics, primarily isoflurane and dexflurane, late in SRSE unresponsive to MDZ, propofol, and pentobarbital. In published cases, both isoflurane and dexflurane were effective in stopping seizures and achieving burst suppression; however, seizures recurred frequently after discontinuation. Complications of isoflurane and dexflurane have included hypotension, atelectasis, infections, paralytic ileus, and deep vein thrombosis; with death in 3/7 patients in one series [72]. In a recent case report, two patients with prolonged isoflurane use showed MRI changes in the thalamus and cerebellum, raising concerns for neurotoxicity [73]. More frequent hippocampal changes on MRI were seen in patients receiving isoflurane for RSE compared to matched controls that received only intravenous anesthetics; with these changes being related to longer duration of isoflurane use [74]. Given the logistical difficulties and high incidence of complications with prolonged use of inhalational anesthetics, the risk/benefit should be carefully considered before pursuing this course of therapy.

CONSEQUENCES OF RSE/SRSE
The adverse consequences of RSE/SRSE can be divided into immediate complications and longer term neuro- morbidity and mortality (Web Table 1). The interim complications mainly result from aberrant pathophysiological processes that are often initiated in an attempt to control the prolonged seizure but may fail or get out-of-hand and result in neuronal injury. Additionally, patients with RSE/SRSE also face complications resulting from its treatment and those from prolonged intensive care, as summarized in Web Table 1. More protracted consequences of RSE/SRSE are conventionally classified into short-term (during hospitalization or within 30 days of onset of SE) and long-term (within 10 years following initial survival 30 days after SE onset).

In a multicenter Canadian study of 374 patients with newly diagnosed epilepsy, occurrence of convulsive SE in 22 children was associated with poor health-related quality of life after 24 months follow-up [75]. In general, RSE/SRSE have significantly higher morbidity and mortality compared to SE of shorter duration. In children, RSE is associated with mortality in 11%-44% of patients and long-term neurological deficits in 25%-100% of the survivors [76-79]. The fatality of convulsive SE was 11%
in the north London study, with cumulative incidence of epilepsy, intellectual disability, and motor impairment of 25%, 12%, and 5%, respectively in survivors after a median follow-up of 9 years [78,79]. This study also reported motor and intellectual disability to be more prevalent in patients with pre-existing epilepsy and neurologic disability. Other relatively smaller studies of pediatric RSE have reported mortality from 16% to 44%, and sequelae in 25%-100% of survivors [47,76,80]. Neurological sequelae of RSE/SRSE appear to have relatively higher incidence in infants. In a large prospective study with mean follow-up of 13.2 months, the incidence of neurological deficits attributable to convulsive SE was 29% in infants ≤1 year of age, 11% in children 1-3 years of age, and 6% in children >3 years of age [81].

The risk of subsequent development of epilepsy is 25%-40% within 2 years after an RSE/SRSE episode, with a higher propensity in those with symptomatic causes [82]. The risk of recurrent SE is estimated to be about 20% within 4 years of the first RSE episode, with the highest risk in the first year. Progressive and remote symptomatic etiologies are associated with a higher risk for recurrent SE compared to febrile SE or acute symptomatic SE [83]. Long term adverse behavioral outcomes are also prevalent. After a mean 8 years of follow-up in the North London cohort, 37% SE patients were noted to have behavioral issues and 28% received a psychiatric diagnosis such as autism, attention deficit hyperactivity disorder, pervasive developmental disorder not otherwise specified, and developmental coordination disorder [84].

Several studies have reported age and etiology to be major determinants of both short-term and long-term mortality in SE [4,85]. A systematic review found mortality to be lower in children as compared to adults and elderly, with short-term mortality up to 9% and long-term mortality up to 7% [4]. Amongst children, infants ≤1 year of age had the highest short-term mortality, up to 18% [4]. Most SE-related deaths in the short term have been noted to occur in children with acute symptomatic etiology [85]. In a cohort study from Kenya, 23% of children with confirmed CSE died before discharge, with 75% of the deaths occurring within 48 hours of onset of SE[86].

Avenues for Future Research

RSE/SRSE presents a host of important unanswered clinical conundrums which have significant potential to impact patient care. Perhaps the foremost among these is to generate randomized, blinded, and adequately controlled evidence for various treatment regimens. Secondly, the optimal target for treatment needs to be defined. This will require a careful evaluation of EEG biomarkers for outcomes of RSE/SRSE. Thirdly, it is desirable to develop multicenter registries of RSE/SRSE with longitudinal data, which can be harnessed for predictive modelling of outcomes. There are unique challenges and opportunities in this regard for pediatricians and neurologists in India. There is a need to generate data about epidemiology, causes, diagnostic, and therapeutic modalities and their yield in India to develop targeted strategies for intervention that are specific to local circumstances.

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Intravenous ketamine in status epilepticus: Efficacy and safety of ketogenic diet for refractory status epilepticus. Epilepsy Res. 2018;144:1-6.


### Web Table I Multisystem Complications of Refractory and Super-refractory Status Epilepticus

<table>
<thead>
<tr>
<th>Related to refractory/super-refractory status epilepticus</th>
<th>Related to drug treatment</th>
<th>Related to prolonged intensive care</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory</strong></td>
<td></td>
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<tr>
<td>Apnea</td>
<td></td>
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</tr>
<tr>
<td>• Acute apnea after a prolonged seizure without antecedent abnormal breathing pattern should alert for a rapidly evolving posterior fossa lesion</td>
<td>Respiratory depression</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Abnormal breathing patterns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• May cause ineffective ventilation to the point of respiratory acidosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cheyne Stokes breathing: waxing waning hyperpnoea, regularly alternating with shorter period of apnea; may be seen in large supra-tentorial lesion(s), deep seated cerebral or diencephalic lesions e.g. subdural hematomas, infarcts, or meningitis, and certain metabolic disturbances. Important to rule out co-existent pulmonary disease.</td>
<td></td>
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</tr>
<tr>
<td>• Central neurogenic hyperventilation: suggests a lesion in lower mid-brain and/or upper pons; important to differentiate from hyperventilation due to medical reasons e.g. Kussmaul’s breathing of metabolic acidosis.</td>
<td></td>
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</tr>
<tr>
<td>• Apneustic breathing: usually seen with low pontine lesions e.g. basilar artery occlusion.</td>
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<td>• Chaotic irregularly interrupted breathing rhythm: each breath varying in depth and rate, may suggest a lesion of dorso-medial part of medulla.</td>
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<tr>
<td><strong>Aspiration</strong></td>
<td></td>
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<tr>
<td>Airway compromise</td>
<td></td>
<td></td>
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<tr>
<td>• Secretions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Hypotonia of tongue or oropharynx</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Non-cardiogenic pulmonary edema</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Hemodynamic</strong></td>
<td></td>
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<tr>
<td>Cardiac arrhythmias</td>
<td>Hypotension</td>
<td></td>
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<tr>
<td>Cardiac failure</td>
<td>Cardiac arrhythmias</td>
<td></td>
</tr>
<tr>
<td>Shock</td>
<td>Cardiac failure</td>
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<tr>
<td>Left ventricular stunning</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myoglobinuria</td>
<td>Rhabdomyolysis</td>
<td>Contractures</td>
</tr>
<tr>
<td>• May cause oliguria or acute tubular necrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Consider urinary alkalization if myoglobinuria is detected or serum creatine kinase is &gt;10 times upper limit of normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td></td>
<td></td>
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<tr>
<td>Joint dislocations: particularly posterior dislocation of shoulder joint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fractures: long bones, vertebral compression fractures</td>
<td></td>
<td></td>
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<tr>
<td>Tongue bites</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Electrolyte abnormalities</strong></td>
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<td></td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Lactic acidosis</td>
<td></td>
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<tr>
<td>Hyponatremia</td>
<td>Hyperosmolality</td>
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<tr>
<td>Metabolic acidosis</td>
<td>Metabolic acidosis</td>
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<tr>
<td>Hyperkalemia</td>
<td>Hyperkalemia</td>
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<tr>
<td>Diabetes insipidus</td>
<td>Diabetes insipidus</td>
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<tr>
<td>Acute neurological</td>
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<tr>
<td>Cerebral edema</td>
<td>Sedation</td>
<td>Critical illness</td>
</tr>
<tr>
<td>Central hyperthermia</td>
<td>Dependence/withdrawal</td>
<td>myopathy</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
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<tr>
<td>Paralytic ileus</td>
<td>Hyperammononemia</td>
<td>Pseudomembranous colitis</td>
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<tr>
<td>Hyperammonemia</td>
<td></td>
<td></td>
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<tr>
<td>Increased risk of infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet function abnormalities, anemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stevens-Johnson syndrome/toxic epidermal necrolysis</td>
<td></td>
<td></td>
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<tr>
<td>Hyperlipidemia</td>
<td></td>
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<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>Catheter-associated infections</td>
<td>Skin breakdown</td>
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<tr>
<td>Catheter-associated infections</td>
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<td>Skin breakdown</td>
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<td>Sepsis</td>
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<td></td>
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<tr>
<td>Catheter-associated infections</td>
<td></td>
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</tbody>
</table>

**Notes:**
- Acute apnea after a prolonged seizure without antecedent abnormal breathing pattern should alert for a rapidly evolving posterior fossa lesion.
- May cause ineffective ventilation to the point of respiratory acidosis.
- Cheyne Stokes breathing: waxing waning hyperpnoea, regularly alternating with shorter period of apnea; may be seen in large supra-tentorial lesion(s), deep seated cerebral or diencephalic lesions e.g. subdural hematomas, infarcts, or meningitis, and certain metabolic disturbances. Important to rule out co-existent pulmonary disease.
- Central neurogenic hyperventilation: suggests a lesion in lower mid-brain and/or upper pons; important to differentiate from hyperventilation due to medical reasons e.g. Kussmaul’s breathing of metabolic acidosis.
- Apneustic breathing: usually seen with low pontine lesions e.g. basilar artery occlusion.
- Chaotic irregularly interrupted breathing rhythm: each breath varying in depth and rate, may suggest a lesion of dorso-medial part of medulla.
Does Normal Saline Have Clinical Effects in Infants with Bronchiolitis?


SUMMARY

The objective of this systematic review and meta-analysis was to measure the short-term association of nebulized normal saline with physiologic measures of respiratory status in children having bronchiolitis by comparing nebulized normal saline with the use of other placebos. Randomized clinical trials comparing children 2 years or younger with bronchiolitis who were treated with nebulized normal saline were included. Studies enrolling a treatment group receiving an alternative placebo were included for comparison of normal saline with other placebos. Pooled estimates of the association with respiratory scores, respiratory rates, and oxygen saturation within 60 minutes of treatment were generated for nebulized NS vs another placebo and for change before and after receiving nebulized normal saline. A total of 29 studies including 1583 patients were included. Standardized mean differences in respiratory scores for nebulized normal saline vs other placebo (3 studies) favored nebulized NS by −0.9 points (95% CI, −1.2 to −0.6 points) at 60 minutes after treatment (P<0.001). The standardized mean difference in respiratory score (25 studies) after nebulized NS was −0.7 (95% CI, −0.7 to −0.6; I² = 62%). The weighted mean difference in respiratory scores using a consistent scale (13 studies) after nebulized NS was −1.6 points (95% CI, −1.9 to −1.3 points; I² = 72%). The weighted mean difference in respiratory rate (17 studies) after nebulized NS was −5.5 breaths per minute (95% CI, −6.3 to −4.6 breaths per minute; I² = 24%). The weighted mean difference in oxygen saturation (23 studies) after nebulized NS was −0.4% (95% CI, −0.6% to −0.2%; I² = 79%). The authors concluded that nebulized normal saline may be an active treatment for acute viral bronchiolitis and recommended that further evaluation should occur to establish whether it is a true placebo.

Critical appraisal: Table 1 summarizes a critical appraisal of the systematic review using one of the checklists designed for this purpose [3]. Several additional points merit considerations.

Although this study [2] is not a systematic review comparing two interventions in the strict sense of the term, for practical purposes it devolves to a comparison of using nebulized normal saline versus not using it. Therefore, the authors chose to include studies having two types of comparisons. One comparison was nebulized saline versus some other placebo (compared against each other). The other comparison was before-versus-after effects of normal saline in trials wherein it was used (as placebo) in one of the arms. It can be argued that the authors should have additionally searched for single-arm studies of nebulized normal saline alone, analyzing the before-versus-after effects. Such studies would likely have been conducted years before active pharmacologic interventions were examined.

Evidence-based Medicine Viewpoint

Relevance: Bronchiolitis is one of the most common pediatric respiratory conditions, yet clinical experience and a vast body of research evidence suggests that ‘nothing really works’ as a treatment. In fact, the evidence for therapeutic options has been explored several times over the past decade in this journal itself, without satisfactory resolution. The United Kingdom National Institute for Health and Clinical Excellence (NICE) guidelines published in 2015, recommend against using hypertonic saline, nebulized adrenaline, salbutamol, montelukast, ipratropium bromide, antibiotics, systemic or inhaled corticosteroids, and combinations of systemic corticosteroids and nebulized adrenaline [1]. These conclusions were based on current evidence failing to demonstrate a lack of superiority of these treatments compared to placebo. It is instructive that almost all experiments on nebulized pharmacologic agents used 0.9% (normal) saline as the vehicle for delivering the medication. Not surprisingly, normal saline was chosen as the placebo in most comparative trials. Recently, House, et al. [2] undertook a systematic review and meta-analysis, re-exploring the evidence base to determine if normal saline has clinical effects and whether it can be truly considered a placebo.

COMMENTARIES
Table I Critical Appraisal of the Systematic Review

Validity

1. Is there a clearly focused clinical question? Although the authors did not explicitly frame a clinical question for the systematic review, the PICOT components can be summarized as:
P: Infants with a clinical diagnosis of acute viral bronchiolitis.
I: Nebulized normal saline
C: No normal saline or any placebo other than normal saline
O: Respiratory distress score, respiratory rate, oxygen saturation
T: Within 60 minutes.

2. What are the criteria for selection of studies? The authors included clinical trials that matched the above PICOT criteria.

3. Is the literature search method specified? Two large databases viz MEDLINE and Scopus, were searched (from inception to March 2019) for relevant literature. The search terms for each database were reported. Additionally, reference lists of relevant publications were hand-searched. There was no language restriction. However, the authors did not search Conference abstracts/proceedings and publicly available student theses. Likewise, registries of clinical trials were not examined.

4. Have the identified studies been evaluated for methodological quality? The authors used the revised Cochrane Risk of Bias tool for methodological assessment, and reported the results.

5. Is it appropriate to combine the results from different studies? The results from the included studies can be combined.

Results

1. Were the results consistent from one study to another? There was significant heterogeneity for some outcomes. The authors explored these through pre-specified subgroup analyses, as well as comparison of results with the fixed versus random effects models of meta-analysis.

2. What were the overall results of the review? Nebulized normal saline versus other placebo
   • Respiratory score SMD: -0.9 (95% CI -1.2, -0.6); 3 trials.
   • Respiratory rate: No statistically significant difference*
   • Oxygen saturation: No statistically significant difference*

   Nebulized normal saline versus no saline (before/after model)
   • Respiratory score SMD: -0.6 (95% CI -0.7, -0.5); 25 studies.
   • Respiratory rate MD: -5.1 (95% CI -6.4, -3.9), 17 studies.
   • Oxygen saturation: MD -0.3 (95% CI -0.7, 0.1), 23 studies.

   Results of subgroup analyses of inpatient versus outpatient treatment were in line with the overall results. Likewise, results of 13 studies that used the same respiratory scoring system were comparable to the overall results. Step-wise sensitivity analyses deleting outlier results, and those with high risk of bias, also yielded comparable results.

3. How precise were the results? The pooled confidence intervals for the three outcomes are very narrow, suggesting high degree of precision.

Applicability

1. Is the local population similar to those included in the original studies? Yes.

2. Is the intervention feasible in my setting? This systematic review was not designed to test the clinical efficacy of nebulized normal saline per se, but to explore whether it can be truly considered a placebo. The intervention should not be tried in any setting for the reasons highlighted in the text.

3. Have all the clinically relevant results been taken into consideration? Only a limited number of outcome measures were considered in this analysis. Further, no outcomes were examined beyond 60 minutes.

4. Do the benefits outweigh the potential harm? See additional comments in the text.

*The authors did not show data for these outcomes, but mentioned the conclusion; MD=Mean difference; SMD=Standardized mean difference.
Although before-versus-after comparison of outcomes within the placebo arm of trials is a smart way to examine potential effects of normal saline, this could be confounded by the effects of supportive management particularly oxygen and/or fluids. In this regard, it is notable that 11 of 14 trials among out-patients used oxygen to drive nebulization. Only two [4,5] used room air; and one [6] did not clearly report the use of oxygen (or otherwise). Only one trial among in-patients [7] did not mention the use of oxygen. Further, before-versus-after analysis of normal saline effects cannot tease out the effect of time on the recovery process in bronchiolitis. Although this is theoretically true of all studies using multiple doses of (any) intervention, it is especially relevant in bronchiolitis.

The authors [2] separately analyzed studies wherein normal saline could be compared against another placebo. This is the only type of study design wherein a potential effect of normal saline can be determined without confounding by factors mentioned above. There were three such studies. Two of these [4,5] by the same group of investigators had an arm wherein infants received oral rehydration solution (ORS) while the third study [8] had an arm wherein infants received “mist in a tent”. However, the details of mist administration were not specified. Combining the trials with ORS, the authors [2] reported the weighted mean difference for respiratory distress score as -1.6 (95% CI -0.8, -0.03), suggesting an overall benefit with saline. However, this seems implausible as the pooled effect lies outside the confidence interval. Further, even if there was a statistically significant reduction in the severity score by 1.6, its clinical significance is questionable given that the scoring system had a range from 0 to 27 [4]. This view is supported by the fact that normal saline did not have any impact on respiratory rate or oxygen saturation. In fact, the authors of one of the trials [4] themselves commented that there was comparable improvement in the three trial arms (nebulized salbutamol, nebulized normal saline, ORS) suggesting that the effect was related to change in the infants’ state and/or disease process with time.

The authors [2] chose to include only three short-term outcomes in the systematic review. Some of the other relevant outcomes are heart rate, need for escalation of therapy/additional doses, failure to improve within 60 minutes, change in sensorium, requirement of intensive care, and ventilation support. Even mortality within the first few hours could be included as an outcome. Among these, heart rate would have been especially useful because decline in heart rate within the first 60 minutes would likely reflect the benefits of oxygen and/or supportive care, rather than saline. Unfortunately, this was not explored.

The forest plot for oxygen saturation in the systematic review [2] shows a marginal but statistically significant decline with nebulized normal saline, but this was erroneously interpreted as “improvement with normal saline.”

Last, but not the least, 14 of the 25 studies in the meta-analysis [2] showed a statistically significant improvement in respiratory score with normal saline. In 10 of these [4-6, 9-15], the effect of nebulized normal saline was comparable to the active intervention. These encompassed a wide variety of nebulized medications viz, salbutamol (in 7 trials), epinephrine (in 4 trials), hypertonic saline (in 2 trials), ipratropium (in 1 trial), terbutaline (in 1 trial), furosemide (in 1 trial), salbutamol + ipratropium (in 1 trial), and salbutamol + hypertonic saline (in 1 trial). If normal saline is interpreted as having statistically significant effects (as reported in the systematic review), then the inescapable conclusion is that all these interventions also have significant effects. Further, in trials showing superiority of various interventions over normal saline (salbutamol in 7 trials, epinephrine in 2 trials, hypertonic saline in 1 trial, ipratropium in 1 trial, epinephrine + dexamethasone in 1 trial) the effects can be attributed to the synergistic combination of the active pharmacologic agent with normal saline (since normal saline was the vehicle for nebulization in all the trials). Further, such an interpretation would necessitate extrapolating this conclusion to other conditions where nebulized treatments work, most notably bronchial asthma! The time, effort, money and risk to patients if this line of thought is pursued through new trials to prove (or disprove) this is unimaginable.

Conclusion: This systematic review [2] raised the possibility that nebulized normal saline may have some clinical effects in infants with bronchiolitis, hence may not truly be a placebo. However, the limited evidence comparing saline against a true placebo, methodological issues, and interpretation of data, make it difficult to concur with this view. In any case, it seems unwise to explore the issue further through new clinical trials.

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Pediatric Pulmonologist’s Viewpoint
Bronchiolitis is a common cause of hospitalization among children less than two years of age. It is a lower airway disease affecting infants and children and caused by viral infections. Most common virus associated with bronchiolitis is RSV, attributed in >80% of children. The pathophysiologic lesion in bronchiolitis is epithelial necrosis and dense plug formation in the bronchiolar lumen leading to air trapping and mechanical interference with ventilation.

Bronchiolitis is a self-limited illness and often resolves without complications in healthy infants. For children with non-severe bronchiolitis, no pharmacologic interventions are recommended as there is no evidence of benefit. It may increase the cost of care and may have adverse effects. Children with severe bronchiolitis, require admission and supportive care. Supportive care includes maintenance of adequate hydration, provision of oxygen and respiratory support as required and disease progression monitoring. Guidelines recommend discouragement of routine use of inhaled bronchodilators (albuterol or epinephrine), nebulized hypertonic saline and systemic/inhaled glucocorticoids. However, a one-time trial of inhaled bronchodilators may be done for children with severe bronchiolitis.

In the index paper (systematic review and meta-analysis), placebo status of nebulized normal saline (NS) was evaluated in acute bronchiolitis. The main outcome measure was the association of nebulized NS with management of bronchiolitis in Egypt. J Pediatr. 1994; 124:131-8.

Funding: None; Competing interests: None stated.

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REFERENCES
Prevalence of Vitamin D Deficiency Among Newborns

We observed that 760 (92.1%) out of 825 healthy newborns at our institution had vitamin D deficiency (VDD) at birth. These observations highlight the importance of regular screening and supplementation of vitamin D in the early years of life.

Keywords: Neonate, Nutrition, Tandem Mass spectroscopy.

Despite the majority of Indian population receiving adequate sunlight throughout the year, the prevalence of vitamin D deficiency (VDD) in India is estimated to be between 40% and 90%, irrespective of age, gender, and geography [1]. It is also highly prevalent among pregnant women, lactating mothers, neonates, and/or exclusively breastfed infants [1]. Apart from skeletal manifestation, VDD has been reported to be associated with type 2 diabetes, cardiovascular dysfunction, and autoimmune diseases during later life [1-3].

Vitamin D levels of newborns are primarily dependent on maternal vitamin D levels; hence, infants born to vitamin D deficient mothers are at a higher risk of developing VDD at birth [4-6]. The objective of this study was to assess the prevalence of VDD among infants born at a single hospital to healthy mothers in Bengaluru, a cosmopolitan city in Southern India.

This study was approved by the management of our hospital. Written informed consent was obtained from the mothers of the participants. This study was performed for a duration of three months between March, 2018 and June, 2018 at Cloudnine Hospitals, Bengaluru, India. All full-term, healthy, singleton infants born during the study period were included. Preterm infants, low birthweight infants, and infants with congenital disorders, sepsis, and jaundice were excluded from the study.

At 36-48 h of life, a venous blood sample (0.5 mL) was drawn from each participant, and 25-OH vitamin D values were measured by Tandem Mass Spectroscopy (TMS). The vitamin D level was calculated by adding the measurements of vitamin D2 and vitamin D3 levels. To facilitate the comparison, we divided the measured values of vitamin D levels into three diagnostic categories, modified from the values suggested by Indian Academy of Pediatrics (IAP) [7]: Vitamin D deficiency, ≤10 ng/mL; vitamin D insufficiency, 10–20 ng/mL; and vitamin D sufficiency, ≥20 ng/mL.

Vitamin D status were compared using the Chi-square test. Statistical analysis was performed using Microsoft Excel (Microsoft Office 2016, Microsoft Corporation, USA). Statistical significance was considered at \( P<0.05 \).

A total of 920 children were born during the study period, of which 825 newborns were included in the study. In all, 786 (95.3%) participants had vitamin D2 levels of <1 ng/mL. The mean (SD) of D3 level and total vitamin D levels were 8.1 (7.6) ng/mL and 8.3 (7.9) ng/mL, respectively. Only 65 (7.9%) infants had normal vitamin D levels (Table I).

This study provides the prevalence of VDD based on the blood samples drawn from newborns, and not from the cord blood [8,9]. Our findings are in line with previously published studies, suggesting a higher prevalence of VDD among Indian newborns [1,8,9]. Although data on maternal vitamin D levels was not collected, most mothers had received antenatal supplementation of vitamin D, suggesting that this was insufficient to prevent neonatal VDD. Additionally, initiatives related to public health including food fortification, public awareness, etc. may be warranted to reduce burden of VDD.

This study further highlights the need for vitamin D supplementation in neonates.

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Contributors: RKK, HD, SVG, AN: Involved in all aspects of the conduct of the study and preparation of manuscript. All authors approved the final manuscript and are accountable for all aspects related to the study.

Funding: None; Competing Interests: None stated.

R KISHORE KUMAR1*, HARI DAS2, SV GIRISH1 AND AKASH NEVILEBASAPPA3

Table I Prevalence of Vitamin D Deficiency Among Newborns*

<table>
<thead>
<tr>
<th>Vitamin D status</th>
<th>Male (n=444)</th>
<th>Female (n=366)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deficient (&lt;10 ng/mL)</td>
<td>313 (70.5)</td>
<td>258 (70.5)</td>
</tr>
<tr>
<td>Insufficient (10-20 ng/mL)</td>
<td>103 (23.2)</td>
<td>73 (20)</td>
</tr>
<tr>
<td>Sufficient (&gt;20 ng/mL)</td>
<td>28 (6.3)</td>
<td>35 (9.6)</td>
</tr>
</tbody>
</table>

*Gender details were missing for 15 newborns; all values in n (%).
Prophylactic Vitamin D Supplementation Practices for Infants: A Survey of Pediatricians From Delhi

This survey was conducted among 125 pediatricians working in public and private child care facilities of Delhi. Prescription rates of routine vitamin D supplementation varied between 70-100% for various groups of infants, despite non-availability of government guidelines. Pediatricians in private practice more frequently prescribed vitamin D supplementation to term healthy infants as compared to government pediatrician (91.4% vs 71.6%; P=0.005).

Keywords: Guidelines, Hypovitaminosis D, Prescription, Rickets.

The global pandemic of Vitamin D deficiency is equally affecting Indian term-born, healthy and exclusively breastfed infants [1,2-5]. Various global associations and Indian Academy of Pediatrics (IAP) recommend daily supplementation of 400 IU to all infants [6-8]. We conducted this study to document the prescription practices of pediatricians in Delhi regarding prophylactic vitamin D supplementation at birth.

This cross-sectional survey was conducted among 125 pediatricians from selected public and private healthcare facilities in Delhi between December, 2017 and February, 2018. A structured questionnaire was administered to a convenience sample of all available pediatricians with either Doctor of Medicine (MD) or Diploma (DCH) in pediatrics qualifications, and having more than six months of experience, stationed in the outpatient department of Medical colleges and associated hospitals, Delhi Government hospitals, Corporate hospitals, Private hospital / Nursing Home / Trust or Non-Government Organization - funded hospitals on the day of visit, and Private clinics of Delhi.

From 67 healthcare facilities located all over Delhi, we enrolled 125 pediatricians; 102 (81.6%) were working in hospitals while rest were practicing in the clinics. Pediatricians from public and private facilities were comparable for their gender, postgraduate qualification, and awareness of IAP guidelines for vitamin D supplementation. A higher number of participants from private sector had been practicing for more than 10 years (P<0.001).

The overall prescription rates for routine supplementation at birth were 80.8%, 94.4%, and 97.6% for term appropriate for gestational age (AGA), term low birthweight (LBW), and preterm infants, respectively. Routine supplementation to term healthy (AGA) infants was prescribed more often by those working in private practice (53/58, 91.4%) as compared to pediatricians working in government facilities (48/67, 71.6%) (P=0.005). All pediatricians in private practice were prescribing vitamin D to term born LBW infants.
Primary source of information on prophylactic vitamin D supplementation for the participants was IAP guidelines (25.6%), followed by pediatric textbooks (23.2%) and American Academy of Pediatrics guidelines (19.2%). One participant cited advertisement made by pharmaceutical representative as his source of information; 7.2% government pediatricians cited the non-availability of vitamin D drops for infants in their hospital supplies, and one participant cited lack of government guidelines on prophylactic vitamin D supplementation as the reasons for non-supplementation.

Lower prescription rates in government sector could be attributed to non-availability of the drug and lack of a government/hospital policy. The Essential drug list of Delhi (2013) or National list of essential medicines (2015) of India do not have vitamin D formulations for infants. Further, there are no government guidelines on vitamin D supplementation to infants in India. Yet our study found 70-90% pediatricians in Delhi were prescribing routine vitamin D supplements to infants. This is may be ascribed to either professional society recommendations or marketing by pharmaceuticals. This is in contrast to poor prescription practices for zinc (recommended by IAP, UNICEF, and Government of India) for supplementation during an episode of diarrhea. National Family Health Survey 4 (2015-16) for Delhi reports that only 25.3% under-five children receive zinc during a diarrheal illness, whereas another study reported that only 61.1% of private practitioners in Gujarat were prescribing zinc supplementation in an episode of diarrhea [9,10]. Could this be because marketing revenues from zinc are not as lucrative as from vitamin D?

This study, first of its kind from India, used a sample of convenience, restricting its generalizability. Moreover, physical verification of prescriptions was not performed, and compliance to the prescriptions was also not examined. In a country like India, where food fortification with vitamin D is limited and scope of sun exposure for adequate endogenous formation of vitamin D has remained unexplored, supplementation as a strategy needs to be clearly stated.

Contributors: PG,NS,HN: Conceived the study.; PG,SK,NS: contributed to the study design; NS: data collection, supervised by HN and PG; Statistical analysis NS and PG. literature search: HN, PG NS, SK; initial draft: NS; edited by HN, PG, HN, SK, PG: provided critical inputs to the draft manuscript. Final manuscript was approved by all authors.

Funding: None; Competing Interests: None stated.

REFERENCES

Undergraduate Medical Students’ Experience with Foundation Course at a Public Medical College in India

The study aimed to explore the perception and knowledge-gain of undergraduate medical students during the Medical Council of India-mandated one month foundation course in August, 2019. A total of 129 consenting students who underwent the foundation course were enrolled and their feedback collected using an email-based structured questionnaire. A majority (>60%) had positive attitudes towards various aspects of the course, with good scores obtained in the post-test by the majority of the students. The information reported will assist in the planning of future foundation course programs.

Keywords: Attitudes Ethics Communication Module (AETCOM), Medical Council of India (MCI), Training.

Medical Council of India (MCI) envisages an Indian medical graduate (IMG) to have both clinical skills and also right attitudes, professionalism, and ethics [1], which were included as an Attitude, ethics and communication (AETCOM) module [2]. Competency-based medical education (CBME) was proposed to revamp the existing medical teaching to replace it with a more uniform and objective prototype [3].

A foundation course of one-month duration has been introduced throughout India from August, 2019 as a compulsory module at the beginning of the MBBS course to sensitize students to information, lifestyle and practical skills required to sail through the training [4]. This study aimed to record the reactions and learning of students who undertook the foundation course.

Data were collected as an online Google form administered in the English language and disseminated via an online link in an email to the students. All undergraduate students who joined our institution, a public medical college in Northern India, were administered the survey before completion of the foundation course in the fourth week of August, 2019.

Permission for the study was obtained from the institutional ethics committee. Consent was obtained before sending the link for the online form. The information was collected in an anonymized form. A provision for the hard copy of the form was available for students who were not well-conversant with the online usage. Faculty-volunteers assisted students who needed language-support for filling the form.

The semi-qualitative questionnaire used consisted of four sections viz., Demographic information; Clinical medicine knowledge and skills; Medical ethics including professionalism (student’s experience and understanding of foundation course, its relevance, competency in medicine, role of a doctor in the community and perception about attitude, ethics, and communication in medical curriculum); and Beyond curriculum (extracurricular activities and interests of students with their perceptions about the need for sports, technology and recreation, and their experiences with peers, seniors and faculty). Clinical medicine section evaluated knowledge-based responses pertaining to skills module and orientation to clinical medicine, which was discussed during the foundation course (post-test). Pretest for this content was not taken separately, as it was considered that factual knowledge on these concepts would not be available to the students. The questions in this section were related to the immunization schedule, first-aid, waste management, universal precautions and basic life support. The responses were converted to a score and scored from 0 to 1. Participants with a correct response to questions were given a score of 1, a partially correct response received 0.5, and an incorrect response received zero.

Data were recorded on a Google excel sheet and analyzed using SPSS version 23. A five-point Likert scale was used to report the overall experience of the foundation course.

Out of a total of 250 students enrolled, only 129 (51.6%) participated, with mean (SD) age 18.2 (1.1) year (range 17-23). Reasons for non-participation among the rest were not available. The majority of respondents (56%) were residents of Delhi, and most were conversant both in English (97.7%) and Hindi (93.8%).

The overall feedback on the foundation course was positive (average score of 3.9 out of 5) on the Likert scale. Table I details the students’ perceptions of the foundation course. The positive experiences with foundation course included interactive sessions and simulation-based learning, team-building activities with peers, seniors and teachers, college campus tours, the inclusion of cultural activities and yoga, and visits to hospital and community outreach center. Three students did not feel the need for a foundation course, and one regretted joining MBBS. The unpleasant experiences highlighted by few included long college hours, long duration of the foundation course, parental separation anxiety, lesser exposure to the clinical side, poorer ice-breaking activities, lack of cleanliness in college campus and hostel, and the requirement for better physical activities and sports. The majority (94%) identified lack of time as a major constraint to pursue hobbies.
The mean knowledge scores under the skill module are shown in Table II. The highest scores were seen in the clinical skill areas (first-aid and safe injection practices, >85%).

A foundation program was initiated in 2004-05 in United Kingdom for newly joined postgraduate students [5], and evaluation of the impact on doctors in training found that foundation course improved the perceived confidence and competence; though, the survey could not reliably assess the quality of care that was provided to patients [5]. Such information for foundation course during undergraduate medical courses are lacking in the published literature.

Studies have shown that learning during the medical curriculum depends upon students’ gender, race and ethnicity [5-7]. The perceptions about the medical school environment also change with the progress of the curriculum [6]. A survey on about 4000 medical students from United States and Canada revealed that perception scores for learning environments had declined during clinical exposures. A systematic review analyzed 28 medical schools with 4664 students for the medical school learning environment survey (MSLES) scores and student characteristics [7]. They found that demographic characteristics across different schools and medical school environment accounted for 2.2% and 15.6% variation in MSLES scores, respectively [7]. Therefore, understanding of students’ perceptions about learning and the environment could facilitate overall course delivery and learning.

Medical informatics is the science and art of processing medical information [8]. Computer-assisted learning and problem-solving learning are powerful tools that can improve lifelong learning of medical students [9]. A fair number of students in the present study were aware of e-learning and its use in the medical field, suggesting that this technology can be used during the curriculum for an improved learning experience, and address the issues of the time- and faculty-shortages.

The present study could not quantify the impact of the foundation course for improvement in knowledge as a pre-test questionnaire was not administered. The change in behavior and improvement in patient-care resulting from the course would need to be studied over the long-term by other researchers. Despite a large sample, this was a single-center study, and the results may not be generalizable to other settings, as the course-content or delivery methods may be different at other centers. However, we have highlighted the key aspects of qualitative experiences related to the foundation course, which may guide curriculum-planners for formulating future programs.

To conclude, the foundation course was reported as a pleasant and beneficial experience by undergraduate students. An improved understanding of their aspirations and concerns will aid in the development of a better curriculum and training module.

Contributors: AD, DV, DK: conceptualized and planned the study; DV: supervised the study conduct and data collection, and would be the guarantor; AD: prepared the initial draft of the manuscript and did the statistical analysis; DK: assisted in

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<th>Table I Perceptions of Undergraduate Medical Students After Completing a One-month Foundation Course (N=129)</th>
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<td>Component of training</td>
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<td>Overall course</td>
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<tr>
<td>Necessary for the right attitude</td>
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<tr>
<td>Provided orientation of knowledge and skills required in MBBS</td>
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<tr>
<td>Helped to identify roles of IMG</td>
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<td>Identified research as important for IMG</td>
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<td>Understood need and role of CBME</td>
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<tr>
<td>Found course boring and lengthy</td>
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<tr>
<td>AETCOM</td>
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<tr>
<td>Empathy, attitude, and communication important for IMG</td>
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<tr>
<td>Role of non-verbal communication in medicine</td>
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<tr>
<td>*Positive response; CBME: competency-based medical education; IMG: Indian medical graduate; AETCOM: Attitudes, ethics and communication module.</td>
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<th>Table II Clinical Medical Knowledge and Skills of Undergraduate Medical Students After a One-month Founduction Course (N=129)</th>
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<tr>
<td>Question</td>
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AYUSH: Ayurved, Unani, Siddha and Homeopathy.
planning the study, participated in data collection, and statistical analysis; DM: assisted in planning, outcome assessment, manuscript finalization and data analysis. All authors approved the final manuscript.

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**REFERENCES**


**Audience Response System**

**Technology for Pediatric Postgraduate Training**

We report our experience of using Audience Response System among 21 pediatric postgraduate residents in pediatrics as a mode of teaching. Apart from significant improvement in test scores, three-fourth of the participants felt it was an interesting way to learn actively and was better than the traditional audiovisual presentation during lectures.

Traditional methods of postgraduate residents teaching program include seminars, didactic lectures, journal club, mortality meet, and clinical case conferences. Most of them have a drawback of passive learning. With the advancement in technology, there is a need to develop new teaching methods that involve active participation of students. Audience response system (ARS) enables learners to answer multiple-choice questions anonymously during the lecture. Result of responses by learners is displayed instantly in form of a histogram that allows the lecturer to assess learners’ understanding of the subject, and also promotes the learners’ engagement with the study material, thereby increasing comprehension and retention of material.

The study participants included 21 second-and third-year pediatric residents who consented to participate in this study. The study was conducted in a tertiary-care teaching hospital of Northern India. A WhatsApp group of participating residents was created prior to the intervention. ARS was administered using website www.polltab.com and the link for the questions were posted in the WhatsApp group.

A 10-minute pretest in the form of video-based multiple-choice questions was administered to establish baseline knowledge of movement disorders in children. It consisted of 10 questions with 10 marks each with a maximum of 100 Marks. Subsequently, a powerpoint presentation on basic principles and tips for recognizing movement disorders were delivered, followed by a case-based discussion with videos depicting each movement.

At the end of each video, ARS was used to assess residents ability to identify the type of movement disorders depicted in the video. The response of residents was displayed simultaneously when they voted, and the lecturer discussed the points concerning that video. At the end of the lecture, all residents completed a post-test evaluation to reassess their knowledge of the topic. In addition, they also completed a feedback form to assess their opinion regarding the usefulness of the ARS.
There was a significant improvement in the mean (SD) post-test scores compared to pretest scores [60 (19.4) vs 18.8 (23.5), \(P<0.001\)]. Majority of the residents (16, 76.2%) ‘strongly’ felt that it was an interesting way to learn, involves active learning, it ensured participation of all residents, avoided embarrassment for giving a wrong response, and were overall satisfied with this mode of teaching. Fifteen of them (71.4%) strongly felt more confident about identifying a movement disorder. Seventeen (81%) found it to be better than traditional video lectures and suggested its incorporation into pediatric postgraduate teaching program.

In the open comments, students expressed following additional comments: “I could understand the video better and had time to think about each video”, “I was happy to see when others were also wrong!” , “It is exciting to see that poll opinion does not necessarily translate into correct response as we could all think in wrong direction”, “we were motivated to read it further”, “it was a good way to teach complex topics like movement disorder”, “For the first time I was not checking my whatsapp for one hour despite being on smartphone!” One of the faculty member who attended the session conveyed that “it is an exciting and novel method to teach the postgraduate students”

Various studies on the use of ARS in medical students demonstrated benefits in form of enhanced attention with long-term retention of knowledge [1,2]. ARS is known to improve engagement of students and their attendance in large group lectures [3]. The present study was conducted among a small group of postgraduate students where video-based teaching was adopted. Video-based lectures have their own strength and it is rather difficult to attribute improved post-test scores to use of the ARS system alone. However, we believe when used in conjunction, this becomes an effective mode of teaching.

The present study demonstrates ARS to be an effective mode of increasing interaction with learners when adopted in a small groups of postgraduate students. In this era of smartphones and ease of internet access, ARS is useful adjunct to lectures and seminars [4]. There are large number of ARS systems available which have their own merits and demerits including cost, ease of use, and limit of number of participants. ARS has also been used for developing consensus statements [5], to verify attendance in lectures [6], and as a modality for course evaluation [7]. The present study intends to sensitize the readers about this simple, low-cost and uncomplicated technology of audience response system in their didactic lectures and seminars to make the class more interactive.

Acknowledgment: Dr Mahima Rajan, Senior resident in execution of this teaching method.

Contributors: JSK: conceptualized the idea; AM, JSK: drafted the manuscript; JSK: provided intellectual inputs; all the authors approved the final version of the manuscript.

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**REFERENCES**

Umbilical Diphtheria: Resurgence of a Forgotten Entity

Diphtheria has had a resurgence in India over the past decade. We present a case of umbilical diphtheria in a neonate, who had a good outcome with administration of anti-toxin and antibiotics.

Keywords: Anti-toxin, Corynebacterium, Neonate.

Diphtheria, a vaccine preventable highly contagious disease is making a resurgence in India [1,2]. Diphtheria of the umbilicus is a rare clinical presentation of diphtheria, with the last report published nearly 80 years back [3]. In this case report, we present a successfully treated case of umbilical diphtheria in a neonate.

A 17-day-old, otherwise well neonate on exclusive breast feeds, presented with a 4-day history of swelling and redness around the umbilicus with pus discharge. He had no fever, poor feeding or lethargy. His mother had an uneventful antenatal period. He was born normally at a hospital at term by normal vaginal delivery with a birthweight of 3.5 kg. The umbilical cord was clamped using a sterile plastic clamp. Umbilical cord fell on day 7 of life. He had no bleeding or pus discharge from the umbilicus when the umbilical cord fell. On examination, he was alert, active, and pink with normal cry and tone, and was growing well. His temperature was 98.7 °F at presentation, and throat was normal. Local examination revealed an inflamed umbilicus that was greyish white with pus discharge. The surrounding area had warmth, erythema and tenderness extending about 3 cm all around the inflamed umbilicus (Web Fig. 1).

Gram stain performed on the pus swab neither showed pus cells nor bacteria. However, sample cultured on blood agar and serum tellurite agar grew C. diphtheriae, which was identified by multiplex real time PCR. Elek’s gel precipitation test was positive for diphtheria toxin. Abdominal ultrasound was normal. He was treated as umbilical diphtheria with 40,000 units of anti-diphtheritic anti-toxin and crystalline penicillin 1 lakh units intravenously every 6 hours for 10 days. He was on contact isolation for 4 days following start of antibiotics. Azithromycin prophylaxis was administered to close household contacts and medical personnel exposed to the child. The redness, swelling and induration around the umbilicus gradually reduced. At review after 3 weeks, he was well, with a healthy umbilicus and weight of 4.55 kg. Mother’s immunization was reportedly complete up to 10 years of age. The mother’s anti-diphtheria toxoid IgG level (EUROIMMUN, Lubeck, Germany) was tested by ELISA and found to be below the protective level at 0.08 IU/mL.

The largest epidemic of umbilical diphtheria was reported in 1919 [3]. It occurs in the newborn and infants up to three weeks of age [3]. Umbilical diphtheria has not been described since long, likely due to widespread vaccination for diphtheria. In our patient, umbilical diphtheria was not considered clinically and the clinical picture was akin to usual bacterial causes of umbilical infection such as Staphylococcus aureus, Streptococcus pyogenes, Pseudomonas spp., Aeromonas spp., and Klebsiella spp. [4]. However, a positive culture provided the diagnosis. In retrospect, the pointers towards umbilical diphtheria in our child were a well-appearing child and absence of fever in spite of widespread inflammation around the umbilicus. A false membrane was; however, not obvious in our child [3]. We could not ascertain how our patient contracted the infection. However, given that the organism is an exclusive inhabitant of human mucus membrane and skin, it is likely that one of the caregivers of the baby was colonized with C. diphtheriae [5]. Diphtheria anti-toxin was administered to our patient even though there was no evidence of the effect of the toxin. Many cases of umbilical diphtheria cases reported in the early 20th century who did not receive anti-toxin died, and the ones who received anti-toxin survived [3].

Our patient likely had a good outcome due to the prompt administration of anti-toxin and antibiotics. Our patient was at risk for diphtheria before his first dose of pentavalent vaccine in view of the waning maternal immunity as confirmed by the mother’s low antibody titre to diphtheria. Implementation of maternal Tdap vaccination during pregnancy, as recommended in some countries, possibly could have prevented umbilical diphtheria in our child [6].

In conclusion, umbilical diphtheria may be under reported as many cases of the umbilical infection are treated without any microbiological evidence and maternal Tdap vaccination should be considered to prevent diphtheria in very young infants.
Esophageal lung is a rare communicating bronchopulmonary foregut malformation with anomalous communication between an isolated portion of respiratory tissue and esophagus. Children present in early life with recurrent cough and pneumonia. Majority of the reported cases are associated with other anomalies like tracheoesophageal fistula. We report a case of a 7-month-old girl with right sided esophageal lung who was misdiagnosed as dextrocardia with right sided pneumonitis.

Keywords: Bronchopulmonary, Dextrocardia, Lung malformation, Recurrent cough.

Esophageal lung is a rare communicating bronchopulmonary foregut malformation with anomalous origin of the main bronchus from the esophagus usually on the right side, which leads to recurrent aspiration pneumonitis. Other associated congenital anomalies of the upper gastro-intestinal tract, ribs and vertebrae may be present. It is diagnosed radiologically and confirmed by broncho-scropy. Few cases have so far been reported in literature [1]. A high index of suspicion should be kept in young children with recurrent chest infection.

A 7-month-old girl presented with recurrent lower respiratory tract infection and episodes of choking following breast feeding since one month of age. She was symptomatic in the present episode for last 7 days for which she received oral amoxycillin for 5 days without improvement. The baby was born full term by normal delivery and was developmentally normal. At admission, child had low weight and length as per age, tachypnea (respiratory rate 72/minute), tachycardia (heart rate 130/minute) with subcostal and intercostal retractions. On auscultation, breath sounds were decreased on right side with apex beat on the right side suggestive of dextrocardia. Hemoglobin was (10g/dL), total leucocyte count was 27700/µL (neutrophils 74%), C-reactive protein was positive, with normal renal and liver functions. Blood culture was sterile. Chest X-ray showed hazy right hemithorax with mediastinal shift to the right side. Contrast enhanced computed tomographic (CT) scan thorax demonstrated right lung hypoplasia with cystic bronchiecatic changes with nonvisualization of right main bronchus, hypoplastic right main pulmonary artery and abnormal bronchopulmonary communication (Fig. 1a, 1b). Barium swallow study showed filling of right main bronchus directly from the esophagus. Rigid bronchoscopy revealed a blind ended right bronchial stump which confirmed the diagnosis of esophageal lung. Ultrasound abdomen and echocardiography were normal. Child improved with oxygen, intravenous antibiotics and nebulisation with bronchodilators. Child started accepting orally and was gradually tapered off oxygen. She was advised operative intervention for esophageal lung (right pneumonectomy with resection of the esophageal bronchus and repair of the esophagus at the site of bronchial communication), which the family refused.
Congenital bronchopulmonary foregut malformation comprises of an abnormal patent tract between respiratory and gastrointestinal tract as a result of anomalous budding of the embryonic foregut and tracheobronchial tree [2]. It has been classified into 4 groups [3] viz, group I (16%) with associated esophageal atresia and tracheoesophageal fistula, group II (33%) where one lung originates from the lower esophagus (esophageal lung), group III (46%) with an abnormal communication between an isolated anatomic lung lobe or segment with the esophagus or stomach (esophageal bronchus), and group IV (5%) with communication of normal bronchial system with esophagus. Patients present with failure to thrive, chronic cough and recurrent pneumonia. Those with severe anomalies present early in life with cough on feeding, also known as Ono’s sign [4]. Eosophageal lung is commonly seen in females with a ratio 1.5 to 1 with preferential right lung involvement like index case [5]. This probably results from proximity of the right mainstem bronchus with the esophagus. Esophageal lung can be associated with other anomalies of cardiac, respiratory or gastrointestinal tract. The definitive treatment is surgical correction.

All children with recurrent pneumonitis and cough following feeds should be thoroughly investigated. The present case was referred with diagnosis of dextrocardia with pneumonia. Radiological investigations were suggestive of esophageal lung. A high index of suspicion and detailed work up should be done in children with recurrent pneumonia.

Contributors: NT, DA, DS: case management; SN: radiological investigations. All the authors were involved in drafting the manuscript reviewing the literature and approve the final manuscript.

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**Delayed Presentation of Respiratory Symptoms and Prolonged Survival in Homozygous α3 Integrin Deficiency**

Interstitial lung disease with nephrotic syndrome and junctional epidermolysis bullosa is caused by biallelic mutations in the integrin gene ITGA3 and is associated with death in infancy. We describe a variant of this syndrome with delayed presentation of symptoms and prolonged survival.

**Keywords:** Epidermolysis bullosa, INLNEB syndrome, Nephrotic syndrome.

Integrins play a vital role in cellular interactions. Interstitial lung disease with nephrotic syndrome and junctional epidermolysis bullosa (INLNEB syndrome) is an autosomal recessive disorder caused due to deficiency of integrin α3. Of the reported 9 cases [1-6], most patients with homoyzygous ITGA3 mutations died in infancy. We present a variant of INLNEB syndrome with delayed presentation of renal and life-threatening respiratory symptoms and prolonged survival past early childhood.

A 9-year-old female child, second born to third degree consanguineous parents, was admitted with complaints of insidious onset breathlessness for 6 months. She was apparently normal till 2 years of age when she developed blistering skin lesions that healed with scarring. She complained of passing foamy, frothy urine, and periorbital puffiness on and off from 4 years of age but was never treated with any chronic medications. Renal symptoms had not progressed for last five years. She also had a history of excessive tearing of eyes and loss of eye lashes and eyebrows. The antenatal and perinatal history was uneventful and developmental milestones were appropriate for age. Examination revealed growth retardation, normal mentation, superciliary madarosis, epiphora, scarring alopecia of scalp, ichthyosis in both arms, forearms, and legs, toe nail dystrophy, healed atrophic scars over body, hyperlinearity of palms and soles, and clubbing of digits (Web Fig. 1 a-d). She was tachypneic at rest with an oxygen saturation of 95% in room air. Investigations showed blood urea 35 mg/dL, serum creatinine 0.7 mg/dL, serum sodium 136 mEq/L, serum potassium 3.9 mEq/L, urine albumin 3+, urine protein/creatinine ratio 6.9, 24-hour urine protein 4.95 g/day, serum albumin 3 g/dL, serum cholesterol 397 mg/dL, and respiratory alkalosis with normal anion gap metabolic acidosis on blood gas. Ultrasound abdomen revealed contracted right kidney (6.3 cm), a cortical cyst (1.5 cm) over the left kidney (8.6 cm) and grade 2 renal parenchymal disease indicative of bilateral hypo-

dysplastic kidneys (an anomaly in the CAKUT spectrum). A micturating cystourethrogram was normal, ruling out vesicourethral reflux. Considering her clinical scenario, the renal biopsy was deferred. High resolution computed tomography of the chest showed features of interstitial lung disease (Web Fig. 1e). Skin biopsy done at the age of 4 years had revealed blisters within the lamina lucida, and she currently had atrophic scars. A provisional diagnosis of INLNEB syndrome was made. Next generation sequencing of an EDTA sample of her peripheral blood revealed a homozygous 3’ splice site mutation (c.1825-1G>A) in intron 13 of the ITGA3 gene which resulted in frameshift and formation of a premature termination codon in exon 14, p.(Val609SerfsTer31) (Web Fig. 1f). She was advised for regular follow-up but succumbed to respiratory complications after 6 months.

Nine patients have been reported earlier [1-6], 7 among them had homozygous ITGA3 mutations. Six among these 7 cases presented with symptoms at birth and expired before two year of age [1-4]. The seventh patient presented in his late teens with isolated involvement of skin and mucosa without any systemic symptoms. The authors suggest that the low level of mutant ITGA3 expression might explain the lack of systemic involvement in this patient. Two other patients were siblings with compound heterozygous ITGA3 mutations without renal involvement and were viable [5]. The case presented here has a homozygous ITGA3 mutation that that is predicted to result in a truncated or dysfunctional ITGA3 protein. Residual activity of the truncated ITGA3 protein could explain the survival of this patient past infancy. Unlike other reported cases of INLNEB where respiratory involvement manifested within few days of life, the present case manifested with dermatological symptoms earlier and later developed renal and respiratory symptoms.

Presence of skin and renal complaints in a patient should make us suspect pulmonary involvement. This will allow an early diagnosis of the disease in order to initiate appropriate management of the complications and genetic counselling.

**Contributors:** SUT: worked up the case and drafted the manuscript; SS,AS: helped in diagnosis, management, and manuscript revision.

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**Competing interest:** None stated.

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Successful Right Atrium-Pulmonary Artery ECMO in an Infant With Severe Necrotizing Pneumonia and Bilateral Bronchopleural Fistula

We report an infant with necrotizing pneumonia and bilateral bronchopleural fistula, who failed on conventional and high frequency ventilation and was managed successfully on Veno-venous Extra Corporeal Membrane Oxygenator (V-V ECMO) with a unique configuration for 12 days, and weaned off successfully.

Keywords: Severe Pneumonia, Management, Ventilation.

Necrotizing pneumonia is a rare form of complicated pneumonia, which often develops secondary to organisms like *Staphylococcus aureus* and *Streptococcus pneumoniae*. It is often difficult to manage, and occasionally develops complications like pneumothorax and broncho-pleural fistula (BPF).

An 11-month-old infant, weighing 9 kg, was referred to us for respiratory distress and fever of 3 days. He had no significant past medical history, was immunized for age and thriving well. Clinical examination revealed features of bronchopneumonia. He was started on high flow nasal cannula (HFNC) oxygen and broad-spectrum antibiotics. Investigations revealed pancytopenia with elevated inflammatory markers. His clinical condition worsened on day 3 of admission with increasing oxygen requirement (FiO₂ 60%) and High flow nasal cannula (HFNC) support (flow 20L/min). He was electively ventilated and put on pressure regulated volume control (PRVC) mode of ventilation. Ventilation protocol was set to targets as suggested in Pediatric acute respiratory syndrome (pARDS) guidelines. The PaO₂/FiO₂ (PF ratio) was less than 150 with PCO₂ <70mm Hg and PH >7.2. Initial blood culture grew *Psuedomonas* and injectable meropenam treatment was started. Prone ventilation was tried but had to be discontinued after two hours as saturations worsened. X-ray showed multiple large pneumatoceles. On day 7, he developed pneumothorax on right side; draining intercostal tube showed continuous bubbling suggesting a bronchopleural fistula (BPF). Ventilation was continued with high frequency oscillatory ventilation (HFOV). Maximum settings on HFOV were FiO₂ of 60%, mean airway pressure (MAP) of 16 cm H₂O and amplitude (delta P) of 45. Child did show some improvement with improving blood gases and was maintained on neuro-paralysis. After one week on HFOV, X-ray showed regressing pneumatoceles with PF ratio improving to >200. PaCO₂ was consistently less than 60 mm Hg and PH>7.3 with HFOV settings of FiO₂ 40%, MAP of 14 cm H2O and amplitude of 40. On day 13, he was weaned off paralysis and changed back to PRVC mode, but developed tension pneumothorax on left side on the next day.

Considering the child to have refractory Acute respiratory distress syndrome (ARDS) with bilateral air leak, Veno-Venous ECMO was initiated on day 15 of hospital admission. Patient’s jugular vein on ultrasound was found to be small hence we decided for central open ECMO. Child was initially put on Veno–venous configuration with inflow and outflow cannulas in right atrium, but had to be re-configured in view of poor flow and re-circulation. Right atrium was cannulated with 22F cannula and pulmonary artery with 14 F cannula, and flow of 900-1000 mL/min was obtained. He was maintained on ECMO for 12 days. On day 12 of ECMO, prior to weaning a bronchoscopic clearance and lavage was taken, which showed carbapenam resistant *Acinetobacter* on culture. Antibiotics were accordingly changed to colistin and tigecycline. Post-ECMO weaning on ventilator, child did
not have air leak on either side and intercostal tubes were removed. He was successfully discharged after 55 days of hospital stay. Chest X-ray before discharge showed near total resolution of pneumatoceles.

The exact pathogenesis of necrotizing pneumonia is not completely understood [1,2]. Necrotic areas may give way resulting in pneumothorax or BPF. When air leak develops the ventilation often becomes challenging. Ensuring acceptable gas exchange with minimum added barotrauma from ventilation is essential. Bilateral broncho-pleural fistula has a mortality risk of 20-50% [3]. Split lung ventilation or differential lung ventilation has been described in necrotizing pneumonia with unilateral broncho-pleural fistula. Several other strategies include endobronchial plugging with human fibrin glue in small fistulas [4], autologous pleural patch, video-assisted thoracoscopic fistulectomy or stapling and pneumonectomy are described in selected cases [5]. Our patient had limited options, as the disease was bilateral and extensive with multiple necrotic areas. High frequency oscillatory ventilation (HFOV) is an option for refractory ARDS and air leaks who fail on conventional ventilation [6]. HFOV eliminates the ‘inflation-deflation’ cycle. It maintains gas exchange with very low tidal volume and optimum mean airway pressure, but this child developed pneumothorax on weaning back to conventional mode.

Veno-arterial (VA) configuration was avoided for ECMO because of higher rates of complications in infants and is not the preferred mode for respiratory failure [7,8]. ECMO cannulation mostly performed in infants is a double lumen internal jugular venous (IJV) cannulation but in our patient IJV lumen was small on screening ultrasound. We initially resorted to an open chest central cannulation with two different cannulas in right atrium. This had to be revised due to poor blood flow and significant re-circulation. We finally tried a unique but less performed, Right atrium-pulmonary artery (RA-PA) configuration to completely eliminate re-circulation.

We have not come across any reports on RA-PA configuration in small children. The main disadvantages of a central open chest ECMO are higher chances of infection and bleeding. The insertion time and bleeding from cannulation site were significantly higher than that described in literature for dual lumen IJV cannula [9]. The case highlights the importance of considering ECMO as a salvage but feasible option in selected cases of severe pneumonia with refractory respiratory failure even in developing countries.

Contributors: BJ: involved in care of patient, preparing the manuscript and literature review; will act as the primary and corresponding author; RS: Involved in care of patient, preparing the manuscript, critical review; MS,JA: Involved in care of patient, review of literature. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.

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Web Fig. 1 Inflamed umbilicus in a neonate with umbilical diphtheria.
Web Fig. 1 (a) Scarring alopecia of the scalp; (b) Healed atrophic scars over both shins and knees; (c) Toe nail dystrophy; (d) Clubbing of digits due to interstitial lung disease; (e) High resolution CT of the chest with features of interstitial lung disease; (f) the homozygous ITGA3 mutation c. 1825-1G>A leads to frameshift with formation of a premature termination codon in exon 14, P. (Val609SerfsTer31).
Musings from Office Practice

Childhood is a short season but may be considered one of the most beautiful ones. As a pediatrician one has the pleasure and privilege to help children navigate it. Each child we encounter is a divine appointment; these little ones touch your heart and embrace your mind giving you a lighter view of life. As I grow older, I look back at the lessons I learnt from some of my most memorable encounters in practice.

Shakespeare said ‘What’s in a name?’ To learn more, read on. As a young child entered my cabin, I called him by the name on the file. The father replied that this was his birth name. On being asked the child said his name was ‘Lucky’. The mother explained that this was his pet name. So I asked the child for his name again. Now his answer was ‘Bahubali’. Both parents laughed and said this was his self proclaimed name. I prodded the child to tell me the name that was used in school and he replied ‘Scholar’. His parents added that all his school mates called him by this name. I patiently waited for his real name and finally was rewarded with a loud ‘Hrishi’ that was spelled out for me in the next breath so that I would write it correctly. I learnt that day the venerable bard could be wrong on occasion.

Children are spontaneous in nature. They have wonderful outbursts that just come out unplanned, unbridled and full of surprises. As a child walked into my office, I extended my hand and said ‘Hello’. In response, he immediately placed his hands next to his ears and loudly said ‘Hello’ mimicking the action of talking on a cell phone. On enquiring ‘How is school?’ he replied ‘Today is a holiday’. When I protested that it wasn’t a holiday for me, pat came the response ‘You should start going to school’. It made me realize that spontaneity is a skill mastered in childhood and lost with age!

Children are fond of games, and to get the child talking I always ask him or her about their favorite ones. Recently, a smart one eagerly started enumerating the name of the games he played – Turbo fast, Masha and the beast, Poptropica etc. Looking at my puzzled face, the mother intervened to say that these were his favorite mobile games. That is when I realized that mobiles are the new playgrounds and playmates for kids in the 21st century.

An obstinate child is a source of headaches and heartaches for parents. A parent once told me that he was being blackmailed. When I wondered whether he had come to the right place, he clarified that the blackmailer was his son. The child refused to do anything unless he got a toy, car, chocolate or his demands were met beforehand. The father was fed up with this behavior and pleaded me to find a way to stop this harassment from the child. I referred him to a book on parenting and a counselor. Many children instruct their parents not to divulge their bad habits (love for junk food and excessive TV watching) to me. When the parents narrate these with the hope that I shall instill some wisdom in child’s head, they look angrily at their parents for exposing them, pout, and refuse to interact after becoming “katti” with both - parents and me. The parents look at me in anticipation, whereas I do not know whether to smile or pretend to scold the child.

While we attempt to teach our children all about life, our children end up teaching us what life is all about. The world indeed appears very beautiful if we learn to look it through a child’s eyes. Let us all try to rediscover the ‘child’ within us.

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Post Doctoral Fellowships in Pediatric Subspecialties

Greetings! Bharati Vidyapeeth Deemed to be University has been reaccredited “A” grade by NAAC and as on today is recognized by the UGC as one of the 20 universities in India for global promotion of education. Bharati Vidyapeeth Deemed to be University Medical College, Pune has an advanced Department of Pediatrics and state-of-the-art infrastructure with multiple well developed Pediatric subspecialties that offer Fellowship training of a national standing.

**Meritorious candidates after successful completion of their training program will be given the opportunity to pursue a 3-month “self-sponsored observership” at Birmingham Women’s and Children’s Hospital, NHS Foundation, UK.**

Courses Available

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<td>Fellowship in Pediatric Rheumatology</td>
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Eligibility: MD / DNB (Pediatrics) / Equivalent Degree, age preferably less than 35 years

Sponsored candidates from Medical colleges can also apply with relevant certificates and documents, last date of application submission being 31\textsuperscript{st} July 2020. The fellowship course is offered purely on merit basis with 20% seats reserved for SAARC countries and other overseas students.

The candidates will be selected on the basis of an interview which will be held in the 2\textsuperscript{nd} week of August 2020 at BVDU Medical College, Pune. Selected candidates will receive free shared accommodation and a monthly stipend as per the University policy.

Eligible and interested candidates may apply with complete biodata and relevant certificates to -

Dr. S. K. Lalwani, Vice Principal, Medical Director, Professor and Head – Pediatrics, 3\textsuperscript{rd} floor, Bharati Hospital, Pune Satara Road, Katraj, Pune – 411 043, MAHARASHTRA.
Phone: 020-24375541 Fax: 020-24375541.

OR
E-mail your application with Curriculum vitae to bvpedfellowship@gmail.com by 31\textsuperscript{st} July 2020
Use of Mobile Phones to Aid Learning in Medical Undergraduates

The new competency-based undergraduate medical program emphasizes on the use of technology for imparting knowledge, and promoting self-directed learning in Indian medical graduate [1], including e-learning [2]. With the easy availability of the internet and smart phones, messages via phone lines (SMS) [2] or via social media ie, What App, Messenger etc are highly prevalent [3]. I read with interest the recent article by Kapoor, et al. [4] reporting on use of What App as a tool for undergraduate classroom teaching. I compliment the authors for addressing this under-explored area in medical education in India. I have the following observations related to the study.

First, only 40 students (32.2%) were enrolled out of a total of 124 students. The principle strength of e-learning tools is their easy availability at all times, thus facilitating asynchronous learning [5] and the ability to overcome resource-constraints. If only 1/3rd of the students are using a modality routinely, it may not be an efficacious educational aid in real life, howsoever effective it may be in an experimental study. Secondly, there was no comparison done of the intervention group (WhatsApp group) with the control group (conventional classroom teaching), this may introduce multiple problems in assessing the effect, the main one being the Hawthorne effect [6]. Thirdly, less than 50% of the volunteer students participated in the discussion. The reason for low participation was not collected, but would have been an important addition to the literature. It is not clarified in the paper whether a pretest was done after conventional classroom teaching of the topic, or without any educational inputs. It would have been still better if the post test scores of both intervention and non intervention groups could have been compared. We have recently used this methodology in a study assessing effect of text messaging (SMS)-based instructions on 92 undergraduate medical students [7]. However, we did not find a significant difference in post-test scores of intervention and control groups, despite good acceptability.

Thus, using e-learning to overcome the reported faculty crunch in medical education in India is a pressing need, given its low cost and high student acceptance [5]. However, more well-conducted research on easily acceptable e-learning modalities in the Indian context is needed to demonstrate its place in the current medical education setting.

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REFERENCES

AUTHORS’ REPLY
We thank the reader for showing interest in our study. This study was done in December, 2015 - February, 2016 with 9th semester students after completion of topics on cardiovascular system. Methodology was informed to them before recruitment; participation had to be voluntary but those who participated, had to attempt pre-post tests. Reasons for relatively low percentage of students volunteering to participate were time constraints due to pressure of university exams.
(February-March 2016) and apprehension of pre-post tests. In fact, pre-university exams were held during study period with interruption in discussion for two weeks. Not many students were having smartphones or using WhatsApp at that time compared to now.

Secondly, study was designed as non-comparative trial with the objectives to determine the acceptability and efficacy of WhatsApp as teaching-learning media in promoting problem-solving skills and self-study beyond classroom and not to compare with conventional classroom teaching [1]. Though less than 50% of the volunteer students participated in the discussion, Hawthorne effect can not be ruled out. In order to avoid bias in online teaching and discussion, pre and post test sheets were assessed only after the post-test was over. Design of study was based on Case-based learning (CBL) and students applied their previous knowledge, did self-reading, step-by-step analysis, shared answers with reasoning and resources on WhatsApp. Timely feedback helped them to clear doubts and promoted learning beyond classrooms. There is evidence that CBL links theory to practice, promotes self-directed, collaborative and active learning amongst students which help them to learn better and gain in confidence [2].

Thirdly, reasons for low participation of volunteer students as per their feedback were: difficulty to find time for going through discussion (18.7%), not comfortable in participating on WhatsApp (8.1%) and some had problem of net-connectivity. Discussion used to be at a fast pace during late-night hours as it was not permitted during college timings. Many students would be asleep by that time. Later when they could go through the discussion, it would have moved forward and they kept on trailing behind. Despite this, 94.6% read all the discussion as per their convenience and more than 80% felt they benefitted from it. Hence, we consider this as strength of our study.

We agree, more studies are required as WhatsApp has potential to be adapted as a teaching-learning media for medical education due to ease of availability and flexibility to participate and/or review and revise content as per one’s convenience.

ANIL KAPOOR and ANJU KAPOOR*
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REFERENCES

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NOVEL CORONAVIRUS (COVID-19) EPIDEMIC

Corona means crown in Latin. The now infamous Corona virus got its name from a spiky crown of glycoproteins on its surface. This RNA virus typically infects mammals and birds. It has caused two previous human outbreaks - SARS CoV and MERS CoV. The SARS CoV epidemic, which began in a hotel in Hong Kong in 2002-2003, infected 8098 cases with a mortality of 10%. The 2012 MERS CoV outbreak in the Middle East had infected 855 cases with a mortality of 37%. In the current Coronavirus epidemic in China the first case was reported in Wuhan on 1st December, 2019 and as of 9 February, the total number of cases documented officially had crossed 37,000 and it appears to have a mortality of 2-3%.

The virus seems to have originated in the Huanan seafood market in Wuhan in China and was probably transmitted by pangolins (ant eater) to humans. In the first article published in the Lancet, the clinical symptoms of 41 patients (median age 49 year) infected with the COVID-19 included fever, cough, myalgia, hemoptysis and dyspnea. Investigations revealed lymphopenia, bilateral fluffy shadows or ground glass appearance on the chest X ray and elevated cytokines and troponin I in the critically ill patients. Of the 41 patients, one third were admitted to ICU and 6 died. Diagnosis is being made using RT-PCR and treatment includes supportive care and empirical use of antivirals including oseltamivir, lopinavir and ritonavir.

Incubation period appears to be 2-14 days. Unlike SARS and MERS CoV, which had gastrointestinal symptoms in 20-25%, these are rare in the COVID-19 infection. However, a subsequent study published in JAMA analyzed 138 patients of whom 40 were health care workers. In this series, a patient admitted in a surgical ward with abdominal symptoms went on to infect 10 more healthcare workers. The high mortality appears to be due to a cytokine storm; though, the use of corticosteroids in these patients did not appear to improve outcomes and also delayed viral clearance. Medical personal are advised to use fitted N95 respiratory masks to limit exposure besides routine precautions of hand washing and precautions with aerosol.

(The Lancet 29 Jan 2020; JAMA 7 Feb 2020)

THE ROBOT RADIOLOGIST

The use of artificial intelligence (AI) in radiology has recently skyrocketed. A 2018 market survey found that 84% of radiology clinics in the US were either using or planning to use artificial intelligence systems. However, the data and algorithms that these systems use to make a diagnosis are sometimes inexplicable to humans. This is called the black box problem. A case pinpoint would be a study published in 2019 in JAMA Network Open studied 85000 chest X rays in people followed over 12 years. Raw data is fed into the computer and then the computer creates its own algorithms to predict outcomes. This is called deep learning. Impressed by the accuracy of the programs predictive ability, when researchers analyzed what it was the computer used to predict mortality, many unusual data was noticed. For example, one parameter the computer used was regions below the shoulder which has no known medical significance. Retrospectively it is felt that the parameter represents flexibility and hence may predict mortality. This discordance of human and computer-aided thought process is called the black box problem since it is virtually invisible to human understanding.

What is still unclear is that if medical AI systems make a mistake who will bear the responsibility. One way around the problem is to develop transparent systems which explain the factors taken into building the algorithm at every stage. Another variable in medical AI systems is that they change and improve over time as they get access to more data and their performance is in constant flux. For now the FDA has developed guidelines for algorithms which evolve over time.

It appears that AI may not replace radiologists in the near future, but “radiologists who use AI will replace radiologists who do not.”
(Scientific American 1 February 2020)

DRONE DELIVERY OF BLOOD PRODUCTS

In the East African nation of Rwanda, medical history is being quietly written. On 21 December, 2016, a 2-year-old girl with severe malaria became the first person to receive a drone delivery of packed RBCs. Since then, more than 4000 units of blood products have been delivered using drones by a US-based startup called Zipline. This technology has reduced the time to deliver blood products in remote areas from nearly 3 or more hours to barely 15 minutes. Till some years ago maternal mortality due to postpartum hemorrhage was a huge problem in Rwanda. The rapid delivery of blood has helped to save precious lives.

It all began when robotics expert Keller Rinaudo and aviation expert Will Hetzler met public health researcher Zachary Mtema in Tanzania. For many of the critical medical problems like availability of blood products, anti-snake venom and anti-rabies immunoglobulins, drone delivery seemed to be an ideal solution. A company was founded and a deal struck with the Rwandan government to build a distribution center near Muhanga. The companies drones, deliver medical supplies within an 80 Km radius of a distribution center. The cost per service is same as the previous motorcycle service but more reliable. In India, Maharashtra has announced that Zipline will provide emergency medicines in the entire state this year. These drones have been listed on Time magazine’s best inventions of 2018.
(www.who.int 12 June 2019)

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Air pollution does not increase asthma risk (Environ Int. 2020 Jan 18;136:105474)

There is uncertainty regarding the role of air pollution on pediatric asthma and allergic conditions, especially as air pollution levels have started to decrease in recent decades in many parts of the world. In five European countries, the association of long-term air pollution levels at the home with pediatric eczema, rhinoconjunctivitis and asthma prevalence in five birth cohorts was studied. Current eczema, rhinoconjunctivitis and asthma were assessed in children aged four (n = 6527) and eight years (n = 2489). Individual outdoor levels of nitrogen dioxide (NO2), nitrogen oxides, mass of particulate matter with a diameter <10 μm (PM10), 10-2.5 μm (PMcoarse) and <2.5 μm (PM2.5), and PM2.5 absorbance were assigned to the birth, four- and eight-year home addresses using highly defined spatial air pollution exposure models. The overall prevalence of pediatric eczema, rhinoconjunctivitis and asthma at four years was 15.4%, 5.9% and 12.4%. No increase was found in the prevalence of these outcomes at four or eight years with increasing air pollution exposure.

In this large meta-analysis of five birth cohorts, there was no indication of adverse effects of long-term air pollution exposure on the prevalence of current pediatric eczema, rhinoconjunctivitis or asthma.


Continuous positive airway pressure (CPAP) has been used in infants with bronchiolitis for decades. Recently, high flow nasal cannula (HFNC) therapy has been introduced. In this study, 50 children with bronchiolitis were randomized to treatment with CPAP or HFNC. Objectives were to compare the respiratory rate, pCO2, and Modified Woods Clinical Asthma Score (M-WCAS) in groups receiving CPAP or HFNC. Neonatal Infant Pain Score (NIPS), treatment duration, treatment failure, and hospitalization length were also compared. No differences were observed in development of respiratory rate, pCO2, or M-WCAS. NIPS was higher in the CPAP group. Treatment failure was scarce in both groups. No significant differences in treatment duration or length of hospitalization were observed.

In infants and young children with bronchiolitis, HFNC may be an effective and pleasant alternative to CPAP. Larger multicenter studies are needed to further explore differences in treatment failure and treatment duration.

Breast feeding delays menopause (JAMA New Open. 2020;3(1):e1919615)

Pregnancy and breastfeeding prevent ovulation and may slow the depletion of the ovarian follicle pool. These factors may lower the risk of early menopause, a condition associated with increased risk of cardiovascular disease and other adverse health outcomes. In this study the association of parity and breastfeeding with the risk of early menopause was studied.

This population-based cohort study within the Nurses' Health Study II cohort (1989-2015) included premenopausal participants who were aged 25 to 42 years at baseline. Response rates were 85% to 90% for each cycle, and follow-up continued until menopause, age 45 years, hysterectomy, oophorectomy, death, cancer diagnosis, loss to follow-up, or end of follow-up in May, 2015. History and duration of total and exclusive breastfeeding were assessed three times during follow-up. Menopause status and age were assessed every 2 years.

In a stratified analysis of parous women, risk of early menopause was lowest among those reporting exclusive breastfeeding for 7 to 12 months in each level of parity (women with 2 pregnancies and 7-12 months of breastfeeding: HR, 0.79; 95% CI, 0.66-0.96; ≥3 pregnancies and 7-12 months of breastfeeding: HR, 0.68; 95% CI, 0.52-0.88; 2 pregnancies and ≥13 months of breastfeeding: HR, 0.87; 95% CI, 0.66-1.15; ≥3 pregnancies and 13-18 months of breastfeeding: HR, 0.86; 95% CI, 0.66-1.13; and ≥3 pregnancies and ≥19 months of breastfeeding: HR, 0.98; 95% CI, 0.72-1.32).

In this study, an inverse association of parity with risk of early menopause was observed. Breastfeeding was associated with significantly lower risk, even after accounting for parity.


The objectives of this prospective case-control study were to determine liver stiffness (LSM) by transient elastography (TE) in children with newly diagnosed chronic liver disease (CLD) and to find out normal values in healthy Indian children. Two groups (50 CLD who underwent liver biopsy and 50 healthy children) aged 5-18 years were recruited prospectively. Liver biopsies were scored as per Metavir scoring and compared with TE. The median age of 100 recruited children was 13.6 years. In healthy children, normal LSM was 4.9 (2.5-7.3) kPa with significantly higher LSM in adolescent males (5.6 (4.1-7.3) kPa) as compared with females (4.3 (3.7-4.9) kPa), P=0.001. In the CLD group, TE was excellent in discriminating significant fibrosis (≥F2) at a cut-off value of 10.6 kPa with area under receiver operating characteristic curve of 0.96. Metavir fibrosis stage and age were independent variables associated with higher LSM in stepwise multiple logistic regression analysis. Normal liver stiffness depends on race, gender, and age. TE is an excellent non-invasive tool to assess significant liver fibrosis and can be used as an alternative to liver biopsy.

This is the first study from India to show the normative data of transient elastography in healthy Indian children.

Dr K. Rajeshwari

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