INDIAN JOURNAL OF PRACTICAL PEDIATRICS

- **IJPP is a quarterly subscription journal of the Indian Academy of Pediatrics committed to presenting practical pediatric issues and management updates in a simple and clear manner**
- **Indexed in Excerpta Medica, CABI Publishing, Scopus**

Vol.20 No.4	**OCT.- DEC. 2018**
Dr.N.C.Gowrishankar Editor-in-Chief	**Dr.S.Thangavelu** Executive Editor

CONTENTS

TOPIC OF INTEREST - "IAP-IJPP CME 2018"

Journal Office and address for communications: Dr. N.C.Gowrishankar, Editor-in-Chief, Indian Journal of Practical Pediatrics, 1A, Block II, Krsna Apartments, 50, Halls Road, Egmore, Chennai - 600 008. Tamil Nadu, India. Tel.No. : 044-28190032 E.mail : ijpp_iap@rediffmail.com

Published by Dr.N.C.Gowrishankar, Editor-in-Chief, IJPP, on behalf of Indian Academy of Pediatrics, from 1A, Block II, Krsna Apartments, 50, Halls Road, Egmore, Chennai - 600 008. Tamil Nadu, India and Printed by Mr. D.Ramanathan, at Alamu Printing Works, 9, Iyyah Street, Royapettah, Chennai-14.

INSTRUCTIONS TO AUTHORS

General

Print the manuscript on one side of standard size A4, white bond paper, with margins of at least 2.5 cm (1") in double space typescript on each side. Use American English using Times New Roman font 12 size. Submit four complete sets of the manuscript.

They are considered for publication on the understanding that they are contributed to this journal solely.

All pages are numbered at the top of the right corner, beginning with the title page.

All manuscripts should be sent to: The Editor-in-Chief, Indian Journal of Practical Pediatrics

Manuscript

1st Page –

Title

Name of the author and affiliation

Institution

Address for correspondence (Email, Phone, Fax if any)

Word count

No. of figures (colour / black and white)

No. of references

Authors contribution

2nd Page –

Abstract (unstructured, not exceeding 100 words) with key words (not exceeding 4)

3rd Page -

Acknowledgement

Points to remember (not more than 5 points)

Text

References

Tables

Legends

Figures – should be good quality, 4 copies black & white / colour,*

(4 x 6 inches – Maxi size) Glossy print

* Each colour image will be charged Rs. 1,000./- separately, with effect from January 2006 (Except for invited articles).

Text

Only generic names should be used

Measurements must be in metric units with System International (SI) Equivalents given in parentheses.

References

Recent and relevant references only

Strictly adhere to Vancouver style

Should be identified in the text by Arabic numerals as superscript.

Type double-space on separate sheets and number consecutively as they appear in the text.

Articles without references / defective references will entail rejection of article.

Tables

Numbered with Roman numerals and typed on separate sheets.

Title should be centered above the table and explanatory notes below the table.

Figures and legends

Unmounted and with figure number, first author's name and top location indicated on the back of each figure.

Legends typed double-space on separate sheet. No title on figure.

All manuscripts, which are rejected will not be returned to author. Those submitting articles should therefore ensure that they retain at least one copy and the illustration, if any.

Article Categories

Review article

Article should be informative covering the recent and practical aspects in that field. Main articles can be in 1500 – 2000 words with 12 – 15 recent references and abstract not exceeding 100 words.

Case report (covering practical importance)

250 – 600 words, 8 – 10 recent references

Clinical spotters section

150 – 200 words write up

With 1 or 2 images of clinically recognizable condition

(of which one could be in the form of clinical photograph / specimen photograph / investigation)

Letters to the Editor

200 – 250 words pertaining to the articles published in the journal or practical viewpoints with scientific backing and appropriate references in Vancouver style.

Check List

Covering letter by corresponding author

Declaration (as enclosed) signed by all authors **

Manuscript (4 copies)

Accompanied by a copy in CD / or submit as an email attachment in addition to hard copy.

Failing to comply with the requirement at the time of submission would lead to the rejection of the article.

Author's contribution / Authorship Criteria

All persons designated as authors should qualify for the authorship. Authorship credit should be based on substantial contributions to i) concept and design, or collection of data, or analysis and interpretation of data; ii) drafting the article or revising it critically for important intellectual content; and iii) final approval of the version to be published. All conditions 1, 2 and 3 must be met. Participation solely in the collection of data does not justify authorship and can be mentioned in the acknowledgement if wanted.

**** Declaration by authors**

I/We certify that the manuscript titled '…….' represents valid work and that neither this manuscript nor one with substantially similar content under my/our authorship has been published or is being considered for publication elsewhere. The author(s) undersigned hereby transfer(s), assign(s), or otherwise convey(s) all copyright ownership, including any and all rights incidental thereto, exclusively to the Indian Journal of Practical Pediatrics, in the event that such work is published in Indian Journal of Practical Pediatrics. I / we assume full responsibility for any infringement of copyright or plagiarism.

Authors' name(s) in order of appearance in the manuscript Signatures (date)

Selection procedures

All articles including invited articles will be peer reviewed by two masked reviewers. The decision of the Editorial Board based on the reviewer's comments is final. All manuscripts, which are rejected will not be returned to author. Those submitting articles should therefore ensure that they retain at least one copy and the illustration, if any.

IAP - IJPP CME 2018

SURFACTANT THERAPY- EVOLUTION AND NEWER TRENDS

***Giridhar Sethuraman**
****Sasi Bhushan Gottimukkala***

Abstract: *Respiratory distress syndrome is an important cause of mortality in preterm babies and surfactant replacement therapy forms an important part of its treatment. However, recent studies have shown that very early administration of continuous positive airway pressure and selective rescue surfactant administration, in extremely preterm infants, increases survival and reduces bronchopulmonary dysplasia, when compared to early intubation and surfactant administration. Less invasive methods of surfactant instillation in spontaneously breathing infants, avoiding intubation and mechanical ventilation are being explored. Also newer synthetic surfactants and surfactant-drug combinations are being studied to improve efficacy and reduce bronchopulmonary dysplasia.*

Keywords: *Surfactant, Respiratory distress syndrome, Preterm, Bronchopulmonary dysplasia.*

Respiratory distress syndrome (RDS) is a common problem in premature newborns resulting in hypoxemic respiratory failure (Fig.1). This occurs because of inadequacy of a highly surface-active phospholipid rich material called surfactant lining the alveoli of the lung, which prevents lung collapse on expiration. The incidence is inversely proportional to the gestational age.

The discovery of surfactant was one of the biggest advances in neonatal intensive care that has dramatically improved the survival of preterm infants. Surfactant replacement therapy is already a well investigated and established therapy in neonatology. However, recent trials showing superiority of non-invasive respiratory support over invasive mechanical ventilation and surfactant use, in reducing mortality and respiratory morbidities, have spurred interest in alternate surfactant administrative methods.

* Associate Professor of Neonatology

** DM Postgraduate - Neonatology,
Chettinad Hospital and Research Institute,
Kanchipuram, Tamil Nadu.

email: giridharsethu@gmail.com

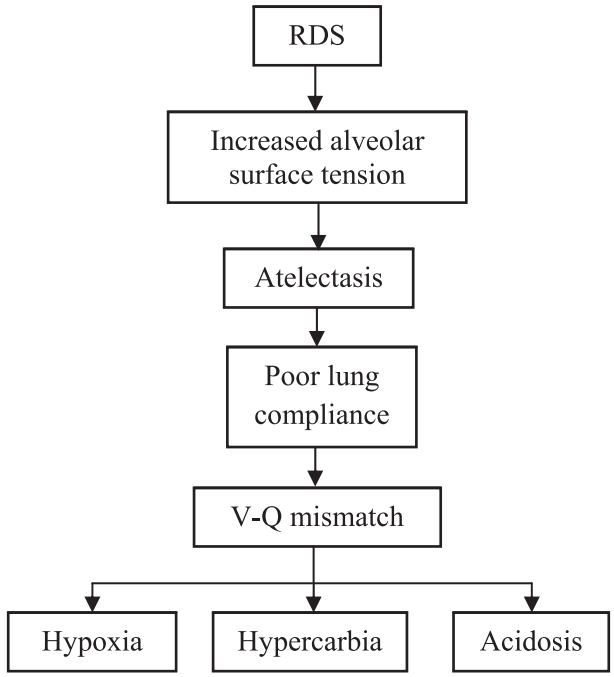

Fig.1. Respiratory distress syndrome – Effect on neonatal lung

Evolution of surfactant use

The role of a surface active agent in maintaining lung mechanics was first suggested by Von Neergard in 1929 and later confirmed by Greunwald.[1] Three decades later, Pattle and then Clements demonstrated the properties and function of surfactant.[2,3] Avery and Mead demonstrated the clinical importance of surfactant when they found that the lungs of babies who died from the hyaline membrane disease were deficient in surfactant.[4]

After Patrick Bouvier Kennedy (son of the then US President John F Kennedy) died of RDS, in spite of receiving the then standard of care treatment, research on surfactants picked up pace and the first trials of nebulized synthetic (protein-free) surfactant to prevent RDS were published soon. These trials were unsuccessful. However, Goran Enhorning and Bengt Robertson in the early 1970's demonstrated that natural surfactants (containing proteins)

were effective in an immature rabbit model of RDS, and this was confirmed by Jobe et al in preterm lambs.[5,6]

Finally, in 1980, Fujiwara, et al reported the first human clinical trial in preterm infants with RDS using bovine surfactant.[7] Over the next few years, the composition and biosynthesis of surfactant was extensively studied and numerous randomized controlled trials of many different natural and synthetic surfactants, demonstrated reduction in pulmonary air leaks and neonatal mortality.

Surfactants - Natural and synthetic

Surfactant preparations are divided into two groups - natural and synthetic surfactants. Although natural surfactants were the first to be synthesized, research in the 1990's focused mainly on synthetic surfactants as the natural surfactants differed in their concentration of phospholipids and surfactant proteins. However,multiple surfactant trials, either as prophylaxis or treatment of RDS, have proven that natural surfactants are superior to the first generation protein-free synthetic products like Exosurf as they reduced air leaks by 35% and mortality by 11%.[8] This effect is primarily due to the lack of surfactant protein-B useful for binding the phospholipids together and spreading of the surfactant. The 21st century, saw the introduction of Lucinactant (Surfaxin), with additional peptides mimicking surfactant protein-B. When compared with animal-derived surfactant (beractant or poractant), lucinactant was shown to be equivalent.[9,10] Even though Lucinactant was approved in 2012, production was stopped in 2015 due to logistic reasons. Another novel synthetic surfactant enriched by two recombinant surfactant proteins B and C (CHF5633) was compared with poractant alpha and found to have comparable efficacy.[11] As none of these synthetic surfactants are under production, only currently available natural surfactants should be used.

Natural surfactants: Preparations and dosage

The natural surfactant preparations currently available in India are listed in Table I. Even though initial trials comparing natural surfactants showed similar efficacy, Ramanathan et al, [12] in a trial comparing two doses of poractant alfa, at either 100 or 200 mg/kg bodyweight, with beractant at 100 mg/kg body weight, demonstrated that at 100 mg/kg both preparations had similar efficacy, but an initial dose of 200 mg/kg of poractant alfa resulted in lower mortality at 36 weeks compared to 100mg/kg beractant initial dose. Subsequently, the 2015 Cochrane meta-analysis also confirmed the survival benefit with the higher dosage of poractant alfa.[13] Thus an initial dose of 100-200mg/kg of natural surfactant should be administered and a higher 200mg/kg initial dose of poractant alfa is to be preferred. Repeat doses of surfactant administration may be required with ongoing evidence of RDS, such as the need for continued mechanical ventilation or oxygen dependence and this strategy has been demonstrated in a Cochrane review to reduce the risk of pneumothorax.

Surfactant – Methods of administration

Although nebulized surfactant administration in RDS was reported as early as 1964, the time-tested method of surfactant administration is tracheal instillation through an endotracheal tube.[15] As more trials demonstrated the clinical efficacy of very early Continuous Positive Airway Pressure (CPAP) over mechanical ventilation in reducing bronchopulmonary dysplasia (BPD), even in extremely low birth weight (ELBW) infants, interest in administration of surfactant without intubation in spontaneously breathing infants receiving CPAP, grew. The first successful protocol was an interruption for intubation and surfactant administration followed by a short interval of positive pressure ventilation followed by rapid extubation using intubation–surfactant–extubation (INSURE) technique.

Table I. Surfactant preparations available in India (as of 2018)

Source	Brand	Content	Concentration (per ml)	Dosage (recommended)	Interval between doses	Max. number of doses
Bovine minced	Beractant (Survanta)	8ml & 4ml	1ml=25mg	100mg per kg	6 hours	4
Porcine minced	Poractant alfa (Curosurf)	1.5ml & 3ml	1ml=80mg	200mg per kg (first) 100mg per kg (repeat)	12 hours	3
Bovine lavage	Neosurf	5ml & 3ml	1ml=27mg	135mg per kg	Not specified	4

The INSURE protocol was first introduced by Verder, et al in 1994 and after various trials, gained popularity around the world as a less invasive modality of surfactant administration.[16] However, in ELBW infants, rapid extubation to CPAP after brief mechanical ventilation is not always possible, resulting in ventilation induced lung injury. Recent trials and a meta-analysis comparing early INSURE with CPAP demonstrated that the outcomes were not significantly different.[17-20] Currently, there is no evidence to suggest that either early INSURE or CPAP alone is superior to the other.

As the lack of perceived clinical benefit with INSURE was often attributed to the brief mechanical ventilation involved, researchers looked at alternate options of administering surfactant intra-tracheally without intubation. Kribs, et al reported the "COLOGNE" method with surfactant being administered via a narrow intratracheal catheter (4-5 F) placed with Magill forceps.[21] They reported a reduction in the need for mechanical ventilation and BPD compared with invasive mechanical ventilation. Later techniques like "HOBART" by Dargville, et al in 2011, using semi-rigid 16 G Angiocath and "TAKE CARE" by Kanmaz, et al in 2012 using 5 Fr feeding tube without the use of Magill's forceps, were shown to be useful in minimizing the trauma of intubation and need for mechanical ventilation.[22,23] These similar looking newer approaches were collectively termed as Less Invasive Surfactant Administration (LISA) or Minimally Invasive Surfactant Therapy (MIST). They have been shown to reduce the rates of BPD and/or death when compared to invasive mechanical ventilation in various recent meta-analyses.[25-27] A summary of the various tracheal MIST approaches is provided in Table II.

LISA failure has been deûned differently by various groups and can be summarized as need for inspired oxygen fraction (FiO_2) of > 0.45-0.6, partial pressure of carbon dioxide of more than 60-65 mm Hg and a pH of <7.15. Failure rates have been reported to range from 75% in infants of 23-26 weeks of gestation to 41% in infants with a birth weight of <1500 g.[28,29] Even though MIST appears to be a promising modification of tracheal surfactant administration, further clarifications are required regarding the optimum dosage and timing of surfactant administration, the optimum surfactant and whether to re-administer additional surfactant doses if there is regurgitation of surfactant.

Non-tracheal surfactant administration methods

Surfactant nebulization is the oldest concept, which exemplified MIST in its truest sense. But this technique was plagued by many technical problems like inability to achieve an aerosol particle size of 0.5 to 2 mm with existing nebulizers and non-availability of a suitable interface to deliver surfactant and reduce wastage of surfactant. However, a customized vibrating membrane nebulizer (eFlow Neonatal Nebulizer System, Pari Pharma GmbH, Starnberg, Germany) used in a recent trial to deliver surfactant, resulted in promising results.[30] Also a promising investigational surfactant/aerosol product, Aerosurf (Wind tree Therapeutics Inc, Pennsylvania, United States), that combines synthetic KL-4 surfactant with a unique capillary aerosol generator (CAG) technology showed promising results in a phase 2b clinical trial, with a good safety profile compared to CPAP (unpublished data).

Intra-pharyngeal surfactant instillation is also an old approach, first applied by Enhorning and Robertson in 1972, where the surfactant is injected into the pharynx before the first breath. In 2011, a Cochrane meta-analysis concluded that this method is potentially feasible, safe and may be effective, but well-designed randomized controlled trials were required.[31]

Table II. Tracheal catheterization techniques of surfactant administration

Method	Author, Year	Catheter	Magill forceps used	Dose and mode of surfactant delivey
COLOGNE	Kribs, 2007[21]	4- to 5-FG feeding tube	Yes	100 mg/kg slow push,1-3 minute
HOBART	Dargaville 2011,2013[22]	16-G Angiocath	No	100–200 mg/kg3-4 boluses,15-30 second
TAKE CARE	Kanmaz, 2012[23]	5-F feeding tube	No	100 mg/kg Slow bolus,30-60 second
SONSURE	Aguar, 2014[24]	4-F feeding tube	Yes	100 mg/kg Slow push,1-3 minute

In 2004, Brimacombe, et al reported surfactant administration using the laryngeal mask airway (LMA), which is a supraglottic emergency airway device.[32] Later, a trial done, using LMA, in larger infants (>1000g) has shown promising results in reducing need for subsequent mechanical ventilation.[33] Also a recent study (CALMEST) combined the use of an LMA as a guide for a LISA catheter to administer surfactant.[34] However, more data is needed especially in ELBW infants, before LMA can be definitely recommended as a surfactant administration tool.

Surfactant administration - Timing

Prophylactic (intubation and surfactant administration within 10-30 minutes after birth to infants at high risk of developing RDS) and early rescue surfactant administration (within <2 hours after birth) were earlier recommended as preferred strategies, as the then meta-analysis had clearly shown benefits in reducing mortality and air leaks with these strategies.[35] However, their applicability in the current era of early CPAP and more prevalent antenatal steroid coverage, is doubtful.

Recent large clinical trials in ELBW infants (COIN,[36] SUPPORT[37] and VON-DRM[17]) have concluded that it was better to start with CPAP support in the delivery room if possible and intubate and administer surfactant only to infants with signs of RDS. A recent Cochrane meta-analysis,[38] including these studies using early CPAP, clearly showed that the benefits of prophylactic surfactant on mortality and air leaks could no longer be demonstrated now. Also there was a higher incidence of BPD or death in infants who received prophylactic surfactant. Hence, the prophylactic surfactant administration strategy could no longer be recommended.

However, the early rescue strategy of surfactant administration still continues to be recommended and a recent Cochrane meta-analysis has shown that this strategy reduced mortality, air leaks, chronic lung disease and chronic lung disease or death.[39]

Most studies included in the meta-analysis administered surfactant as rescue treatment, when a FiO_2 of > 40% was reached. However, definite evidence on what is the FiO_2 threshold for rescue surfactant administration is lacking and the recent third update of the European Guidelines for the management of RDS suggested administering rescue treatment to extremely preterm infants < 26 weeks and requiring > 0.3 of FiO_2, and that the commonly used threshold of 0.4 should be reserved for preterm infants born > 26 weeks of gestation.[40] Also the optimal timing of treatment for LISA/MIST also needs to be determined.

Surfactant plus therapies

The success of surfactant is greatly supplemented by the use of prenatal corticosteroids and early postnatal CPAP. A single course of betamethasone or dexamethasone causes a significant reduction in mortality, RDS, necrotizing enterocolitis and intraventricular hemorrhage and is recommended in all pregnancies with threatened preterm labour <34 weeks' gestation. As BPD remains a significant concern, in spite of surfactants and non-invasive ventilation, intra-tracheal administration of a surfactant-budesonide mixture was studied in preterm infants as a remedy. A recent meta-analysis of the two clinical trials revealed that infants who received this intervention demonstrated 43% reduction in the risk of BPD.[41] However, larger trials are required before this mixture can be recommended.

Surfactant for respiratory disorders other than RDS

Secondary surfactant deficiency occurs in many neonatal respiratory disorders like meconium aspiration syndrome (MAS), congenital pneumonia, pulmonary haemorrhage and pulmonary hypertension. Surfactant replacement therapy for meconium aspiration is the most studied of the lot and the Cochrane meta-analysis has shown that surfactant replacement reduces the need for extra corporeal membrane oxygenation.[42] However, mortality is not reduced and most of the trials used higher and frequent doses of surfactant. Also surfactant lung lavage (saline diluted surfactant) for MAS did not show much benefit.[43-45] The implications of these findings for low and middle income countries is important as surfactant is an extremely expensive drug and extra corporeal life support is often not an option in these countries. Hence, further cost-benefit analysis is required before recommending either of the surfactant delivery modes in neonates with MAS. Benefits of surfactant therapy for other respiratory disorders have been shown only in small observational studies and hence no definite recommendations can be made.

Points to Remember

- ***Surfactant replacement therapy should be considered for all preterm infants with RDS.***
- ***Natural surfactant preparations are preferred over synthetic preparations.***
- ***Early rescue surfactant therapy should be considered for babies <26 weeks' gestation when FiO_2 requirements >0.3 and >26 weeks' when FiO_2 requirements >0.4.***

- ***Newer surfactant administration methods (LISA/ MIST) may be preferred over INSURE for surfactant administration. However the best minimally invasive method of surfactant administration is yet to be identified.***
- ***Antenatal steroids work additively with postnatal surfactant and is recommended in all pregnancies with threatened preterm labour <34 weeks' gestation.***

References

1. Gruenwald P. Surface tension as a factor in the resistance of neonatal lungs to aeration. Am J Obstet Gynecol 1947; 53:996-1007.
2. Pattle RE. Properties, function and origin of the alveolar lining layer. Nature 1955; 175: 1125-1126.
3. Clements JA, Brown ES, Johnson RP. Pulmonary surface tension and the mucus lining of the lungs: some theoretical considerations. J Appl Physiol 1958; 12:262-268.
4. Avery ME, Mead J. Surface properties in relation to atelectasis and hyaline membrane disease. AMA J Dis Child 1959; 97:517-523.
5. Enhorning G, Robertson B. Lung expansion in the premature rabbit fetus after tracheal deposition of surfactant. Pediatrics 1972; 50:58-66.
6. Jobe A, Ikegami M, Glatz T, Yoshida Y, Diakomanolis E, Padbury J. Duration and characteristics of treatment of premature lambs with natural surfactant. J Clin Invest 1981; 67:370-375.
7. Fujiwara T, Maeta H, Chida S, Morita T, Watabe Y, Abe T. Artificial surfactant therapy in hyaline-membrane disease. Lancet 1980; 1:55-59.
8. Soll RF, Blanco F. Natural surfactant extract versus synthetic surfactant for neonatal respiratory distress syndrome. Cochrane Database Syst Rev. 2001; (2):CD000144.
9. Sinha SK, Lacaze-Masmonteil T, Valls i Soler A, Wiswell TE, Gadzinowski J, Hajdu J, et al; Surfaxin Therapy Against Respiratory Distress Syndrome Collaborative Group. A multicenter, randomized, controlled trial of lucinactant versus poractant alfa among very premature infants at high risk for respiratory distress syndrome. Pediatrics. 2005; 115(4):1030-1038.
10. Moya F, Sinha S, Gadzinowski J, D'Agostino R, Segal R, Guardia C, et al; SELECT and STAR Study Investigators. One year follow-up of very preterm infants who received lucinactant for prevention of respiratory distress syndrome: results from 2 multicenter randomized, controlled trials. Pediatrics 2007; 119(6)%: e1361-70. Epub 2007 May 28.
11. Ricci F, Murgia X, Razzetti R, Pelizzi N, Salomone F. In vitro and in vivo comparison between poractant alfa and the new generation synthetic surfactant CHF5633. Pediatr Res. 2017 Feb; 81(2):369-375.
12. Ramanathan R, Rasmussen MR, Gerstmann DR, Finer N, Sekar K, North American Study G. A randomized, multicenter masked comparison trial of poractant alfa (Curosurf) versus beractant (Survanta) in the treatment of respiratory distress syndrome in preterm infants. Am J Perinatol 2004; 21:109-119.
13. Ardell S, Pfister RH, Soll R. Animal derived surfactant extract versus protein free synthetic surfactant for the prevention and treatment of respiratory distress syndrome. Cochrane Database Syst Rev 2015; 8:CD000144.
14. Soll R, Ozek E. Multiple versus single doses of exogenous surfactant for the prevention or treatment of neonatal respiratory distress syndrome. Cochrane Database Syst Rev 2009; (1):CD000141.
15. Robillard E, Alarie Y, Dagenais-Perusse P, Baril E, Guilbeault A. Microaerosol administration of synthetic beta-gammadipalmitoyl- L-alpha-lecithin in the respiratory distress syndrome: a preliminary report. Can Med Assoc J 1964; 90:55-57.
16. Verder H, Robertson B, Greisen G, Ebbesen F, Albertsen P, Lundstrom K, et al. Surfactant therapy and nasal continuous positive airway pressure for newborns with respiratory distress syndrome. Danish-Swedish Multicenter Study Group. N Engl J Med 1994; 331:1051-1055.
17. Dunn MS, Kaempf J, de Klerk A, de Klerk R, Reilly M, Howard D, et al; Vermont Oxford Network DRM Study Group: Randomized trial comparing 3 approaches to the initial respiratory management of preterm neonates. Pediatrics 2011; 128:e1069-e1076.
18. Rojas MA, Lozano JM, Rojas MX, Laughon M, Bose CL, Rondon MA, Charry L, et al; Colombian Neonatal Research Network: Very early surfactant without mandatory ventilation in premature infants treated with early continuous positive airway pressure: a randomized, controlled trial. Pediatrics 2009; 123:137-142.
19. Sandri F, Plavka R, Ancora G, Simeoni U, Stranak Z, Martinelli, et al. Prophylactic or early selective surfactant combined with nCPAP in very preterm infants. Pediatrics 2010; 125:e1402-e1409.
20. Isayama T, Chai-Adisaksopha C, McDonald SD. Noninvasive ventilation with vs without early surfactant to prevent chronic lung disease in preterm infants: a systematic review and meta-analysis. JAMA Pediatr 2015; 169:731-739.
21. Kribs A, Pillekamp F, Hunseler C, Vierzig A, Roth B: Early administration of surfactant in spontaneous breathing with nCPAP: feasibility and outcome in extremely premature infants (postmenstrual age d"27 weeks). PaediatrAnaest 2007; 17:364-369.
22. Dargaville PA, Aiyappan A, Cornelius A, Williams C, De Paoli AG: Preliminary evaluation of a new technique of minimally invasive surfactant therapy. Arch Dis Child Fetal Neonatal Ed 2011; 96:F243-F248.

23. Kanmaz HG, Erdeve O, Canpolat FE, Mutlu B, Dilmen U. Surfactant administration via thin catheter during spontaneous breathing: randomized controlled trial. Pediatrics 2013; 131(2):e502-e509.
24. Aguar M, Cernada M, Brugada M, Gimeno A, Gutierrez A, Vento M. Minimally invasive surfactant therapy with a gastric tube is as effective as the intubation, surfactant, and extubation technique in preterm babies. Acta Paediatr 2014; 103:e229–e233.
25. Aldana-Aguirre JC, Pinto M, Featherstone RM, Kumar M: Less invasive surfactant administration versus intubation for surfactant delivery in preterm infants with respiratory distress syndrome: a systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed 2017; 102:F17-F23.
26. Rigo V, Lefebvre C, Broux I: Surfactant instillation in spontaneously breathing preterm infants: a systematic review and meta-analysis. Eur J Pediatr 2016; 175:1933-1942.
27. Isayama T, Chai-Adisaksopha C, McDonald SD Noninvasive Ventilation With vs Without Early Surfactant to Prevent Chronic Lung Disease in Preterm Infants: A Systematic Review and Meta-analysis. JAMA Pediatr. 2015; 169(8):731-739.
28. Gopel W, Kribs A, Ziegler A, Laux R, Hoehn T, Wieg C, et al. Avoidance of mechanical ventilation by surfactant treatment of spontaneously breathing preterm infants (AMV): an openlabel, randomised, controlled trial. Lancet 2011; 378:1627-1634.
29. Kribs A, Hartel C, Kattner E, Vochem M, Kuster H, Moller J, et al. Surfactant without intubation in preterm infants with respiratory distress: First multi-center data. Klin Padiatr 2010; 222:13-17.
30. Minocchieri S, Berry CA, Pillow JJ; CureNeb Study Team. Nebulised surfactant to reduce severity of respiratory distress: a blinded, parallel, randomised controlled trial. Arch Dis Child Fetal Neonatal Ed. 2018 Jul 26. [Epub ahead of print]
31. Abdel-Latif ME, Osborn DA, Pharyngeal instillation of surfactant before the first breath for prevention of morbidity and mortality in preterm infants at risk of respiratory distress syndrome. Cochrane Database Syst Rev. 2011 Mar 16; (3):CD008311.
32. Brimacombe J, Gandini D, Keller C: The laryngeal mask airway for administration of surfactant in two neonates with respiratory distress syndrome. PaediatrAnaes 2004; 14:188-190.
33. Pinheiro JM, Santana-Rivas Q, Pezzano C: Randomized trial of laryngeal mask airway versus endotracheal intubation for surfactant delivery. J Perinatol 2016; 36: 196-201.
34. Vannozzi I, Ciantelli M, Moscuzza F, Scaramuzzo RT, Panizza D, Sigali E, Boldrini A, Cuttano A. Catheter and Laryngeal Mask Endotracheal Surfactant Therapy: the CALMEST approach as a novel MIST technique. J Matern Fetal Neonatal Med. 2017 Oct; 30(19):2375-2377.
35. Soll RF, Morley CJ. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. Cochrane Database Syst Rev. 2001; (2):CD000510.
36. Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB, Investigators CT: Nasal CPAP or intubation at birth for very preterm infants. N Engl J Med 2008; 358:700-708.
37. SUPPORT Study Group of the Eunice Shriver NICHD Neonatal Research Network: Early CPAP versus surfactant in extremely preterm infants. N Engl J Med 2010; 362:1970-1979.
38. Rojas-Reyes MX, Morley CJ, Soll R. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. Cochrane Database Syst Rev 2012; 3(3):CD000510.
39. Bahadue FL, Soll R. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. Cochrane Database Syst Rev 2012; 11(11):CD001456.
40. Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Plavka R, et al. European consensus guidelines on the management of respiratory distress syndrome – 2016 update. Neonatology 2017; 111:107-125.
41. Venkataraman R, Kamaluddeen M, Hasan SU, Robertson HL, Lodha A. Intratracheal Administration of Budesonide - Surfactant in Prevention of Bronchopulmonary Dysplasia in Very Low Birth Weight Infants: A Systematic Review and Meta-Analysis. Pediatr Pulmonol 2017; 52(7):968-975.
42. El Shahed AI, Dargaville PA, Ohlsson A, Soll R. Surfactant for meconium aspiration syndrome in term and late preterm infants. Cochrane Database Syst Rev 2014 Dec 14; (12):CD002054.
43. Hahn S, Choi HJ, Soll R, Dargaville PA. Lung lavage for meconium aspiration syndrome in newborn infants. Cochrane Database Syst Rev. 2013 Apr 30; (4):CD003486.
44. Choi HJ, Hahn S, Lee J, Park BJ, Lee SM, Kim HS, Bae CW. Surfactant lavage therapy for meconium aspiration syndrome: a systematic review and meta-analysis. Neonatology. 2012; 101(3):183-191
45. Bandiya P, Nangia S, Saili A.Surfactant Lung Lavage vs. Standard Care in the Treatment of Meconium Aspiration Syndrome-A Randomized Trial. J Trop Pediatr. 2018 Jun 6. [Epub ahead of print].

IAP - IJPP CME 2018

ACUTE RHEUMATIC FEVER – CURRENT CONCEPTS

Ritchie Sharon Solomon

Abstract: *Acute rheumatic fever is the result of an autoimmune response to group A Streptococcus pharyngitis and the long-term damage to cardiac valves is known as rheumatic heart disease and is a notable cause of morbidity and mortality in resource-poor settings around the world. Recognizing the variability in clinical presentation in high-risk population groups, there has been a revision of Jones criteria, which now brings it into closer alignment with other international guidelines for the diagnosis of acute rheumatic fever. Doppler echocardiography has also been included as a tool to diagnose cardiac involvement.*

Keywords: *Rheumatic fever, Jones criteria, Revised.*

Rheumatic fever (RF) and rheumatic heart disease (RHD) continue to be a major health hazard in most developing countries. Rheumatic heart disease remains an important preventable cause of cardiovascular disability and death, particularly in low and middle-income countries.

Rheumatic heart disease that follows RF is a non-suppurative manifestation of group A beta hemolytic streptococcal (GAS) pharyngitis. RF is widely accepted as an immunological disorder that follows GAS infection. RHD has almost been eliminated with improved social and health infrastructure in affluent countries. Better living conditions, nutrition and access to affordable health care have been the fundamental reasons for the significant disease reduction in industrialized countries. The high incidence and prevalence of the disease in indigenous communities within affluent countries such as Australia, New Zealand and American Samoa are classic examples of how community socioeconomic status is a major determinant in the incidence of the rheumatic fever.[1,2] Recent data reveals that the major burden of rheumatic heart disease is found mostly in low-income and middle income countries and among immigrants and older adults in high-income countries.[3,4]

There is a wide variation in the clinical manifestations of GAS infection. Pharyngitis (streptococcal sore throat), mainly affecting children between the ages of 5 and 15, is thought to be the most common clinical presentation linked to acute rheumatic fever (ARF). ARF is an autoimmune inflammatory process in which antibodies formed to target antigenic bacterial epitopes cross-react with proteins found in synovial, cardiac, and neuronal tissues. ARF can manifest with arthritis, carditis, subcutaneous nodules, erythema marginatum and Sydenham chorea. Most of the ARF manifestations are self-limited; however, valvular disease resulting from repeated or severe episodes of rheumatic fever leads to irreversible valvular thickening and fibrosis. The long-term sequelae of valvular regurgitation and eventually valvular stenosis are the hallmark of RHD.

Pathophysiology

Following GAS infection of pharynx, neutrophils, macrophages and dendritic cells phagocytose bacteria and present the antigen to T cells. Both B and T cells initially respond by antibody production (IgM and IgG) and subsequently through T cell activation (mainly CD4+ cells). In susceptible individuals, the host response against GAS will trigger autoimmune reactions against host tissues (like the heart, joints, brain and/or skin) mediated by both streptococcus specific antibodies and T cells through a process called molecular mimicry. The sharing of antibody or T cell epitopes between the host and the microorganism is called as molecular mimicry. Hence, following infection, there is generation of antibodies or T cells against the infectious pathogen to clear the infection from the host and these antibodies and T cells also recognize host antigens. In rheumatic fever, antibodies are formed against the host antigens located in heart, brain, joints and skin.[5,6]

The cross-reactive immune response results in transient migratory polyarthritis as a result of the formation of immune complexes, Sydenham's chorea as the antibodies bind to basal ganglia and neuronal cells, erythema marginatum and subcutaneous nodules in the skin as antibodies bind to keratin and leads to inflammation of both heart valves and the myocardium. The rarer skin

* Assistant Professor of Pediatric Cardiology, Institute of Child Health and Hospital for Children, Madras Medical College, Chennai.

email: ritchie_sharon@yahoo.com

manifestation erythema marginatum might be due to antibodies against group A carbohydrate cross-reacting with keratin.[7,8] Subcutaneous nodules that sometimes form in ARF might be granulomatous lesions that develop in the dermis of the skin as a result of delayed hypersensitivity against GAS antigens or these nodules formation might be driven by similar mechanisms to Aschoff bodies that are granulomatous lesions that form in the heart valve.

The targets of the cross-reactive antibodies are cardiac myosin in the myocardium and laminin in the valve endothelium and basement membrane and these antibodies cross-react with the group A carbohydrate or streptococcal M protein. There is an immunological relationship between GAS polysaccharide and the structural glycoproteins of the heart valve which is supported by the fact that the cross-reactive antibodies might also recognize glycosylated proteins or carbohydrate epitopes on the valve.[9] Studies have shown that α-helical protein structures found in streptococcal M proteins, cardiac myosin, keratin and laminin are involved in cross-reactivity with antibodies that react to the group A carbohydrate epitope N-acetyl-β-D-glucosamine (Table I). This supports the fact that α-helical protein epitopes and group A carbohydrate epitope N-acetyl-β-D-glucosamine are important targets of cross-reactive antibodies in ARF.[10,11] Polymorphisms in several genes coding for immune-related proteins has been associated with ARF and RHD susceptibility.

Epidemiological background

The pattern of disease in the high-prevalence regions is often hyperendemic, with cases occurring throughout the year and a virtual absence of outbreaks. The pattern of disease in affluent regions is a low background incidence of ARF with periodic outbreaks. There are differences in incidence even in populations within the same country (Maori group within New Zealand population). In conclusion, the global distribution of ARF/RHD is clearly disproportionate.

This has led to concern regarding the uniform sensitivity of the Jones criteria, when applied to geographic areas or to populations within those areas where ARF is hyperendemic. A single set of diagnostic criteria may no longer be sufficient for all population groups and in all geographic regions in view of the heterogeneity in disease pattern. There should be variability in applying diagnostic criteria in low risk compared with high-risk populations to avoid over diagnosis in low incidence populations and to avoid under diagnosis in high-risk populations.

Revised Jones criteria[12]

The American Heart Association's Council on Cardiovascular Disease in the young decided to review the historic Jones criteria used to diagnose ARF in the context of the current epidemiology of the disease. They had to consider the changes in presentation that can result from the now worldwide usage of nonsteroidal anti-inflammatory drugs. They had to review the numerous published studies that support the use of Doppler echocardiography as a means to diagnose cardiac involvement in acute rheumatic fever, even when overt clinical findings are not apparent. A meticulous assessment was undertaken to determine the evidence for defining subclinical carditis and to consider the possibility of including it as a major criterion of the Jones criteria. This effort had resulted in the first substantial revision to the Jones criteria by the American Heart Association (AHA) since 1992 and the first application of the Classification of Recommendations and Levels of Evidence categories to

Table I. Molecular mimicry and cross-reactive immune response

Manifestations	Specific target for cross reactive antibodies
Transient migratory polyarthritis	Immune complexes targeting proteins of synovium and cartilage
Sydenham's chorea	Basal ganglia and neuronal cells
Erythema marginatum	Keratin
Subcutaneous nodules	Keratin Additional mechanism: delayed hypersensitivity against GAS antigens (Aschoff bodies are similar granulomatous lesions that form in the heart valve)
Myocardial involvement	Cardiac myosin in the myocardium
Valvular involvement	Laminin in the valve endothelium and basement membrane

Table II. Revised Jones criteria 2015[12]

Level of risk	Major	Minor
Low risk (RF incidence ≤2/ 100,000 school-aged children or all-age RHD prevalence of <1/1,000 population/ year)	• Carditis - Clinical and/or subclinical • Arthritis - Polyarthritis only • Chorea • Erythema marginatum • Subcutaneous nodules	• Polyarthralgia • Fever (>38.5 °C) • Erythrocyte sedimentation rate (ESR) >60 mm in the first hour and/or C-Reactive protein (CRP) >3.0 mg/dL • Prolonged PR interval (unless carditis is a major criterion)
Moderate and high risk (RF incidence >2/100,000 school-aged children or all-age RHD prevalence of >1/1,000 population/ year)	• Carditis - Clinical and/or subclinical • Arthritis - Monoarthritis or polyarthritis- Polyarthralgia • Chorea • Erythema marginatum • Subcutaneous nodules	• Monoarthralgia • Fever (>38 °C) • ESR >30 mm/hour and/or CRP >3.0 mg/dL • Prolonged PR interval (unless carditis is a major criterion)
Initial attack of ARF - two major manifestations or one major plus two minor manifestations with evidence of preceding GAS infection. *Recurrent RF - two major or one major and two minor or three minor manifestations are sufficient with evidence of preceding GAS infection.* *Exceptions for evidence of preceding GAS infection - chorea and chronic indolent rheumatic carditis with insidious onset and slow progression.*		

the Jones criteria (Table II). The changes made in Jones criteria following major reviews are listed in Table III.

Laboratory evidence of antecedent group A streptococcal infection is needed whenever possible and the diagnosis is in doubt when such evidence is not available. A negative streptococcal antibody test helps to exclude a recent infection, but a positive test does not necessarily indicate an infection in the past few months. Increased or rising anti-streptolysin O titer or other streptococcal antibodies (anti-DNAse B) can be an evidence of preceding infection. A rise in titer is a better evidence than a single titer result. A positive throat culture for GAS or a positive rapid GAS antigen test are also taken as evidences for probable streptococcal pharyngitis.

The significant changes in the revised Jones criteria are mainly in the area of carditis, arthritis, fever and cutoff for inflammatory markers.

Sub clinical carditis

Clinical carditis remains universally accepted as a major manifestation in all populations. The concept of subclinical carditis has become incorporated into other guidelines as a valid major manifestation of ARF.[12] Subclinical carditis (SC) refers exclusively to a situation in which classic auscultatory findings of valvular dysfunction either are not present or are not recognized by the diagnosing clinician but echocardiography/Doppler studies reveal mitral or aortic valvulitis.

Studies on patients with ARF using echocardiography have brought out the shortcomings of auscultation in identifying valve disease that does not result in haemodynamic abnormalities consisting of regurgitant systolic or diastolic murmurs. This has resulted in the identification of sub-clinical carditis. Data for SC are now available from a number of studies though follow up data are insufficient. SC has been found in 5 to 29% of acute RF patients.[13,14] More than twenty five studies have reported echocardiography/Doppler evidence of mitral or aortic valve regurgitation in patients with ARF despite the absence of classic auscultatory findings.

Studies have shown the validity of Doppler echocardiography in diagnosing carditis in ARF. In asymptomatic children, it is important to differentiate physiological regurgitation from pathological regurgitation. For a regurgitant jet to be considered pathological, all four criteria should be met as mentioned in Table IV. All substantial regurgitant jets should produce a high velocity signal with a complete envelope on continuous-wave Doppler echocardiography. Non-rheumatic causes of mitral valve finding to be considered include physiological

Table III. Major changes in Jones criteria over the years

Sl. No.	Manifestations	Original Jones criteria 1944	AHA modified 1956	AHA update 1992	Revised Jones criteria AHA 2015
1.	Carditis	Major	Major	Major	Major
2.	Long PR		Minor	Minor	Minor
3.	Arthritis		Major	Major	**Major:** *Low risk area*- Polyarthritis only *High risk area*- Polyarthritis & Monoarthritis
4.	Arthralgia	Major	Minor	Minor	**Major:** *High risk area*-Polyarthralgia **Minor:** *Low risk area*- Polyarthralgia *High risk area*-Monoarthralgia
5.	Subcutaneous nodules	Major	Major	Major	Major
6.	Chorea	Major	Major	Major	Major
7.	Erythema marginatum	Minor	Major	Major	Major
8.	Pre-existing RF/RHD	Major	Minor	Minor	
9.	Fever, WBC, ESR,CRP	Minor	Minor	Minor	**Minor:** *Low risk area:* Fever >38.5°C, ESR>60mm, CRP>3mg/dL *High risk area:* Fever >38°C, ESR>30mm, CRP>3mg/dL
10.	Epistaxis, Abdominal pain, anemia	Minor			
11.	Recent streptococcal infection		Minor	Special consideration	Special consideration
12.	Subclinical carditis				Major

mitral regurgitation, mitral valve prolapse, myxomatous mitral valve and congenital mitral valve disease. Endocarditis and annular dilation from conditions associated with left-sided heart dilation, including myocarditis and cardiomyopathy are also to be considered in the differential diagnosis.

Hence, the consensus statement states that echocardiography with Doppler should be performed in all cases of confirmed and suspected ARF[12] (Class I; Level of Evidence B). It is reasonable to consider performing serial echocardiography/ Doppler studies in any patient with diagnosed or suspected ARF even if documented

Table IV. Doppler findings for pathological regurgitation

	Pathological mitral regurgitation (all 4 criteria met)	Pathological aortic regurgitation (all 4 criteria met)
1.	Seen in at least 2 views	Seen in at least 2 views
2.	Jet length >2 cm in at least 1 view	Jet length >1 cm in at least 1 view
3.	Peak velocity >3 m/s	Peak velocity >3 m/s
4.	Pan systolic jet in at least 1 envelope	Pan diastolic jet in at least 1 envelope

carditis is not present on diagnosis (Class IIa; Level of Evidence C). Echocardiography/Doppler testing should be performed to assess whether carditis is present in the absence of auscultatory findings, particularly in moderate- to high-risk populations and when ARF is considered likely (Class I; Level of Evidence B). Echocardiography/Doppler findings not consistent with carditis should exclude that diagnosis in patients with a heart murmur otherwise thought to indicate rheumatic carditis (Class I; Level of Evidence B).

Aseptic monoarthritis

Studies from India, Australia and Fiji have indicated that aseptic mono arthritis may be important as a clinical manifestation of ARF in selected high-risk populations. As per revised Jones criteria, consideration that mono arthritis may be part of the ARF spectrum should be limited to patients from moderate- to high-risk populations (Class I; Level of Evidence C).[12]

Polyarthralgia

Polyarthralgia is a very common, highly nonspecific manifestation of a number of rheumatologic disorders. The inclusion of polyarthralgia as a major manifestation is applicable only for moderate- or high-incidence populations and only after careful consideration and exclusion of other causes of arthralgia such as autoimmune, viral or reactive arthropathies (Class IIb; Level of Evidence C).[12]

Minor manifestations

In a high-risk group like the Aboriginal Australian population, the definition of fever as a temperature >38°C has resulted in improved sensitivity, with 75% of individuals with ARF meeting this criterion compared with only 25% when a cutoff value of >39°C was used. Fever associated with ARF usually exceeds 38.5°C orally in most of the cases including all low risk population. Hence, fever more than 38.5°C is considered as a minor criterion in low risk population whereas the cut off in high-risk population is 38°C. For most populations, an ESR >60 mm in the first hour and CRP >3.0 mg/dL are considered typical of ARF. In the latest revision of Jones criteria the cutoff of ESR to be considered as a minor criterion in high-risk population and low risk population are 30 mm and 60 mm in one hour respectively. Normal ESR and CRP levels should prompt serious reconsideration of the diagnosis of ARF because except for patients with isolated chorea, these values are almost never normal in ARF.

Possible rheumatic fever

In some situations, a given clinical presentation may not fulfill these updated Jones criteria, but the clinician may still strongly suspect that ARF is the diagnosis. This may occur in areas where laboratory tests for acute phase reactants or for confirmation of recent streptococcal infection are not available, documentation of clinical features is not clear, or the history is not considered to be reliable. In such situations, clinicians should use their discretion and clinical acumen to make the diagnosis that they consider most likely and manage the patient accordingly. Hence, the consensus statement states that whenever there is genuine uncertainty, it is reasonable to consider 12 months of secondary prophylaxis followed by detailed reevaluation with history, physical examination and repeat echocardiogram.

Points to Remember

- ***Global distribution of ARF/RHD is clearly disproportionate.***
- ***Subclinical carditis has been made as a major criterion in all population groups.***
- ***Echocardiography/Doppler studies helps to identify pathological regurgitation (mitral/aortic valvulitis)***
- ***Aseptic mono arthritis is an important clinical manifestation in specific population groups.***

- ***Normal ESR and CRP levels should prompt serious reconsideration of the diagnosis of ARF except in patients with isolated chorea.***

References

1. Lawrence JG, Carapetis JR, Griffiths K, Edwards K, Condon JR. Acute rheumatic fever and rheumatic heart disease: Incidence and progression in the Northern Territory of Australia, 1997 to 2010. Circulation 2013; 128:492-501.
2. Beaudoin A, Edison L, Introcaso CE, Goh L, Marrone J, Mejia A, et al. Acute rheumatic fever and rheumatic heart diseaseamong children-American Samoa, 2011-2012. MMWRMorb Mortal Wkly Rep 2015; 64:555-558.
3. Doukky R, Abusin SA, Bayissa YA, Kelly RF, Ansari AH. Rheumatic heart disease in modern urban America: a cohort study of immigrant and indigenous patients in Chicago. Int J Cardiol 2014; 175:178-180.
4. Rothenbuhler M, O'Sullivan CJ, Stortecky S, Stefanini GG, Spitzer E, Estill J, et al. Active surveillance for rheumatic heart disease in endemic regions: a systematic review and meta-analysis of prevalence among children and adolescents. Lancet Glob Health 2014; 2(12): e717-e726.
5. Ben-Pazi H, Stoner JA, Cunningham MW. Dopamine receptor autoantibodies correlate with symptoms in Sydenham's chorea. PLoS ONE. 2013; 8:e73516.
6. Husby G, van de Rijn I, Zabriskie JB, Abdin ZH, Williams RC. Antibodies reacting with cytoplasm of subthalamic and caudate nuclei neurons in chorea and acute rheumatic fever. J Exp Med 1976; 144:1094-1110.
7. Shikhman AR, Cunningham MW. Immunological mimicry between N-acetyl-beta-D-glucosamine and cytokeratin peptides. Evidence for a microbially driven anti-keratin antibody response. J Immunol 1994; 152:4375-4387.
8. Swerlick RA, Cunningham MW, Hall NK. Monoclonal antibodies cross-reactive with group A streptococci and normal and psoriatic human skin. J Invest Dermatol 1986; 87:367-371.
9. Goldstein I, Halpern B, Robert L. Immunological relationship between streptococcus A polysaccharide and the structural glycoproteins of heart valve. Nature 1967; 213:44-47.
10. Shikhman AR, Cunningham MW. Immunological mimicry between N-acetyl-beta-D-glucosamine and cytokeratin peptides. Evidence for a microbially driven anti-keratin antibody response. J Immunol 1994; 152:4375 -4387.
11. Cunningham MW. Pathogenesis of group A streptococcal infections. Clin Microbiol Rev 2000; 13:470-511.
12. Gewitz MH, Baltimore RS, Tani LY, Sable CA, Shulman ST, Carapetis J, et al. Revision of the Jones Criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association. Circulation 2015; 131:1806-1818.
13. Lanna CC, Tonelli E, Barros MV, Goulart EM, Mota CC. Subclinical rheumatic valvitis: a long-term follow-up. Cardiol Young 2003; 13:431-438.
14. Hilário MO, Andrade JL, Gasparian AB, Carvalho AC, Andrade CT, Len CA. The value of echocardiography in the diagnosis and follow up of rheumatic carditis in children and adolescents: a 2 year prospective study. J Rheumatol 2000; 27:1082-1086.

CLIPPINGS

Infant walker - related injuries in the United States.

230676 children <15 months old were treated for infant walker-related injuries in US emergency departments from 1990 to 2014. Infant walkers do not help children to learn walking and they can delay normal motor and mental development. Majority of these injuries occur due to fall down the stairs and majority sustain head injury. Existing data indicate considerable risk of major and minor injuries and even death from the use of walkers, 90% of the injuries are in the head and neck region. 75% are due to fall from stairs. Adult supervision cannot prevent the risk as the speed of the mobile infant walker is 3ft/sec which is tmuch beyond the reaction time of an adult to prevent injury. Alternatively baby walker like devices ie., stationary activity centers which allow children to bounce, swivel and tip can be used. The infant walker related injury rates have declined in US following the restrictions on sale of infant walkers. AAP position statement is to ban the sale of infant walkers and the same should be applicable to other parts of the world as well.

Sims A, Chounthirath T, Yang J, Yang J, Hodges NL, Smith GA. Infant walker - Related injuries in the United States. Pediatrics 2018; 142(4):e20174332.

IAP - IJPP CME 2018

NEPHROTIC SYNDROME - MANAGEMENT GUIDELINES

*Sangeetha G

Abstract: *Steroid sensitive nephrotic syndrome is the most common form of nephrotic syndrome in children. Earlier, dysregulation of T cells was considered as the cause for proteinuria. Molecular mechanisms like podocyte injury, presence of circulating lymphocytotoxin, vascular permeability factor, impaired lymphocyte response with cross talk between T and B cells, etc., have given new insights in the understanding of nephrotic syndrome. Hypothesis about the mechanism of edema is also changing, with more focus on tubular epithelial sodium channels. Glucocorticoid is the cornerstone of treatment as the majority of children achieve complete remission after prednisolone treatment.*

Keywords: *Nephrotic syndrome, Steroid sparing drugs, Diuretics.*

Idiopathic nephrotic syndrome (INS) is the most common type of nephrotic syndrome (NS) seen in children. Heavy nephrotic range proteinuria (urine protein of 3+/4+ or spot urine protein creatinine ratio of >2 or >50mg/kg/day or >40mg/m^2/hour in a timed sample) caused by glomerular lesion leads to the manifestation of edema, hypoalbuminemia (<2.5 g/dL) and hyper lipidemia (cholesterol >200 mg/dL).[1,2] Idiopathic steroid sensitive nephrotic syndrome (SSNS) is the most common form of childhood nephrotic syndrome, representing more than 90 percent of cases between 1 to 10 years of age. An estimated annual incidence of steroid-sensitive nephrotic syndrome in children in the United States of America and in Europe is 1-3/100,000 in children below 16 years of age with a cumulative prevalence of 16/100,000 children. It is six-fold greater in Indian population.[3]

* Assistant Professor,
Department of Pediatric Medicine and
Division of Pediatric Nephrology,
Sri Ramachandra Institute of Higher Education
and Research, Chennai.
email: sangeethaperungo@gmail.com

Approximately 92% of children with nephrotic syndrome respond to corticosteroid therapy.[4] Hence steroid therapy is given to patients with a high probability of having minimal change disease without confirmation of the diagnosis by renal biopsy. The remaining 8% children take the steroid resistant course. Children who are deviating from the normal course will need alternative immnunosuppressive therapy and renal biopsy in certain conditions. Supportive management includes proper fluid, diet, treatment of complications and advise on proper immunization.

Clinical presentation

Presentation of NS is usually between the ages of 2 years and 7 years. Boys are more commonly affected than girls (3.8:1). Onset of the disease is usually preceded by an upper respiratory tract infection, allergic reactions, drugs or vaccinations. But it is not clear whether it is real or simple coincidental event. Sudden onset edema starting from periorbital region may gradually increase and can present with bilateral pitting pedal edema, abdominal distention, sacral edema and reduced urine output. When the edema is severe, it may produce scrotal or labial swelling, pleural and pericardial effusion. Massive ascites can cause dyspnea. Causes for abdominal pain in children with nephrotic syndrome include hypovolemia, peritonitis, thrombosis and rarely pancreatitis. Macroscopic hematuria is rare whereas microscopic hematuria can be there in 20% of children with NS but without any histopathologic or prognostic significance.[5] Examination should include measurement of height, weight and blood pressure with other vitals. Transient hypertension can be found in minority of children during the onset of the disease. However, children on long-term steroids and calcineurin inhibitors can develop hypertension as an adverse effect. Physical examination is mainly meant for documenting the severity of edema, focus of sepsis as well as signs of systemic illnesses like skin rashes, arthritis and hepatosplenomegaly.[6]

Investigations

First and second line investigations in nephrotic syndrome the given in Table I and II.

Table I. Investigations - First line

Investigations	Remarks
Urinalysis	3+ or more proteinuria on three consecutive days by dipstick/heat coagulation method or spot urine protein creatinine ratio of >2 mg/mg or 24 hours urine protein >40 mg/m^2/hour or >50 mg/kg/day indicates nephrotic range proteinuria. Persistent microscopic hematuria (>5RBCs/HPF) may be there in non minimal change disease.
	Maltese cross and lipid cast may be seen.
Complete blood count	To look for any evidence of infection.
Blood urea nitrogen (BUN), serum creatinine and serum electrolytes	Transient elevation of BUN (15 to 40%). Dilutional hyponatremia may be present. Persistent elevation of renal parameters indicates non-minimal change disease.
Serum albumin	<2.5 g/dL
Serum cholesterol	>200 mg/dL
Tuberculin skin test, X-ray chest, sputum / RGJ for AFB	To rule out TB
Ultrasound abdomen	To look for kidney size, site and echogenicity, ascites and pleural effusion.

Table II. Investigations - Second line

Investigations	Remarks
Serum complement C3 levels, antistreptolysin O titers	Helpful in children presenting with acute nephritic onset nephrotic syndrome.
Hepatitis B and C (HBsAg, anti HCV), anti HIV antibodies	History of recent jaundice and raised levels of transaminases.
Complement C3, C4, antinuclear antibody (ANA) and anti-double-stranded DNA (anti-dsDNA)	Suspected systemic causes like systemic lupus erythematosus (SLE) and membrano proliferative glomerulonephritis.
Genetic mutation analysis	Useful in primary steroid resistance, syndromic SRNS, onset less than 1 year of age and family history of nephrotic syndrome.
Renal biopsy	• Age of presentation <1 year and >12 years • Nephrotic syndrome with acute kidney injury after ruling out diuretic usage and hypovolemia • Steroid resistant nephrotic syndrome • Suspected secondary causes like SLE and Henoch Schonlein purpura • Before starting calcineurin inhibitor (CNI) therapy • Re-biopsy after 2 years of CNI therapy to check for toxicity of the drugs

Management

General supportive measures

It includes modification in diet, salt and fluid intake. A normal salt containing balanced diet with adequate proteins (1.5–2.0 g/kg) and calories is recommended. However, salt restriction to 1–2 g/day is advised in children with persistent edema. Fluid restriction is necessary in addition to sodium restriction in these children. In case of severe edema, fluid intake should be restricted to insensible water loss whereas in moderate edema, fluid equivalent to previous day's urine output and insensible water loss can be allowed. Only minimal or no fluid restriction is needed in mild edema. Saturated fat intake is restricted. Children with NS can be allowed to have full activity unless they are sick.

Edema management

In children with moderate-to-severe edema causing discomfort, diuretics should be added. Furosemide increases sodium delivery to the distal nephron. Under normal circumstances only a small fraction of the sodium is reabsorbed from the distal nephron and this leads to natriuretic effect. In contrast, due to induction of $Na^{2+}K^{+}$ATPase channels in NS, there is an increase in sodium reabsorption thereby reducing natriuretic effect of furosemide. This can be overcome by coadministration of amiloride which inhibits the distal sodium reabsorption by blocking the epithelial sodium channels (ENaC). Hence, it is advisable to use combination of diuretics either in the form of loop/thiazide or loop/amiloride rather than a single diuretic.[7] In resistant edema, causes like impaired absorption of oral diuretics due to bowel wall edema, which may reduce the drug's bioavailability, should be considered and intravenous drugs preferred in such situations. In refractory edema, 20% albumin infusion (0.5-1 g/kg) can be tried.[8] It is ideal to give furosemide at the end of infusion in order to prevent pulmonary edema. Albumin is an expensive medicine with only short duration benefit as it is rapidly excreted in the urine. It should be reserved for the most resistant, severe and symptomatic edema. Serial monitoring of electrolytes is needed with diuretic therapy.

Specific management

The goal of management is to induce remission and maintain it with nil or minimal side effects of the medications. Nephrotic syndrome should be treated adequately with proper dose and duration of corticosteroids. The standard steroid of choice for treatment is only prednisolone. The common terminologies used in nephrotic syndrome is given in Table III.

As per Indian society of pediatric nephrology (ISPN) guidelines, initial episode of nephrotic syndrome should be treated with prednisolone at a dose of 2 mg/kg/day (maximum 60 mg in single or divided doses) for 6 weeks, followed by 1.5 mg/kg/day (maximum 40 mg) as a single morning dose on alternate days for the next 6 weeks followed by tapering over 2-4 weeks.[1] After 4 weeks of daily steroids, if the child does not go into remission, he/she is considered to have steroid resistant nephrotic syndrome.

Table III. Common terminologies in nephrotic syndrome

Remission	Urine albumin nil or trace (or proteinuria <4 mg/m^2/hr) for 3 consecutive early morning specimens.
Relapse	Urine albumin 3+ or 4+ (or proteinuria >40 mg/m^2/hr or 50 mg/Kg /24hrs) for 3 consecutive early morning specimens, having been in remission previously.
Frequent relapsing nephrotic syndrome (FRNS)	Two or more relapses in initial six months or more than three relapses in any twelve months period.
Steroid dependent nephrotic syndrome (SDNS)	Two consecutive relapses when on alternate day steroids or within 14 days of its discontinuation.
Early non-responder or primary steroid resistant nephrotic syndrome (SRNS)	Absence of remission despite therapy with prednisolone at a dose of 2 mg/kg/day for 4 weeks during the first episode itself.
Late steroid non-responder	Steroid resistance in a child who had previously responded to steroid therapy
Partial remission	1 to 2+ proteinuria or urine protein to creatinine ratio between 0.2 and 2, serum albumin >2.5 g/dL and no edema

As per Kidney Disease: Improving Global Outcomes (KDIGO) guidelines 60 mg/m^2/day or 2 mg/kg/day (maximum dose 60 mg) is given daily for 6 weeks followed by 40 mg/m^2/day or 1.5 mg/kg/day (maximum dose 40 mg) on alternate days is continued for a period of 2–5 months with tapering of the dose.[9]

Management of steroid sensitive nephrotic syndrome as per Indian Society of Pediatric Nephrology (ISPN) 2008 and Kidney Disease: Improving Global outcomes (KDIGO)2012 is summarised in Table IV.[10]

Steroids can cause increased appetite, gastritis, hyperglycemia, hypertension and cushingoid features

Table IV. Management of steroid sensitive nephrotic syndrome

	Indian Society of Pediatric Nephrology (ISPN) 2008	**Kidney Disease: Improving Global outcomes (KDIGO)2012**
Initial episode	Prednisolone Daily: 2 mg/kg (max. 60 mg) for 6 wk Alternate days (AD): 1.5 mg/kg (max. 40 mg) for 6 weeks; discontinued without taper	Prednisolone Daily: 60 mg/m^2 for 4-6 week AD: 40 mg/m^{2}for 2-5 months, tapered Total duration: >12 weeks
Relapse; infrequent relapses	Prednisolone Daily: 2 mg/kg until remission; then AD: 1.5 mg/kg for 4 week; discontinued	Prednisolone Daily: 60 mg/m^2 till remission AD: 40 mg/m^2 for >4 week
Frequent relapses, steroid dependence	Long term prednisolone: Treat relapse as above, then administer therapy on AD at a dose of 0.5-0.7 mg/kg for 9-18 months	Long term prednisolone: AD for >3 months in lowest dose Administer dose daily during respiratory tract & other infections Administer daily, in lowest dose to maintain remission without major adverse effects, if AD therapy is ineffective
	Corticosteroid sparing agents: Prednisolone threshold >0.5-0.7 mg/kg or if steroid toxicity	Corticosteroid sparing agents: Use if steroid toxicity
	Levamisole: 2-2.5 mg/kg AD for 1-2 year	Levamisole: 2.5 mg/kg AD for >1 year
	Cyclophosphamide[$1]: 2 mg/kg/d for 12 week Chlorambucil: Not recommended	Alkylating agents: For frequent relapses; may use in steroid dependence; avoid second course; initiate therapy in remission
	Calcineurin inhibitors[$2]: Cyclosporine 4-5 mg/kg, tacrolimus 0.1-0.2 mg/kg daily x 1-2 year; levels if non-compliance, toxicity, unsatisfactory response	Calcineurin inhibitors: Cyclosporine or tacrolimus for >1 year; latter preferred if unacceptable cosmetic side effects with cyclosporine; monitor levels during therapy
	Mycophenolatemofetil: 800-1200 mg/m^2 daily for 1-2 year	Mycophenolate mofetil: 1200 mg/m^2 daily for >1 yr
	Mizoribine: Not mentioned	Mizoribine: Suggest that not be used
	Azathioprine: Not mentioned	Azathioprine: Recommend that not be used
	Rituximab: Not mentioned	Rituximab:If failing other agents, serious adverse effects

[$]Prefer in [1]patients with significant steroid toxicity, severe relapses with hypovolemia or thrombosis, poor compliance or difficult follow up; [2]patients who continue to show steroid dependence or frequent relapses despite treatment with agents listed previously.

which are reversible with discontinuation of therapy. Growth retardation, posterior subcapsular cataract, mood swings and osteoporosis are common with long-term steroids.

Role of low dose steroids

Children with FRNS or SDNS may be tried with low dose steroids. Steroid threshold should be less than 0.5-0.7 mg/kg on alternate days and the course can be continued for 9-18 months. If the threshold is high or in case of steroid toxicity, change to alternative drug therapy.[1]

Role of alternative drugs

Levamisole: Children with FRNS or SDNS in whom steroid threshold is high are the ideal candidates for levamisole therapy. It is an immune modulator used for the purpose of steroid sparing effect and hence ideally should be started after inducing remission. Dose is 2-2.5 mg/kg on alternate days for 12-24 months. It is given along with steroids at a dose of 1.5 mg/kg on alternate days which is gradually tapered to a maintenance dose of 0.25-0.5 mg/kg and continued for 6-12 months.[1] Adverse effects are leukopenia, flu-like symptoms, liver toxicity, convulsions and skin rashes. Total leukocyte count should be monitored every 12-16 weeks. Counts less than 4,000/ mm^3 need discontinuation of the drug.

Cyclophosphamide: It is a cytotoxic alkylating agent which depletes cells of the immune system. Again, the indications are FRNS and SDNS. It is given at the dose of 2-2.5 mg/kg/day for 12 weeks orally or as monthly pulse dose for 6 months through intravenous route but cumulative dosage should not exceed 168 mg/kg/course. It should be initiated following remission of proteinuria in FRNS and SDNS. Prednisolone is co-administered for 6-12 months.

Short-term adverse effects are nausea, vomiting, hemorrhagic cystitis, leucopoenia and alopecia. Total leukocyte counts are monitored every 2 weeks. Drug should be temporarily discontinued if the blood counts fall below 4,000/ mm^3. Maintenance of good hydration (2 L/m^2/day) and administration of mesna prevents the complication of hemorrhagic cystitis. Dosage of injection mesna is 20% of cyclophosphamide dose which is given at 0, 3, 6 and 9 hours of infusion. Long-term side effects are malignancy and gonadal toxicity which is often seen in post-pubertal males if the recommended dose is exceeded.

Mycophenolate mofetil (MMF): It is an antiproliferative agent that inhibits T and B lymphocyte proliferation by inhibition of inosine monophosphate dehydrogenase, which is a key enzyme in purine biosynthesis. It is given at the dosage of 800-1,200 mg/m^2/day in two divided doses along with tapering doses of prednisolone for 12-24 months. Leukopenia, gastrointestinal discomfort and diarrhea are the few potential adverse reactions with MMF use. Leukocyte counts and transaminases levels should be monitored every 1-2 months and like cyclophosphamide, treatment is usually withheld if counts fall below 4000/ mm^3.

Calcineurin inhibitors (CNIs): Children with SDNS or FRNS who have failed to attain remission with the above drugs and SRNS children should be treated with calcineurin inhibitors. However, renal biopsy is mandatory before initiating CNI therapy. Calcineurin inhibitors prevent T-cell activation through inhibition of calcineurin-induced IL-2 gene expression as well as stabilization of the podocyte actin cytoskeleton. Cyclosporine (CsA) is given at a dose of 4-5 mg/kg/day for 12-24 months. Dosage of tacrolimus is 0.1-0.2 mg/kg/day for 12-24 months. Prednisolone is co-administered and tapered to a low maintenance dose of 0.25-0.5 mg/kg on alternate days which is continued for 6-12 months. Tacrolimus is preferred over cyclosporine in view of lack of cosmetic side effects such as hirsutism and gingival hyperplasia, which is seen with cyclosporine.

Children on tacrolimus and cyclosporine should be checked for renal function and blood sugar, blood pressure every 2-3 months and lipid profile annually. Blood levels of CNIs should be measured 2-4 weeks after initiation of therapy. Subsequent drug level monitoring is needed in case of suspected noncompliance, unsatisfactory response and renal toxicity which is proven by elevated serum creatinine level of 30% or more from the baseline value.[2] Trough (12-hour) blood levels of cyclosporine should be maintained at 80-120 ng/mL and tacrolimus at 5-8 ng/mL.

Rituximab: It is a novel genetically-engineered chimeric anti-CD20 monoclonal antibody that selectively targets CD20-positive B cells. It causes Fc-mediated apoptosis and cell lysis of B cells through complement dependent as well as independent mechanisms. Proposed mechanism is that depletion of B cells might alter T cell function, restoration of T regulatory cell populations and upregulation of their functions.[11] Rituximab is found to be very effective in difficult SDNS/FRNS but it shows variable results for SRNS. Dosage is 375 mg/m^2 once a week for two doses in SDNS/FRNS and four doses for SRNS. Goal of therapy is to keep CD19 levels below 1% of leukocytes. With the recovery of B cells, relapse is expected.

Adverse reactions in the form of infusion reactions such as flu-like symptoms, tachycardia, hypotension or hypertension can be seen. It is also associated with long-

term risk of infections, restrictive lung disease and progressive multifocal leukoencephalopathy.

Role of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) are the drug of choice for hypertension in children with NS. These drugs also have the added advantage of antiproteinuric effect. Serum creatinine and potassium are monitored 2 weeks after initiating the therapy, followed by once in 2-3 months. These agents should be avoided if the estimated GFR is less than 30 mL/minute/1.73 m^2. Calcium-channel blockers and β-adrenergic antagonists are the second-line drugs. All children with SRNS should be initiated on ACEI.[9] Children intolerant to ACEI can be started on ARBs for the antiproteinuric effect.

Lipid lowering drugs

Lipid profile is monitored annually in SRNS children. Children with persistent abnormal lipid profile despite 3-6 months of specific treatment are treated with lipid-lowering agents. Total serum cholesterol greater than 200 mg/dL, LDL cholesterol greater than 130 mg/dL and triglycerides greater than 200 mg/dL require therapy with HMG-CoA reductase inhibitors.

Immunization

Live attenuated vaccines are contraindicated in immune compromised children. Children receiving prednisolone at a dose of greater than 2 mg/kg/day or greater than 20 mg/day in children weighing above 10 kg for more than 14 days are considered immune compromised. However, inactivated or killed vaccines can be given. Live vaccines are administered once the child is off immunosuppressive medications for at least 4 weeks. These vaccines may be given to children receiving alternate day prednisolone at dose less than 0.5 mg/kg. All children with nephrotic syndrome should receive immunization against pneumococcal infections, as spontaneous bacterial peritonitis is common in them. Two to four doses of the heptavalent conjugate pneumococcal vaccine is given for children below 2 years of age. For previously unimmunized children between 2 and 6 years, two doses of the pneumococcal conjugate vaccine (PCV) has to given followed by a dose of 23 valent polysaccharide vaccine 8 weeks later. A single dose of PCV 13 followed 8 weeks later by polysaccharide vaccine is advisable in children older than 6 years. Two doses of varicella vaccination at 8 weeks interval are given when the child is in remission. Oral polio vaccine should not be given to the siblings of active nephrotic syndrome child as it carries the transmission risk.

Stress dose of steroids

Children who have received high dose steroids for more than 2 weeks in the past 1 year are at risk of suppression of the hypothalamic-pituitary-adrenal axis during the period of stress. These children should be treated with steroids during stress like surgery, anesthesia and serious infections. Corticosteroids can be used as parenteral hydrocortisone at a dose of 2-4 mg/kg/day or oral prednisolone at a dose of 0.3-1 mg/kg/day. This is given for the duration of stress and the same can be tapered rapidly.

Points to Remember

- ***Idiopathic nephrotic syndrome is the most common among childhood nephrotic syndrome.***
- ***Nephrotic syndrome should be treated adequately with corticosteroids both in terms of dosage and duration.***
- ***In case of relapse, adequate treatment of infection may result in spontaneous remission.***
- ***Low dose steroid is always coadministered with steroid sparing drugs in the initial period of treatment of FRNS and SDNS.***
- ***All steroid sparing drugs have their own benefits and adverse effects and needs serial monitoring.***
- ***Rituximab which selectively targets CD20-positive B cells is useful in difficult SDNS and FRNS. It may have variable results for SRNS.***
- ***Nephrotic edema should be treated cautiously with serial monitoring of electrolytes.***
- ***Parents of nephrotic syndrome children should be counselled regarding the need for vaccination during remission, particularly pneumococcal and varicella vaccination.***
- ***Children with risk of suppression of hypothalamic-pituitary-adrenal axis should get stress dose steroids during the period of stress.***

References

1. Bagga A, Ali U, Banerjee S, Kanitkar M, Phadke KD, Senguttuvan P, et al. Indian Pediatric Nephrology Group, Indian Academy of Paediatrics. Management of Steroid Sensitive Nephrotic Syndrome: Revised guidelines. Indian Pediatr 2008; 45: 203-214.

2. Gulati A, Bagga A, Gulati S, Mehta KP, Vijayakumar M. Indian Society of Pediatric Nephrology, Indian Academy of Pediatrics. Management of Steroid Resistant Nephrotic Syndrome. Indian Pediatr 2009; 46(1):35-47.
3. Niaudet P, Boyer O. Idiopathic nephrotic syndrome in children: clinical aspects. In: Avner ED, Harmon WE, Niaudet P, Yoshikawa NEmma F, Goldstein SL (Eds). Pediatric Nephrology, 7th Edn, Verlag Berlin Heidelberg: Springer; 2016; pp839-882.
4. McCaffrey J, Lennon R, Webb NJ. The non-immunosuppressive management of childhood nephrotic syndrome. Pediatr Nephrol 2016; 31(9):1383-1402.
5. Andolino TP, Reid-Adam J. Nephrotic Syndrome. Pediatr Rev 2015; 36(3): 117-125.
6. Gbadegesin R, Smoyer WE. Nephrotic syndrome. In: Geary DF, Schaefer F (Eds). Comprehensive Pediatric Nephrology, 1st Edn, Philadelphia: Mosby Elsevier; 2008; pp204-218.
7. Siddall EC, Radhakrishnan J. The pathophysiology of edema formation in the nephrotic syndrome. Kidney Int 2012; 82(6):635-642.
8. Saravanan G, Amish Udani, Vijayakumar M. Steroid sensitive nephrotic syndrome. In: Vijayakumar M, Nammalwar BR (Eds). Principles and Practice of Pediatric Nephrology, 2nd Edn, New Delhi: Jaypee Brothers Medical Publishers; 2013; pp324-343.
9. Steroid-sensitive nephrotic syndrome in children. Kidney Int Suppl (2011) 2012; 2(2): 163-171.
10. Bagga A, Sinha A. Pathogenesis and therapy of nephrotic syndrome. Indian J Pract Pediatr 2017; 19(2):140-155.
11. Sinha A and Bagga A. Rituximab therapy in nephrotic syndrome: implications for patients' management. Nat Rev Nephrol 2013; 9(3):154-169. doi:10.1038 nrneph. 2012.289.

CLIPPINGS

Clinical trial of fluid infusion rates for pediatric diabetic ketoacidosis.

Recent trial conducted among children with DKA with regard to the type and rate of fluid administration and its outcome. Cerebral edema is a well known complication of DKA and despite decades of therapy the etiology and predisposing factors are not clearly known. A total of 1389 episodes of diabetic ketoacidosis were reported in 1255 children. The Glasgow Coma Scale score declined to less than 14 in 48 episodes (3.5%), and clinically apparent brain injury occurred in 12 episodes (0.9%). Four groups of fluid trial undertaken with 0.45 saline at two differentrates and 0.9 saline at two different rates. It was concluded that neither the rate of administration nor the sodium chloride content of intravenous fluids significantly influenced neurologic outcomes in children with diabetic ketoacidosis.

Kuppermann N, Ghetti S, Schunk JE, Stoner MJ, Rewers A, McManemy JK, et al., for the PECARN DKA FLUID Study Group. Clinical Trial of Fluid Infusion Rates for Pediatric Diabetic Ketoacidosis. N Engl J Med 2018; 378(24):2275-2287.

Does early-onset asthma increase childhood obesity risk? A pooled analysis of 16 European cohorts.

Study was conducted to know whether early-onset asthma and related phenotypes are associated with the risk of developing obesity in childhood.21130 non-obese children were followed up at 3–4 years of age for incident obesity up to 8 years of age. Physician-diagnosed asthma, wheezing, and allergic rhinitis were assessed up to 3-4 years of age Children with physician-diagnosed asthma had a higher risk for incident obesity than those without asthma. Children with active asthma (wheeze in the last 12 months and physician-diagnosed asthma), exhibited a higher risk for obesity than those without wheeze and asthma.Early-onset asthma and wheezing may contribute to an increased risk of developing obesity in later childhood.

Contreras ZA, Chen Z, Roumeliotaki T, Annesi-Maesano I, Baïz N, von Berg A, et al. Does early-onset asthma increase childhood obesity risk? A pooled analysis of 16 European cohorts Eur Respir J 2018.

IAP - IJPP CME 2018

SEIZURE MIMICS – NONEPILEPTIC PAROXYSMS

Lakshminarayanan Kannan

Abstract: *Differentiating seizures and seizure mimics is purely clinical and is not straight forward many a times. Correct clinical diagnosis is the most critical step leading to further relevant investigations and appropriate management. Systematic approach with detailed interview of the first hand witness, review of videos of the episodes if available and thorough physical examination help in correctly identifying seizure mimics in most cases. This article enumerates practical clues to recognise the most prevalent seizure mimics and discusses the role of video-EEG.*

Keywords: *Seizure mimic, Psychogenic non-epileptic episode, Syncope, Shuddering attacks.*

Seizure and epilepsy are diagnosed on clinical grounds.[1,2,3] Seizure mimics are the close differential diagnoses considered whenever a diagnosis of seizure is made. Seizure mimics do not have abnormal excessive electrical activity in the brain as their pathophysiological basis is contrary to epileptic seizures. Detailed history from the eye witnesses should include context and circumstances surrounding the episodes, phenomenology of the episodes themselves, sequence of events, accompaniments and the way the episodes resolve (postictal state). Allowing parents to describe the episodes in their own words and get them to act out the episodes if possible, are rewarding. Leading questions should be reserved to the end of the interview, if at all, to those parents who are less observant and who have difficulty in describing the details. Home video recording of the typical episodes with the help of smart phones is of paramount importance and the same should be encouraged.

One of the neglected aspects of the history in such scenario is asking questions directly to the child as to what he or she experiences just before and during the episodes. If this direct question to the child is not put forth, this critical piece of information will be lost forever. The most important part of the seizures is "aura"; which is a subjective feeling experienced only by the patients. Presence of consistent aura just before every episode is a strong pointer towards focal seizures. One will be surprised to know that some children as young as four or five years old could describe the aura well.

Correctly recognising seizure mimics avoids erroneous diagnosis of epilepsy, averts unnecessary EEG, neuroimaging and other investigations, spares the child (and the family) of social stigma of epilepsy and unwarranted exposure to antiepileptic medications and their adverse effects on the developing brain. When a child presents with uncontrolled epilepsy not responding to multiple anti-epileptic drugs, the diagnosis must be revisited to exclude misclassification of non-epileptic paroxysms as epilepsy. Twenty to thirty percent of patients presenting with drug resistant epilepsy have non epileptic episodes. Detailed history, examination and review of videos of the episodes suffice to differentiate between epileptic and non-epileptic attacks in most cases. In difficult cases, a 24 hour video-EEG study to record the episodes (ictal EEG) in question is the gold standard to confirm the epileptic or non epileptic basis of the episodes.

Role of EEG

Routine interictal EEG as a tool to distinguish between seizure and seizure mimics should be avoided. This is because, a normal EEG does not rule out epilepsy and an abnormal EEG per se is not diagnostic of epilepsy. As a rule, EEG should only be ordered in cases of epileptic seizures and epilepsy that are clinically diagnosed. EEG only supports the clinical diagnosis of epilepsy. There is no role for EEG in a clinically diagnosed case of seizure mimic such as breath-holding spell or syncope. EEG is a highly operator dependent investigation. It is technically demanding to record a good quality EEG, more so in an uncooperative crying child. Oral sedation with triclofos or melatonin is used to get sleep EEG recordings in young children and developmentally delayed or uncooperative children. Interpreting pediatric EEGs is much trickier than

* Senior Consultant Pediatric Neurologist and Epileptologist,
Rainbow Children's Hospital, Chennai
email: dr_kln@yahoo.co.in

the adult EEGs. Neurologists with limited exposure to pediatric EEGs tend to over-report benign variants and normal physiological sleep transients that are of high amplitude as epileptiform abnormalities. Many a times, antiepileptic medications are commenced based on abnormal EEG reports irrespective of the clinical diagnosis. This is because many pediatricians and physicians think that the abnormal EEG findings supersede the clinical diagnosis of seizure mimic. This article focuses on practical approach to distinguish between the different types of seizure mimics and epileptic seizures. Seizure mimics vary depending on the age of the patient.[1,3]

Seizure mimics in neonates

Jitteriness, hyperekplexia and benign sleep myoclonus are commonly mistaken for seizures in the neonatal period.

Jitteriness is repetitive rhythmic involuntary oscillatory movements that are stimulus sensitive and ceases with slight flexion or repositioning of the limb or restraint. Jitteriness is one of the most common movement disorders in the newborn. Jitteriness can be physiological when no associated cause is identified or pathological when it is associated with metabolic abnormalities like hypoglycemia, hypocalcemia or hyponatremia, or hypoxic-ischemic encephalopathy. Physiological jitteriness is mostly self-limiting whereas treatment of the underlying metabolic abnormality is sufficient to control the pathological ones. Jitteriness when coarse and of higher amplitude can be easily mistaken for seizures.

Benign sleep myoclonus is another most common movement abnormalities found in newborns. Multifocal myoclonic jerks in series occurring in an asynchronous fashion across different limbs during sleep which disappears on waking is the characteristic finding. Multifocality is the rule in benign sleep myoclonus. Unifocal clonic seizures of any single limb in newborn should raise a suspicion for neonatal stroke and appropriately evaluated. Sometimes the individual myoclonic jerks can be of high amplitude, flinging and dramatic. Benign sleep myoclonus is physiological and spontaneously remits in few weeks in most babies. Persistence of the benign sleep myoclonus beyond age 6 months of age is noted rarely. For obvious reasons, no treatment is warranted for benign sleep myoclonus.

Hyperekplexia is characterised by sudden excessive startle to tactile, auditory or visual stimuli. Occasionally hyperekplexia can cause apnea. Startle seizures are the close mimics but are very rare in the neonatal period. Startle seizures occur following loud noise and tactile stimuli especially in those with large hemispheric brain lesions like porencephaly. Benzodiazepines and valproate are effective medications to control hyperekplexia.

Seizure mimics in infants

Infants have a wide array of unusual movements, most of them transitory. Physiological infantile behaviour movements last for few weeks to few months before remitting spontaneously. Differentiating seizures and seizure mimics is tricky in neonates and infants among all the age groups. Breath-holding spells, sleep myoclonus, shuddering attacks, spasmus nutans, infantile self-stimulation behaviour and Sandifer syndrome (retrocollis due to gastroesophageal reflux) are the common seizure mimics in infancy.

Breath-holding spells are most commonly mistaken for seizures in infancy as these episodes are very dramatic and associated with unresponsiveness, apnea and cyanosis.[4,5] Mostly the limbs go into a brief stiffening and the eyes are usually closed or uprolled. Breath-holding spells are more commonly reported in the Indian subcontinent than in other regions of the world. There can be associated clonic jerking of the limbs at the end of the episode and rarely urinary incontinence. Thus, clonic jerking and urinary incontinence alone should not be taken as diagnostic of epileptic seizures. The characteristic context in which these occur like emotional upset or falling down and hitting the head followed by hyperventilation and crying and the typical sequence of events as a whole should clinch the diagnosis. Video-EEG, if recorded, during breath-holding spells show characteristic runs of high amplitude diffuse rhythmic 1.5-2.5 Hz delta activity (during crying hyperventilating phase) followed by generalised flattening of the traces (during limp or tonic phase) associated with bradycardia, brief asystole and desaturation. These later EEG findings are similar to that recorded during syncopal attacks. Ordering routine EEGs in cases of breath-holding spells should be avoided as the interictal EEG is usually normal in these infants. Anti-epileptic medications are not warranted in this benign self-limiting condition, even if the interictal EEG is reported to be abnormal. Iron deficiency is one of the common accompaniments in these infants and iron supplements reduce the frequency of episodes or lead onto complete remission.

Infantile self-stimulation (masturbation) behaviours are common in infants and young children. These stereotyped episodes occur in a semireclined or supine positions with adduction and repeated rubbing of both thighs. Associated staring, unresponsiveness, tachycardia

and sweating are typical. The child becomes irritable and cries if he or she is disturbed during these episodes but easy distractibility is also noted in many cases, especially early on during the episodes. This is a self-limiting condition and does not warrant any treatment. Correct diagnosis based on home videos and typical description and counselling the parents about the benign nature of these episodes are all that is required.

Shuddering attacks have characteristic sudden brief shivering like movements of head and shoulder lasting for a second or two, occurring only while awake. The infant remains responsive and mostly smiling throughout. These episodes occur in a cluster and usually noted in sitting position whenever the infant is happy, excited, feeding or during nappy change. Shuddering attacks begin in infancy and usually resolve by the age two to three years.

Infantile tremor syndrome is one of the characteristic infantile movement disorder reported from the Indian subcontinent. Rapid fine tremors of the head, trunk and limbs occur in a malnourished child and is typically associated with developmental regression. It is considered to be a micronutrient deficiency disorder. Vitamin B12 deficiency and magnesium deficiency are thought to be causally related.

Seizure mimics in children

Tics, hypnic jerks (involuntary muscle twitches in the arms, legs, or entire body occurring at the moment of falling asleep), syncope and psychogenic nonepileptic attacks are the most common nonepileptic paroxysmal events mistaken for seizures in school going children.

Tics are the most common movement disorders in childhood. Simple motor tic usually affects eyelid, face, neck and shoulders. Simple vocal tic is more common than recognised. Many patients complain pain (sensory urge) in the body part involved compelling the movement. As with many other movement disorders tics also completely disappear during sleep. Many cases are temporary, resolving in a few months and mostly by two years. Medications are not warranted in most cases and are prescribed only in cases of extreme bizarre neck movements affecting the airway and other vital functions, in violent motor tics, in severe social dysfunction and in cases of Tourette syndrome haloperidol, clonazepam and clonidine are the most commonly prescribed medications for tics.

Syncope is more common in older children and teenagers especially among girls. Syncopal attacks on prolonged standing in the morning school prayer meetings on a hot humid day is not uncommon. Illnesses, sleep deprivation, dehydration, fatigue, hunger and stress increase the risk of syncope. Characteristic prodromal symptoms (light-headedness, darkening of vision, feeling of falling down, palpitation, sweating, a sense of ear blockage and nausea), associated cardiac symptoms, and a relationship to postural changes or Valsalva are helpful clues to the diagnosis of syncope. Sudden collapse and falling down are usually syncope rather than seizures. Vasovagal syncope is the commonest in children and cardiac evaluation is usually normal. But repeated episodes occurring on exertion (running, playing and bathing) should prompt evaluation for cardiac cause of syncope. A 12-lead ECG with long rhythm strip, echocardiogram and pediatric cardiology consultation are indicated in such cases.[6] Holter monitoring for 24 hours may be required in rare cases. Some patients can have tonic stiffening and clonic jerking of the limbs at the end of syncope. Prompt recovery without postictal confusion is the rule in syncope. Some patients are predisposed to have recurrent episodes of vasovagal syncope for many years before achieving spontaneous remission.

Parasomnias like confused arousals, night terror, sleep walking and night mares could be mistaken for nocturnal seizures. Multiple, highly stereotyped brief episodes occurring at night are characteristic of nocturnal frontal lobe epilepsy, whereas parasomnias are longer in duration and occur once in a few nights in a variable fashion. Responsiveness to antiepileptic medications should not be used to diagnose epilepsy as parasomnias and other nonepileptic paroxysms can remit with antiepileptic medications especially benzodiazepines. On the other hand, non-responsiveness to antiepileptic medications should not be used to rule out epilepsy.

Psychogenic non-epileptic episodes

Psychogenic non-epileptic episodes (PNEE) are the most common seizure mimic in older children, teenagers and young adults. Many of these patients are misdiagnosed as epilepsy and are on multiple anti-epileptic medications for many years before they are correctly diagnosed. Long duration of episodes (over three minutes), a gradual onset with motor features that wax and wane and start and stop throughout the episode, bizarre motor movements, side-to-side head movements, pelvic thrusting, variable amplitude, velocity and directionality of the limb movements are the usual clues to this diagnosis. Many patients with PNEE report panic attack symptoms such as palpitations, sweating, choking, breathlessness, fear of dying, and paresthesias.[7] Though urinary incontinence and tongue bite are usually associated with epileptic seizures, these have been reported rarely in patients with

psychogenic non-epileptic events. Review of the home video recordings is critical to clinch the diagnosis. When in doubt, video-EEG recording of the habitual episode confirms the diagnosis but the same is not necessary in most of the cases. Coexistence of psychogenic episodes in patients with known epilepsy is not uncommon. Recent worsening in seizure frequency, change in seizure semiology and presence of acute stressor should raise the clinical suspicion. Video-EEG is very helpful in managing patients with co-existing epilepsy and PNEE. Routine EEGs do not have a role in these cases and should be avoided.

Prolonged episodes of motionless unresponsiveness occurring only in front of the audience or occurring in front of the doctor or in the doctor waiting room raise the suspicion. Child abuse including sexual abuse should be ruled out, as these dramatic non-epileptic attacks may be the way of seeking others attention to the problem.[8,9] Interview with the child alone and parents alone is very useful in these cases. Getting the child to write his/her worries and problems is a tool to bring out the acute stressor leading on to the psychogenic episodes. Repeated sessions of counselling to the child and family separately help in achieving remission in many cases. The role of removing the underlying acute stressor cannot be overemphasised. Major depression, suicidal ideation, suspected underlying psychiatric disorder and uncontrolled episodes are the indications for psychiatry consult.

Conclusion

Thorough and systematic approach should be followed to distinguish between epileptic seizures and seizure mimics. This distinction is purely clinical. Home video recordings of the typical habitual episodes are the most important integral part of this diagnostic approach. EEG and video-EEG should be judiciously utilized in indicated cases. Correct diagnosis, parental counselling and follow up alone are sufficient in most cases of seizure mimics. Medication is required only in selected cases.

Points to Remember

- ***Normal EEG does not rule out epilepsy while an abnormal EEG per se is not diagnostic of epilepsy.***
- ***Coexistence of psychogenic non-epileptic episodes in patients with known epilepsy is not uncommon.***
- ***Sudden collapsing episodes on exertion are usually not seizures and need cardiac evaluation.***

References

1. Park EG, Lee J, Lee BL, Lee M, Lee J. Paroxysmal nonepileptic events in pediatric patients. Epilepsy Behav 2015; 48:83-87.
2. Crompton DE, Berkovic SF. The borderland of epilepsy: clinical and molecular features of phenomena that mimic epileptic seizures. Lancet Neurol 2009; 8(4):370-381.
3. Kotagal P, Costa M, Wyllie E, Wolgamuth B. Paroxysmal nonepileptic events in children and adolescents. Pediatrics 2002; 110(4):e46.
4. Leung AKC, Leung AAM, Wong AHC, Hon KL. Breath-Holding Spells in Pediatrics: A Narrative Review of the Current Evidence. Curr Pediatr Rev 2018. doi: 10.2174/1573396314666181113094047.
5. Goldman RD. Breath-holding spells in infants. Can Fam Physician 2015; 61(2):149-150.
6. Fant C, Cohen A. Syncope In Pediatric Patients: A Practical Approach To Differential Diagnosis And Management In The Emergency Department. Pediatr Emerg Med Pract 2017; 14(4):1-28.
7. Hendrickson R, Popescu A, Dixit R, Ghearing G, Bagic A. Panic attack symptoms differentiate patients with epilepsy from those with psychogenic nonepileptic spells (PNES). Epilepsy Behav 2014; 37:210-214.
8. Reilly C, Menlove L, Fenton V, Das KB. Psychogenic nonepileptic seizures in children: a review. Epilepsia 2013; 54(10):1715-1724.
9. Vincentiis S, Valente KD, Thomé-Souza S, Kuczinsky E, Fiore LA, Negrão N. Risk factors for psychogenic nonepileptic seizures in children and adolescents with epilepsy. Epilepsy Behav 2006; 8(1):294-298.

NEWS AND NOTES

ISIEM 2019:
5th National Conference of the Indian Society For Inborn Errors In Metabolism (ISIEM), Pune, Maharashtra

Date: 18-20 January, 2019

Contact : Dr.Chaitanya Datar

Mobile: 09763301410

Email: isiempune2019@gmail.com

Website: www.isiem.org

IAP - IJPP CME 2018

ACUTE LIVER FAILURE IN CHILDREN – NEWER CONCEPTS IN MANAGEMENT

Naresh P Shanmugam

Abstract: *With more understanding on liver regeneration, the management of liver failure is aimed towards supporting regeneration rather than replacement. Renal replacement therapy, plasmapheresis and auxiliary liver transplantation are the currently available option in India to support regeneration. Caution should be exercised and supportive regeneration should be attempted only in centre with pediatric liver transplant facility as there is always a chance that these children would require liver transplantation.*

Keywords: *Acute liver failure, Auxiliary liver transplantation, Plasmapheresis, Hepatocyte transfusion.*

The definition of acute liver failure (ALF) was coined nearly five decades ago. It had encephalopathy as an essential diagnostic criterion along with liver dysfunction to make a diagnosis of ALF. Due to the practical difficulty in the diagnosis of encephalopathy in children, Pediatric Acute Liver Failure (PALF) study group used the following criteria to identify acute liver failure in children, (i) hepatic-based coagulopathy defined as a prothrombin time (PT) =15 seconds or international normalized ratio (INR) =1.5 not corrected by vitamin K in the presence of clinical hepatic encephalopathy (HE) or a PT =20 seconds or INR =2.0 regardless of the presence or absence of clinical hepatic encephalopathy (HE), (ii) biochemical evidence of acute liver injury and (iii) no known evidence of chronic liver disease.[1]

Supportive management and disease specific management have remained the main stay of treatment until a couple of decades ago. Currently liver transplantation has been found to change the outcome. In those who fulfil liver transplant criteria, the outcome was abysmal if not transplanted. Now the focus is moving towards native liver regeneration instead of transplantation. With more understanding of disease process and pathophysiology, intensive care management and newer transplant techniques such as auxiliary liver transplantation have made it possible for native liver regeneration. Much awaited studies on role of n-acetyl cysteine in ALF due to non-acetaminophen related causes did not show any significant benefit in children.

* Consultant Pediatric Hepatologist and Gastroenterologist,
Institute of Advanced Pediatrics,
Dr. Rela Institute & Medical Centre, Chennai
email: drnareshps@gmail.com

Newer concepts in the management of ALF

The scope of this article is limited to the discussion on newer concepts of management available. Etiology, lab diagnosis, intensive care stabilisation of ALF in children are outlined in standard textbook, which are not discussed here.[2] With more understanding of the pathophysiology, the management concepts are directed towards liver regeneration. These newer concepts of management are extracorporeal support, auxiliary liver transplantation and hepatocyte transfusion.

(1) Extracorporeal support

Liver support devices could be broadly classified into cell-free cleansing devices and bioartificial liver support system which contains human or animal liver cells. Cleansing devices perform only the detoxifying function of the liver, whereas bioartificial liver support systems have a theoretic advantage of providing the synthetic and detoxifying properties. As bioartificial devices are still in research phase, only the cell free cleansing methods are described below which would be helpful in practice.

(a) Renal replacement therapy: Liver failure could be associated with secondary organ dysfunction, where kidneys could fail. Renal dysfunction in the background of liver failure can have a significant impact on mortality and morbidity. Renal replacement therapy (RRT) is used either to support failing kidney or to facilitate excretion of toxic products such as ammonia that can have detrimental effect on other organ systems.[3] The indications of RRT in ALF is given in Box 1.

(a) Plasmapheresis: Therapeutic plasmapheresis and therapeutic plasma exchange (TPE) are terms that are often used synonymously. TPE seems to be an effective approach

Box 1. Indications of RRT in ALF

- Hepatic encephalopathy grade 3-4
- Ammonia >150 mmol/L and increasing progressively or an absolute value >200 mmol/L
- Metabolic and or lactic acidosis, dyselectrolytemia
- Renal dysfunction
- Fluid overload

for clearing toxins, immune-mediated antigens and other particles from the circulation. TPE restores haemostasis by supplying the coagulation factors and removing activated clotting factors, tissue plasminogen activator, fibrin and fibrinogen degradation products.[4] In Wilson disease presenting as ALF, it can rapidly remove significant amount of copper in serum and thereby, reduces hemolysis, prevent progression to renal failure and provide clinical stabilization. Improved cerebral blood flow, mean arterial pressure, cerebral perfusion pressure, cerebral metabolic rate and increased hepatic blood flow are also reported after TPE. TPE has been increasingly used over the past decade as a first-line and life saving treatment for various conditions. It has been reported to be used as a bridge to LT or can lead to elimination of the need for urgent LT.

(2) Auxiliary liver transplantation

Liver transplant remains the only proven treatment that has improved the outcome of ALF. Though there are lot of criteria for LT in ALF, INR >4 is used universally as transplant criteria.[5] When INR crosses 4, it indirectly implicates that the functioning hepatocyte cell mass is below critical value and the mortality risk is high without LT. The standard technique is called orthotopic liver

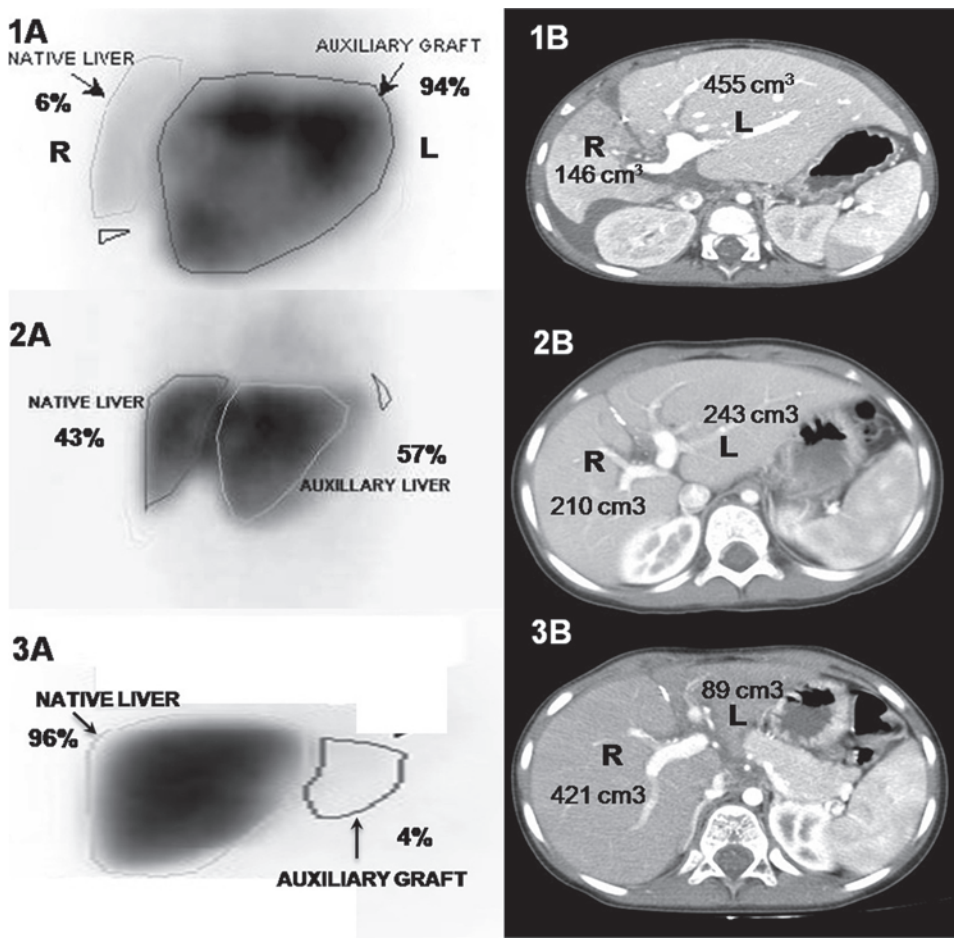

Fig.1. Serial DISIDA scan at 1, 24 and 30 months after APOLT - Gradual recovery of native liver (right lobe) function (1A,2A,3A). Corresponding CT images - Gradual volumetric regeneration of native liver (right lobe) (1B,2B,3B).

L:left lobe (transplanted liver), R:right lobe (native liver)

DISIDA: di-isopropyl iminodiacetic acid, CT: Computer tomography

transplantation (OLT), where the diseased liver is removed and replaced with healthy donor liver. Improved surgical techniques such as split liver grafts, reduced grafts and living related donors have increased the timely availability of donor organs. The donor organs are usually blood group matched. By Indian law only a blood relative could be an organ donor, altruistic donation is not allowed. In emergency situations ABO-incompatible liver transplantation could be done, but is associated with lower graft survival.

Auxiliary liver transplant could be orthotopic (part of the native liver is resected and replaced with a reduced-size graft) or heterotopic (the donor graft is placed alongside the native liver in the right upper quadrant). Commonly used procedure is auxiliary partial orthotopic liver transplant (APOLT), where right or left lobe of donor liver is placed in the space created by partial hepatectomy of recipient. The rationale behind auxiliary liver transplant is that the allograft provides liver function while the native liver regenerates and then immunosuppression could be weaned and eventually stopped. In a series from King's college hospital, of the 20 children who received auxiliary liver transplantation, for ALF, patient survival was 85% and graft survival was 100% at end of one year.[6] Among the 17 survivors, 14 (82%) have successfully regenerated their native liver. This treatment option is available in India and has shown successful regeneration of native liver.[7] The native liver regeneration of a two year old child who has ALF due to hepatitis E is shown in Fig.1A, IB, 2A, 2B, 3A and 3B.[7] Immunosuppression was withdrawn once the native liver volume and functionality became 50% of total volume and functionality. Indications for APOLT is limited to disorders that cause one time insult such as hepatitis A, E induced ALF, poisoning etc. This would be an ideal option in ALF due to indeterminate etiology, as spontaneous regeneration of native liver remains a possibility.

(3) Hepatocyte transplantation

Hepatocyte transplantation, where hepatocytes are infused intraportally into the patient's liver, where a proportion of cells will engraft has been tried with variable success in certain liver based metabolic disorders. Its use in ALF still remains experimental. Lack of surrogate markers of rejection poses an important problem, as it is difficult to titrate the immunosuppression. A novel technique, where alginate-encapsualted hepatocytes could be injected intraperitoneally is under trial. This technique avoids the complications of coagulopathy, porto-systemic shunting of infused cells and protects the cells from direct immune attack, allowing immunosuppression free transplantation.

Conclusion

Liver failure is a dynamic disease where there is possibility of liver regeneration. Any child with ALF who has progressive worsening of coagulopathy has to be referred at the earliest to tertiary centre with transplant facilities.

Points to Remember

- ***Liver transplant has changed the outcome in pediatric acute liver failure.***
- ***Current management of liver failure is aimed towards supporting regeneration (renal replacement therapy, plasmapheresis and auxiliary liver transplantation) rather than replacement.***
- ***Auxiliary liver transplant allows the regeneration of native liver and withdrawal of immunosuppression.***

References

1. Squires RH Jr, Shneider BL, Bucuvalas J, Alonso E, Sokol RJ, Narkewicz MR, et al. Acute liver failure in children: the first 348 patients in the pediatric acute liver failure study group. J Pediatr 2006; 148(5): p. 652-658.
2. Shanmugam N, Dhawan A. Acute Liver Failure in Children: Intensive Care Management Protocol. In: Pediatric Liver Intensive Care, Naresh Shanmugam, Anil Dhawan, eds. 2018, Springer Singapore: Springer Nature Singapore Pte Ltd. pp7-17.
3. Zoica BS, Deep A. Renal replacement therapy in Liver disease. In: Pediatric Liver Intensive care, Naresh Shanmugam, Anil Dhawan, eds. Springer Singapore: Springer Nature Singapore Pvt. Ltd. 2018; pp65-70.
4. Sachan D, Extracorporeal Support in Liver Disease: Plasma Exchange/Plasmapheresis. Paediatric Liver Intensive care, ed. A.D. Naresh Shanmugam. Springer Singapore: Springer Nature Singapore Pvt. Ltd. 2018; pp71-74.
5. Shanmugam NP, Dhawan A. Selection criteria for liver transplantation in paediatric acute liver failure: the saga continues. Pediatr Transplant 2011; 15(1): p5-6.
6. Faraj W, Dar F, Bartlett A, Melendez HV, Marangoni G, Mukherji D, et al. Auxiliary liver transplantation for acute liver failure in children. Ann Surg 2010; 251: 351-356.
7. Shanmugam NP, Al-Lawati T, Kelgeri C, Rela M. Auxiliary Liver Transplantation for Acute Liver Failure. Indian Pediatr 2016; 53(1): p67-69.

IAP - IJPP CME 2018

BACTERIAL INFECTIONS OF SKIN - AN APPROACH

Anandan V

Abstract: *The commonly encountered skin infection in office practice is caused by bacteria. Among them Staphylococcus and Streptococcus are the common causative organisms. Bacterial skin diseases vary from simple impetigo to severe necrotising fasciitis. Majority of the bacterial skin infections are diagnosed clinically and treated with appropriate topical and oral antibacterials preparations. In rare conditions like cutaneous tuberculosis investigations and biopsy will help in diagnosis. A few conditions like necrotising fasciitis, cellulitis and complications like staphylococcal scalded skin syndrome are to be managed as inpatient with parenteral antibacterials. In a few conditions, bacterial infections may be predisposing to certain dermatoses like guttate psoriasis. Early diagnosis and management will definitely reduce the morbidity and mortality.*

Keywords: *Staphylococcus, Streptococcus, Treatment.*

Bacterial infections of skin are commonly encounters in daily practice. Numerous factors like host resistance, virulence of the organism, barrier defects etc. have been proposed to reason out the occurrence of the disease in certain individuals. Being a tropical country the climatic conditions in India gives a suitable environment for the continuous growth of the infectious agent. Poor living standards, poor hygiene, overcrowding and lack of education is also contributing to the sustainence of bacterial skin infection. Hence it is mandatory for all the pediatricians to have a clear knowledge about the disease manifestations. This article aims at bringing out typical manifesting features of common bacterial infections of skin and their management is also contributing to the sustainence of the bacterial skin infection.

* Professor,
Department of Dermatology,
Government Stanley Medical College,
Chennai

email: dermanandan@gmail.com

Impetigo contagiosum[1]

It is one of the most common pyoderma encountered in daily practice where the pre-school or the young school going children of either sex presents usually in two forms as either nonbullous or bullous impetigo.

Nonbullous impetigo: Nonbullous form presents with a thick dirty yellow crusted lesions, mostly over the face, in and around the nose and mouth which is commonly caused by Streptococcus pyogenes (Fig.1). Complications like post-streptococcal glomerulonephritis, scarlet fever, urticaria and erythema multiforme may occur. A few lesions need topical antibiotics preferably mupirocin or fusidic acid for a week. For extensive lesion, topical and systemic antibiotics should be started. Penicillin group of antibiotics like amoxicillin, cloxacillin, cephalexin or amoxicillin with clavulinic acid are preferred. Topical retapamulin is a newer topical antibiotic for which bacterial resistance has not been reported yet.

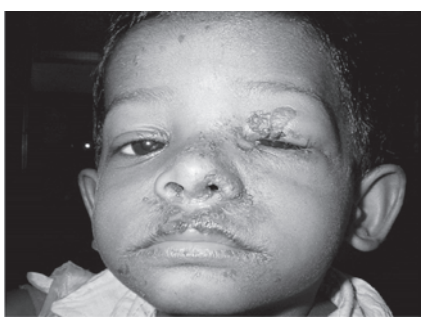

Fig.1. Nonbullous impetigo

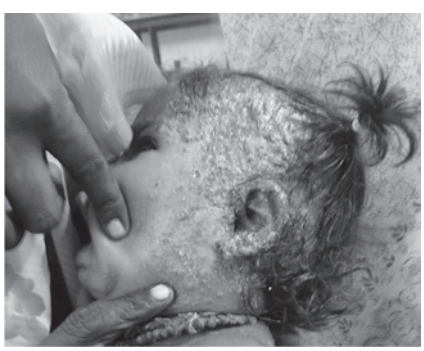

Fig.2. Impetigo with crust

Bullous impetigo: Bullous form presents as bullae filled with clear to cloudy fluid which on rupturing forms thin, flat, brownish crust. Circinate lesions can be seen where there is central healing and peripheral extension of the lesion. This is caused mostly by the Staphylococcus aureus. Buccal mucosa can be rarely involved.

If a child presents with extensive thick adherent yellowish crusted lesion over the scalp and face (Fig.2), the first step of management will be removal of the thick crust as topical antibiotics will not be able to penetrate the thick crust. Saline soaks 3-4 times a day for 3-5 days can be advised for the removal of the crust in a gentle manner. Vigorous removal should not be done as it will worsen the condition. The crust when removed leaves an erythematous area, over which the desired topical agent should be applied.

Cellulitis

Cellulitis is the inflammation of the dermal and the subcutaneous tissue (Fig.3). Boys are most commonly affected than girls. If inadequately treated, may lead on to fasciitis, septicemia, myositis and abscess and is usually caused by Streptococcus. Facial cellulitis in children below 2 years of age is caused by Hemophilus influenza type b.

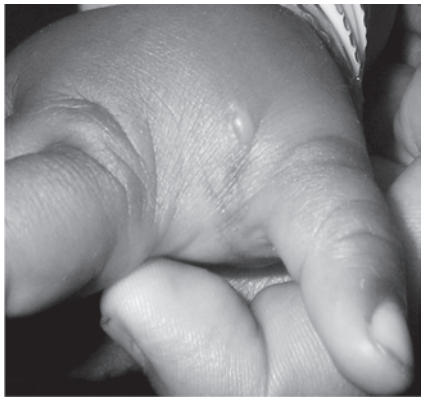

Fig.3. Cellulitis

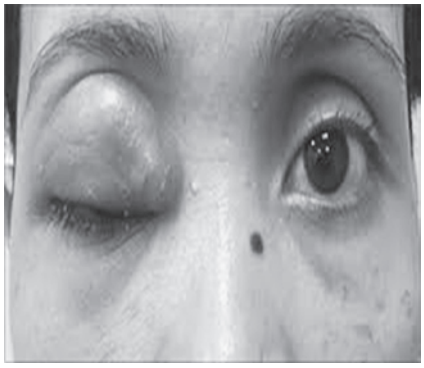

Fig.4. Orbital cellulitis

Table I. Cellulitis and Erysipelas - Differentiating features

Cellulitis	Erysipelas
Deep	Superficial
Involves upto deep dermis and subcutis	Usually limited to upper dermis
Margins are ill defined	Has a definite margin
Bulla formation rare	Bulla formation is very common
Does not involve ear in face due to lack of deep dermis and subcutaneous tissue	Involves ears – Milian's ear sign
Spread is comparatively slow	Spreads rapidly due to superficial plane of involvement
Causative organisms staphylococcus, streptococcus and others	Caused by Streptococci

Orbital cellulitis:[2] In case of orbital cellulitis, the infection is present behind the orbital septum (Fig.4). It may lead on to proptosis, ophthalmoplegia and loss of visual acuity. If untreated, complications like cavernous sinus thrombosis, subperiosteal or cerebral abscess or meningitis can occur. Flucoxacillin, clarithromycin and clindamycin are the first line agents which should be started without any delay. In case of recurrent infection, prophylaxis with penicillin can be given.

Erysipelas

It is a superficial form of cellulitis caused by Group A beta hemolytic streptococci. Other strains implicated are Staphylococcus aureus, Streptococcus pneumonia, Klebsiella pneumonia and Yersinia enterocolitica. Fever and chills occur suddenly. The affected area of the skin has sharp raised border with bright red colour and skin is firm and swollen. Oral or intravenous penicillin is the anbibiotic of choice, Vancomycin is used for facial erysipelas. The difference between cellulitis and erysipelas is given in Table I.

Furunculosis

Furunculosis or boil is an acute necrotic infection of a single hair follicle (Fig.5) and is most commonly caused by Staphylococcus aureus. It is uncommon in early

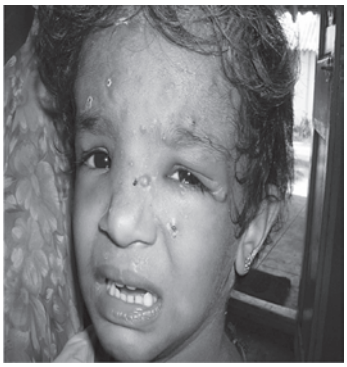

Fig.5. Furunculosis

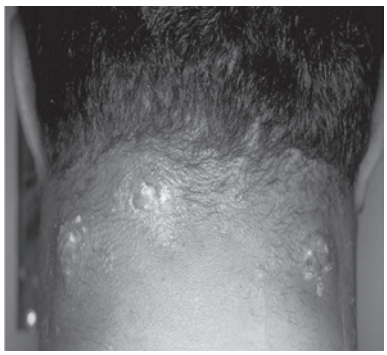

Fig.6. Carbuncle

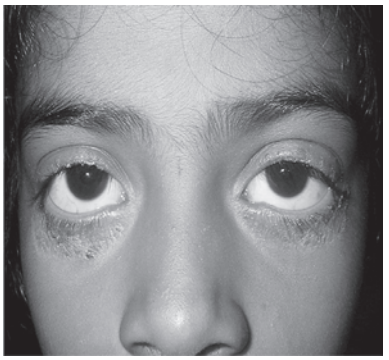

Fig.7. Staphylococcal blepharitis

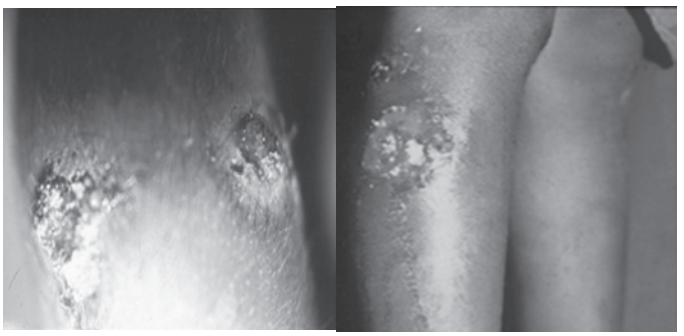

Fig.8. Ecthyma

childhood but can occur in atopics. Adolescence and early adult life is the most common age group to be affected with mild predilection towards boys. Malnutrition and other immunocompromised state of the individual can be predisposing factor. Treatment is with oral penicillin group of antibiotics like amoxicillin, cloxacillin, amoxicillin with clavulinic acid or cephalexin.

Carbuncle[3]

Carbuncle is infection of a group of contagious and is commonly follicle with the inflammation of the underlying connective tissue and subcutaneous fat and is commonly caused by Staphylococcus aureus. It occurs most commonly in middle age group and the most common sites involved are back of neck, shoulders, hips and thighs. It initially starts as smooth, dome shaped, tender papules and pustules which increase in size with pus discharging from the multiple follicular orifices (Fig.6) and is usually associated with constitutional symptoms. Necrosis may occur. Lesion resolves with scarring. Flucloxacillin is the preferred drug and in extensive cases, incision and drainage is required.

Staphylococcal blepharitis

Blepharitis is inflammation of the eyelids. Anterior blepharitis is the involvement of sites which is present outside, which is not in contact with the conjunctiva. Staphylococcal blepharitis and seborrheic blepharitis are the two main cause for anterior blepharitis. Patient usually presents with mild itchy scaly lesions over the eyelids with burning sensation (Fig.7). There may be purulent discharge and when severe, watering of eyes and blurring vision can occur. Warm compresses with topical antibiotics are the preferred mode of management.

Ecthyma[4]

Ecthyma is formation of thick adherent crust which on removal reveals a deep ulcer. This commonly occurs in immunocompromised state and extremes of age (Fig.8). The most common organism causing ecthyma is Streptococcus pyogenes. The most common sites involved are buttocks, legs and thighs but other sites can also be involved. Initially it starts as a vesiculobullous lesion which breaks to leave an ulcer with a thick adherent crust and the ulcer extends by peripheral accretion and the base, indurated. Healing is by scar formation. Topical fusidic acid and mupirocin ointments along with systemic antibiotics. Intravenous antibiotics are preferred for faster resolution.

Streptococcal vulvovaginitis[5]

It is commonly a disease of prepubertal children. The causative organisms can be Streptococcus pyogenes, Escherichia coli, Enterococcus faecalis, Hemophilus influenzae, Proteus mirabilis and Staphylococcus aureus. The presenting compliant is usually irritation, soreness and

Fig.9. Streptococcal vulvovaginitis

painful micturition (Fig.9). Antibiotics like penicillin or erythromycin can be given. Topical clindamycin has also proved to be effective.

Necrotising fasciitis[6]

Necrotising soft tissue infections depending on the depth of involvement can be classified as necrotising cellulitis and myonecrosis. The organisms that are implicated include Group A Streptococci, Vibrio species, Zygomycetes, Streptococcus/Enterobacter species and Bacteroides/Peptostreptococcus. Initially it starts as erythema, edema and tenderness followed by gangrenous skin changes with faster progression to involve fascia to cause necrotising fasciitis and then to the muscle to cause myonecrosis (Fig.10). Exploration and surgical debridement is required along with intravenous antibiotics.

Fig.10. Necrotising fasciitis

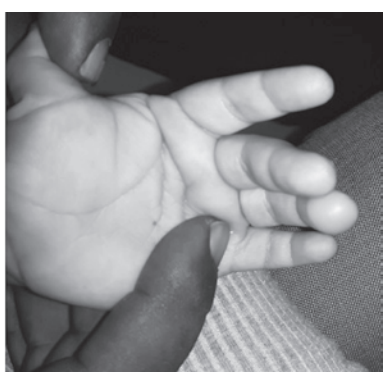

Fig.11. Distal blistering dactylitis

Distal blistering dactylitis[7]

It affects children between 2 and 16 years of age with Streptococcus and Staphylococcus being the common causative agents. The child presents as solitary or multiple bulla containing seropurulent discharge over the volar aspects of the distal phalanges the palmar pads (Fig.11). Draining out the discharge with a sterile needle and leaving the blister roof intact to settle on the raw area serve as a biological dressing along with penicillin group of antibiotics can bring resolution of the lesion. Topical wet dressing can also be used.

Scarlet fever

Scarlet fever is a toxin mediated disease caused by Group A beta hemolytic streptococci. The disease manifests as pharyngitis, fever and a special scarlatiform rash which appears on the second day of pharyngitis as a finely

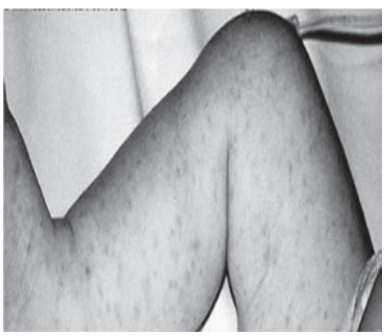

Fig.12. Scarlet fever

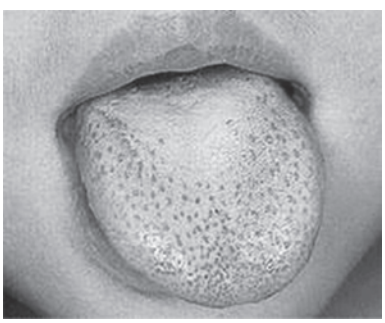

Fig.13. White strawberry tongue

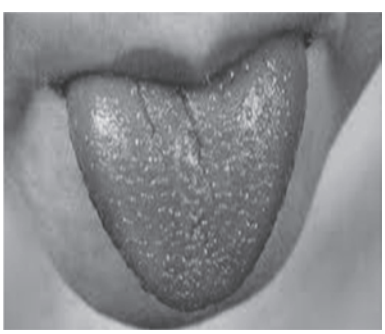

Fig.14. Red strawberry tongue

punctate erythema referred to as 'sunburn with goose pimples'/ 'sandpaper' which resolves by branny scaling over the skin (Fig.12) and large lamellar scaling over the palms and soles. Incubation period is usually 2-5 days. Pastia lines, which are the transverse red streaks can be seen in the flexures. Perioral pallor is highly characteristic of the disease.

In the oral cavity, mucosa appears bright red with bright red punctate spots over the palate. The tongue has a white coating on the first day with swollen red papillae on the second day giving the tongue 'white strawberry tongue' appearance (Fig.13). After the third day, it becomes a red strawberry tongue after shedding of the epithelium (Fig.14). The disease is associated with fever, vomiting, pharyngitis and lymphadenopathy. In severe cases, myocarditis, otitis media and peritonsillar abscess can be associated. Penicillin group of antibiotics can be administered but in severe cases intravenous antibiotics like vancomycin and linezolid may be needed.

Keratolysis punctata

It is a non-inflammatory bacterial infection of the palms and soles caused by Cryptococcus sedentarius, Dermatophilus congolensis, Corynebaterium species and Actinomyces species. Serine proteases secreted by the organism is responsible for degrading the stratum corneum and giving the 'fringe of scale' appearance (Fig.15 and 16) and may be associated with malodour and hyperhidrosis. Topical fusidic acid or azoles are used along with oral erythromycin. In recalcitrant cases, aluminium chloride solution and botulinum injections are used to treat the associated hyperhidrosis.

Lupus vulgaris

It is a form of cutaneous tuberculosis which can be due to direct extension, hematogenous and lymphatic spread from a tuberculous focus. It occurs in a previously sensitized individual. In India, it is more common over the

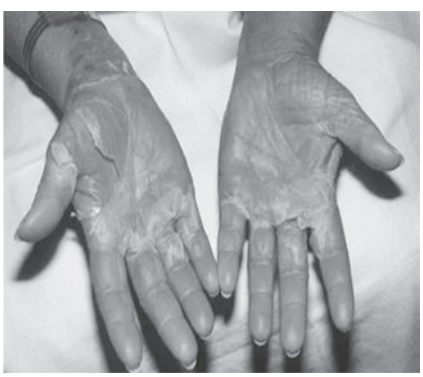

Fig.15. Exfoliation of hands

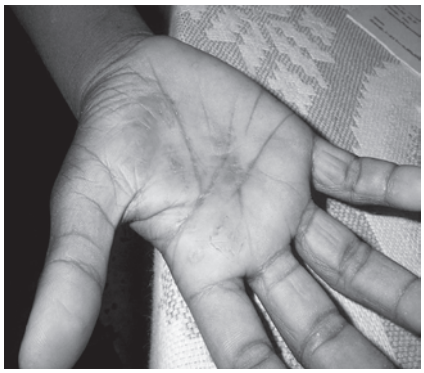

Fig.16. Fringe of scale

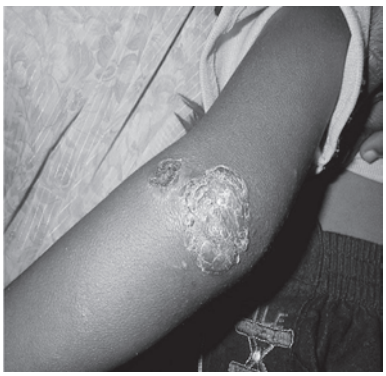

Fig.17. Lupus vulgaris

buttocks and the thighs. The lesion starts as tiny, red-brown soft, flat papule which progresses to form a larger plaque by peripheral extension. The lesion shows a characteristic progression of lesions at the end with atrophy at the healing end (Fig.17). On diascopy, reveals a typical 'apple jelly nodules' and on probing is soft and can be easily pierced by a match stick i.e 'match stick test'. Biopsy and histopathology confirms the diagnosis by the presence of tuberculous granuloma with slight epidermal hyperplasia. Patient is started on the standard anti- tuberculous treatment. Chronicity is the hallmark feature.

Tuberculosis verrucosa cutis

It is also called as Warty tuberculosis, Prosector's wart or Verruca Necrogenica. It the exogenous form of cutaneous tuberculosis where the bacilli is inoculated in a trauma prone site. Most common site is the lower extremities. It usually presents as a solitary nodule with verrucous surface which progresses to form an irregular reddish brown warty plaque with clefts and fissures (Fig.18). Pus and keratinous material may be exuded. The lesion extends centrifugally with central healing. Biopsy and histopathology reveals epitheloid granuloma in the papillary and reticular dermis with variable degrees of epidermal hyperplasia. Patient started on the anti-tuberculous treatment and followed up for the resolution.

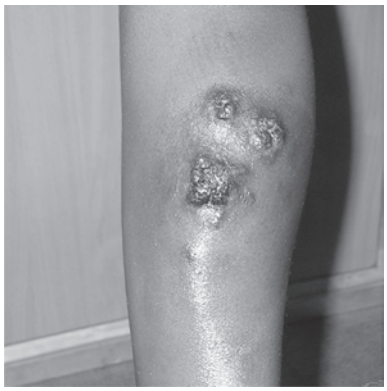

Fig.18. Tuberculosis verrucosa cutis

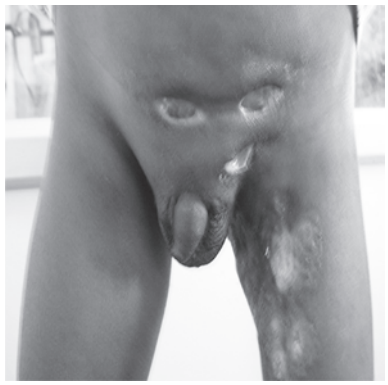

Fig.19.Scrofuloderma

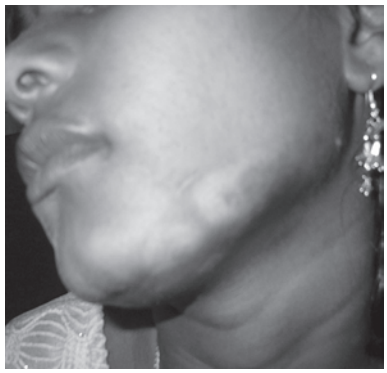

Fig.20. Borderline tuberculoid Hansen

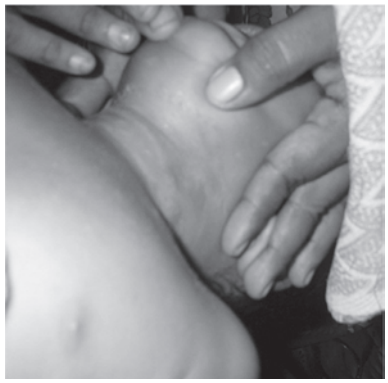

Fig.21. Intertrigo

Scrofuloderma

It is also called as King's Evil, Scrofulous gumma, Tuberculosis cutis colliquativa. This infection is due to the contiguous spread of infection from the underlying focus in the form of lymph nodes, bones, joints or epididymis (Fig.19). It begins as a deep nodule which softens, suppurates and perforates to form an ulcer and sinus. The margins are purplish with undermined edges with granulating floors. Biopsy and histopathology reveals ulceration of the epidermis, superficial abscess in the dermis. Tuberculoid granulomas can be present in the deeper region. Patient needed to be started on standard anti-tuberculous treatment and followed up for the resolution.

Hansen's disease

It is caused by Mycobacterium leprae. Patient classically presents with a hypopigmented hypoanesthetic patch on any site (Fig.20) and peripheral nerve enlargement and nerve tenderness. Depending upon the host immunity and bacterial load, patient may be presenting in any of the following spectrum such as Tuberculoid form, borderline tuberculoid form, midborderline form, borderline lepromatous form and lepromatous leprosy. The most common forms in children is tuberculoid or borderline tuberculoid but other forms do occur. Patient can also present initially with the lepra reaction. Slit skin smear is done either from the lesion or from the ear lobe to reveal pink rod shaped bacilli either solid/fragmented/granular forms. Patient is started on anti-leprosy treatment.

Intertrigo

It is the inflammatory condition of the skin folds precipitated by heat, moisture, maceration and friction. Since the site becomes favourable, it can be colonised by bacteria, candida and viral pathogens. The common presenting complaints are itching, burning and pain in the site (Fig.21). The difference between bacterial intertigo and candida intertrigo is given in Table II.

Table II. Difference between bacterial and candidal intertrigo

Bacterial intertrigo	Candida intertrigo
Intense red in colour	Pink to red in colour
Foul odour present	Foul odour absent
Satellite pustules absent	Satellite pustules present
Associated with constitutional symptoms	Constitutional symptoms are often absent but if present, can be mild.

Management is mainly aimed at advising to minimise the precipitating factors and topical agents like azoles and antibiotics can be prescribed as per the disease etiology.

Allergic contact dermatitis

It usually presents as mild erythematous to hyperpigmented scaly plaques which usually resolves in withdrawing the offending drug. The most common offending agent is present in the ornaments (Fig.22). Any form of chemical like works watch strap, challals, kumkum can causes ACD. Treatment is aimed by withdrawing the offending agent with topical corticosteroids and antihistamines. Patch test is used to find out the etiological agent in the causation of ACD.

Staphylococcal scalded skin syndrome (SSSS) ('Ritter's Disease')

SSSS is an exfoliative dermatosis caused by the exfoliative toxin A and B of Staphylococcus aureus. Initially the lesions simulate impetigo but later it progresses to become extensive with epidermal tenderness and peeling (Fig.23). The toxin are serine proteases that targets the intercellular desmoglein 1 to cause intraepidermal blistering. Bullous impetigo is the localised form of same pathogenesis whereas in SSSS, it extends hematogenously to cause a widespread disease manifestation. Here the mucosa is spared.

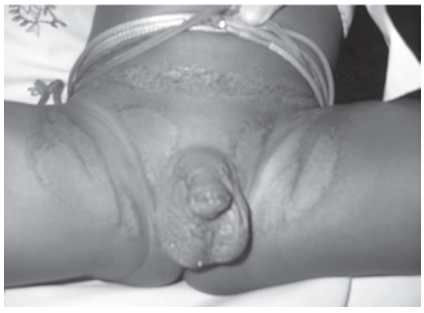

Fig.22. Allergic contact dermatitis

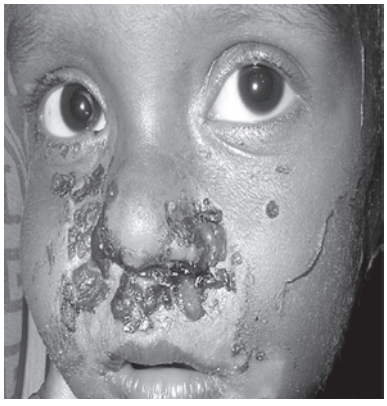

Fig.23. Staphylococcal scalded skin syndrome

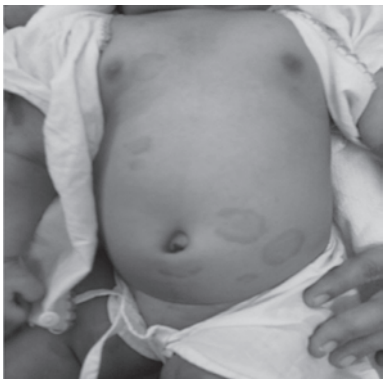

Fig.24. Acute spontaneous urticaria

The bulla leave behind painful erosions which heals in about 2 weeks. Parentral penicillin resistant antibiotics like flucloxacillin, clindamycin, temocillin, tegecycline and daptomycin are the first line drugs. General condition of the patient should be taken care of while combating the organism.

Acute spontaneous urticaria

Infections are also the precipitating factor causing acute spontaneous urticaria (Fig.24) in addition to food and drug intolerance, stings, transfusions, vaccinations and is being idiopathic in more than 50% of patients. Infections like upper respiratory tract infections, hepatitis B, hepatitis C Streptococcus pyogenes, Anisakis simplex (parasite) has been proposed. Also some meta-analysis has proved the positive association between Helicobacter pylori and urticaria. Bowel helminths and candidal infections should also be sought out. Hence ruling out focal sepsis in these patient is of utmost important before tagging it as idiopathic etiology.

Atopics have a higher colonisation of the microbes especially Staphylococcus aureus with the basic pathology proposed as the fillagrin gene mutation causing barrier defect. This ultimately leads on to the increased penetration of foreign objects and hence the disease manifestations. The exotoxins produced by Staphylococcus aureus acts as a superantigen and hence produce an augmented immune response maintaining the disease activity. These patients will have an acute exacerbation on and off and will require long course treatment with antibiotics. Rational use of antibiotics should be considered in these patients to avoid bacterial resistance.

Bacterial infections predisposing to certain dermatosis

Guttate psoriasis

It is a common form of psoriasis in children and young

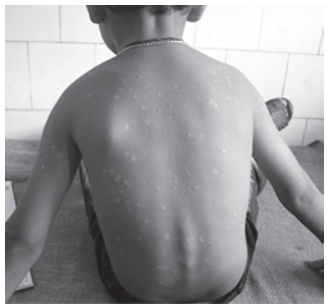

Fig.25. Guttate psoriasis

adults where Group A beta haemolytic streptococci (Fig.25) have been found to be the predisposing factor. The proposed mechanism is the molecular mimicry just as in case of myocardial involvement in rheumatic fever.

History of recent upper respiratory infections and tonsillitis have been elicited in the affected individuals. The patient presents as rain-drop like erythematous papular lesions with an abrupt onset spreading centripetally and involve symmetrically. Prognosis is good with the resolution of lesion in about 3-4 months.

Morphea

Morphea is characterised by a localised condition with varying degrees of sclerosis, fibrosis and atrophy in the skin and the subcutaneous tissue, sometimes extending to involve the deeper structures (Fig.26 a & b).

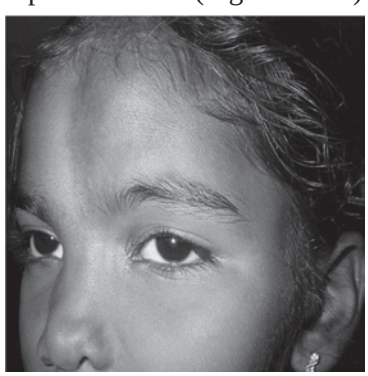

Fig.26a Depressed plaque over forehead

Fig.26b. Depressed plaque over scalp

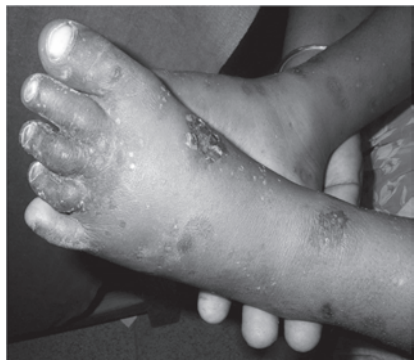

Fig.27. Vasculitis foot

Role of Borrelia has been proposed because of the similarity of morphea with the clinical manifestations of acrodermatitis chronic aatrophicans, a late feature of Lyme's disease. There has been a significant association between serology of borrelia infection and high-titre ANA positivity.

Vasculitis

Infections can be a triggering factor for vasculitis in addition to malignancy, drugs, smoking, hypercoagulable states. Infections like Streptococcus, hepatitis etc have been found to be associated with vasculitis like erythema elevatum diutinum, IgA vasculitis, Hypocomplementemic vasculitis, granulomatosis with polyangitis etc (Fig.27). The foremost management in vascultis is avoidance of triggering agents and prevention of complications. Cultures and serology should be done to know the exact organism and should be treated according to the sensitivity.

Conclusion

Bacterial infections are the common conditions which all physicians and specialists face in day-to-day practice. Knowing the exact causative organism and combating it has become a great challenge. Basic investigations like pus culture and sensitivity can be used to quench the exact organism causing the disease and the sensitivity of the organism to the specific antibiotic is used for reducing the increasing proportions of bacterial resistance. Having a basic knowledge about the manifestations of common bacterial infections of skin is mandatory since it has contributed to the load in all the out-patient departments. Here, we give an overview of the clinical spectrum of various bacterial infections of skin and its management.

Points to Remember

- ***Bacterial skin infections are common in countries with tropical climate country like india.***

- ***Majority of the bacterial skin conditions are diagnosed clinically.***
- ***Shin biopsy may be needed rarely in conditions like shin TB.***
- ***Infections like necrotising fasciitis and scalded shin syndrome need inpatient care with appropriate antibiotics.***

References

1. Loffeld A, Davies P, Lewis A, et al. Seasonal occurrence of impetigo: a retrospective 8 year review (1996–2003). Clin Exper Dermatol 2005; 30:512-514.
2. Rubinstein JD, Handler SD. Orbital and periorbital cellulitis in children. Head Neck Surg 1982; 5:15-21.
3. Hee TG, Jin BJ. The surgical treatment of carbuncles: a tale of two techniques. Iran Red Crescent Med J 2013; 15(4):367-370.
4. Nolting S, Strauss WB. Treatment of impetigo and ecthyma. A comparison of sulconazole with miconazole. Int J Dermatol 1988; 27:716-719.
5. Schwartz RH, Wientzen RL, Barsanti RG. Vulvovaginitis in prepubertal girls: the importance of Group A streptococcus. South Med J 1982; 75:446-447.
6. Anaya DA, Dellinger EP. Necrotizing soft tissue infection: diagnosis and management. Clin Infect Dis 2007; 44:705-710.
7. Frieden IJ. Blistering dactylitis caused by Group B streptococci. Pediatr Dermatol 1989; 6:300-302.

NEWS AND NOTES

ICNC-2019

IAPEN Clinical Nutrition Congress

Date: 9th & 10th February, 2019

Venue: Convention Centre, Kokilaben Dhirubhai Ambani Hospital
Rao Saheb Achutrao Patwardhan Marg, Four Bunglows, Andheri (W), Mumbai

Contact details

Dr.Shilpa Varma

Organizing Secretary

ICNC-2019

Email: iapenmumbai@gmail.com

Mob:0091 9769373742

Pediatric Conference of North India 2019

Organized by : Indian Academy of Pediatrics Delhi

Date: 21st & 22nd September, 2019

Venue: Le Meridien, New Delhi

Secretariat

113-114, First Floor, Bank House

(Punjab & Sind Bank Building),

21, Rajendra Place, New Delhi 110008

25811029, 8447441560

Email : iapdelhi2@gmail.com

Website: iap-delhi.com

IAP - IJPP CME 2018

ACUTE BACTERIAL MENINGITIS - REVISITED

** Leema Pauline C*
*** Viveka Saravanan*
*** Ravi LA*

Abstract: *Bacterial meningitis is a medical emergency that needs a prompt diagnosis and treatment. Causative organisms depend upon age, vaccination status, clinical situation and immune status of the child. Infants and young children usually present with non-specific symptoms and hence a high index of suspicion is essential. Lumbar puncture and CSF analysis remain the corner stone of diagnosis. Appropriate and adequate treatment can save children from mortality and neurological sequelae.*

Keywords: *Meningitis, Cerebrospinal fluid, Management.*

Bacterial meningitis is a potentially devastating medical emergency in children that can lead to death or severe neurologic sequelae if not managed properly and promptly. The frequency of bacterial meningitis among the admitted patients varied from 0.5% to 2.6% with a mean of 1.5%.[1] Despite the availability of a wide range of antibiotics, mortality rate remains significantly high in India and other developing countries, ranging from 16-32%.[2]

Clinical features

The cardinal symptoms of meningitis are fever, nuchal pain and alteration in sensorium. These symptoms are commonly seen in older children, whereas infants usually present with nonspecific symptoms such as lethargy, irritability, incessant cry, poor feeding, fever, hypothermia, vomiting and bulging anterior fontanel.[3] Hence, a high index of suspicion is necessary to diagnose bacterial meningitis in infants and young children. Seizures develop in one third to one fourth of them. Focal deficits including cranial nerve involvement can occur. Children with meningococcemia may present with purpura and shock. Signs of meningeal irritation including neck stiffness, Kernig sign and Brudzinski sign are common. However, absence of meningeal signs does not rule out a diagnosis of bacterial meningitis.[4] Similarly infants less than one year of age often do not exhibit neck rigidity. Papilledema is uncommon in children. Hence, in the presence of papilledema, one should think about other causes or complications of bacterial meningitis.[5]

Etiology

The etiological spectrum of bacterial meningitis in children depends on age and the immunization status of the child. With the introduction of pentavalent vaccine in the universal immunization program, the incidence of meningitis due to H.influenzae *b* is decreasing. S. pneumoniae appears to be the predominant pathogen among laboratory identified bacterial pathogens with 71.7%, followed by H.influenzae *b* (23.8%) and N.meningitidis (4.4%). For S.pneumoniae, 15% of positive cases had serotype data, showing serotypes 19F, 6B, 14, 6A and 14 as predominant serotypes in India.[6] N. meningitidis is predominant in northern India and is very uncommon in the Southern states.[7] The common organisms responsible for bacterial meningitis in various age groups are given in Table I. Certain risk factors predispose children to develop bacterial meningitis. Knowledge about these predisposing factors and the bacterial pathogens will aid in the management (Table II).

Diagnosis

Lumbar puncture

Cerebrospinal fluid (CSF) examination remains the gold standard for diagnosing bacterial meningitis. CSF examination is also useful to identify the causative organism and to determine the antibiotic sensitivity pattern. Lumbar puncture is delayed or deferred only if there are definite contraindications such as significant increase in intra-cranial pressure, severe cardio-respiratory compromise and skin infection over the site of lumbar puncture. Bulging anterior fontanel in the absence of other signs of increased intracranial pressure is not a

* Professor of Pediatric Neurology
** Assistant Professor of Pediatric Neurology,
Institute of Child Health & Hospital for Children,
Madras Medical College,
Chennai.
email: leemapauline@rediffmail.com

Table I. Organisms causing bacterial meningitis

<1 month	1 to 3 months	>3 months
Gram negative organisms	Group B streptococcus	Streptococcus pneumoniae
Group B streptococcus	Listeria monocytogenes	Hemophilus influenzae *b*
Listeria monocytogenes	Streptococcus pneumoniae	Neisseria meningitidis
	Hemophilus influenzae *b*	
	Neisseria meningitidis	

Table II. Predisposing factors and causative organisms

Predisposing factor	Causative organism
Otitis media, mastoiditis, sinusitis	H.influenzae *b*, S.pneumoniae
CSF leak, sickle cell anemia, S.pneumoniae	Splenectomy
Complement, properdin deficiencies	N.meningitidis
Fracture skull, neurosurgery	Staphylococcus aureus
CSF shunts	Coagulase negative staphylococci

contraindication for lumbar puncture.[5] Even though all patients with meningitis have some degree of increased intracranial pressure, herniation is rare in young children.

Indications for CT brain prior to lumbar puncture include focal deficits, increased intracranial pressure, impaired consciousness and child with immunocompromised state.[3] Lumbar puncture must be performed prior to or immediately following empirical antibiotics as antibiotics can rapidly sterilize cerebrospinal fluid.[8] Sterilization of meningococci occurs within 2 hours and pneumococci within 4 hours.[9] If lumbar puncture is delayed for any reason, then blood culture should be taken prior to first dose of antibiotics.

In bacterial meningitis the cerebrospinal fluid is turbid, shows polymorphonuclear pleocytosis, raised protein and low sugar. However, viral infections, especially those caused by enterovirus, may initially cause a predominant polymorph response in the CSF, which may persist throughout the illness.[10] Hypoglycorrachia is a significant finding in bacterial meningitis, however viral meningitis especially herpes simplex, mumps, fungal meningitis and tuberculous meningitis may also show hypoglycorrachia. Normal CSF parameters and CSF findings in various types of meningitis are depicted in Table III.

A CSF glucose concentration of <34 mg/dL, a ratio of CSF to blood glucose of <0.23, a CSF protein concentration of >220 mg/dL, a CSF leukocyte count of >2000 leukocytes/mm^3, or a CSF neutrophil count of >1180 neutrophils/mm^3 were individual predictors of bacterial rather than viral meningitis with ~99% certainty.[11] Gram stain will yield positive results in nearly 60-90% of the patients if done prior to starting antibiotics.[12] Antibiotics decrease the yield by 20%. The staining characteristics of various organisms are depicted in Table IV. Fluorescent microscopy using acridine orange will show the bacteria as bright orange red against the background of yellow or green.

CSF culture remains the gold standard for diagnosing bacterial meningitis. CSF culture is positive in 60-90% of bacterial meningitis patients depending on the definition of bacterial meningitis. Pretreatment with antibiotics decreases the yield of CSF culture by 10-20%.[3]

Table III. CSF findings in various types of meningitis

CSF findings	Normal	Bacterial	Viral	TBM/Fungal
Leucocytes (cells/mm^3)	<5 (0-10)	>500 (10-2000)	<500 (0-1000)	50-750
Polymorphs%	2	>80	<50	<50
Protein(mg/dL)	0-40	>100 (40-500)	<100 (20-200)	50-200 (40-1500)
Sugar (mg/dL)	>60	<40	>40	<40
CSF/blood glucose	>0.6	<0.3	0.3-0.6	<0.4

Table IV. Organisms causing meningitis and their staining characteristics

Staining	Organism
Gram positive cocci	Staphylococcus, Streptococcus, Pneumococcus
Gram negative cocci	Meningococci
Gram positive bacilli	Listeria
Gram negative bacilli	E. coli, Klebsiella, Pseudomonas
Gram negative coccobacillus	H. influenza

Latex agglutination test is an useful adjunct to Gram staining in children who had been pretreated with antibiotics in whom the culture is negative. It detects the bacterial antigens as they persist for several days even after antibiotic therapy.[13] Commercial kits are available that cover N.meningitidis serogroup B, W135, A, C, and Y, S. pneumoniae, H. influenzae type b, E. coli K1, Klebsiella and group B streptococci. It is a rapid test which can be done in 15-20 minutes with just one ml of CSF. However the test cannot provide the antibiotic sensitivity pattern.

Polymerase Chain Reaction (PCR) for bacterial antigens is not yet commonly used as first line diagnostics but is useful in patients who have negative Gram stain and culture.[14] It rapidly detects microbial nucleic acids including from the non-viable organisms. PCR is more sensitive than culture or antigen detection and employing this can significantly increase the speed and accuracy of identification of the pathogen.[15] It has a rapid turnaround time of 1.5 to 2 hours and requires only 0.2 ml of CSF. This can detect as few as 10-100 CFU/ml of bacteria in CSF.[16] Multiplex real time PCR provides an opportunity of detecting multiple potential pathogens simultaneously. It helps in antibiotic stewardship, decreases the length of hospital stay and overall health cost. The limitation is that it cannot provide antibiotic sensitivity pattern.

Table V. Empirical antibiotics in various age groups

Age	Drug
<1 month	Ampicillin + Cefotaxime/Aminoglycoside
1to 3 months	Ampicillin + Cefotaxime/Ceftriaxone + Vancomycin
>3 months	Cefotaxime/ Ceftriaxone +Vancomycin

Neuroimaging

Neuroimaging is neither necessary nor sufficient to diagnose meningitis. However, it may be useful in the management to rule out complications such as subdural effusion/empyema, venous / arterial infarction, hydrocephalus, ventriculitis and brain abscess.[4]

Other investigations

This includes complete blood count, C-reactive protein, renal function tests, liver function tests, serum

Box 1. Case classification (WHO)

Suspected: Any person with sudden onset of fever (> 38.5 °C rectal or 38.0°C axillary) and one of the following signs: neck stiffness, altered consciousness or other meningeal sign.

Probable: A suspected case with CSF examination showing at least one of the following:

- turbid appearance;

- leukocytosis (> 100 cells/mm^3);

- leukocytosis (10-100 cells/ mm^3) AND either an elevated protein (> 100 mg/dl)

or decreased glucose (< 40 mg/dl).

Confirmed: A case that is laboratory-confirmed by growing (i.e. culturing) or identifying

(i.e. by Gram stain or antigen detection methods) a bacterial pathogen (Hib, pneumococcus or meningococcus) in the CSF or from the blood in a child with a clinical syndrome consistent with bacterial meningitis.

(Source: WHO. Recommended standards for surveillance of selected vaccine preventable diseases. WHO/V&B/03.01: Department of Vaccines and Biologicals, 2003.)

Table VI. First line antibiotics and alternate regimen

Organism	First line antibiotics	Alternate	Duration
N.meningitidis	Penicillin G	Ceftriaxone Cefotaxime Meropenem	7 days
H. influenzae	Ceftriaxone Cefotaxime	Cefipime Meropenem	10 days
S.pneumoniae	Ceftriaxone/Cefotaxime Ceftriaxone/Cefotaxime + Vancomycin +/- Rifampin	Cefepime Meropenem	10 - 14 days
Group B streptococcus	Penicillin +/- Gentamicin Ampicillin+/- Gentamicin	Cefotaxime	14 - 21days
L. monocytogenes	Ampicillin+/- Gentamicin	Trimethoprim Sulfamethoxazole	14 - 21 days
Gram negative	Cefotaxime	Cefipime Meropenem Fluoroquinolone	21 -28 days
S. aureus	Nafcillin Oxacillin Vancomycin+/- Rifampin	Linezolid Daptomycin	
S.epidermidis	Vancomycin	Linezolid	
Pseudomonas	Ceftazidime	Meropenem	

Table VII. Antibiotics used in meningitis and doses

Antibiotic	0 – 7 days	8 – 28 days	Infants / children	Maximum dose in a day
Ampicillin	150 - 200 mg/kg/day in 3 divided doses	200 - 300 mg/kg/day in 4 divided doses	200 - 300 mg/kg/day in 4 divided doses	12g
Cefotaxime	100 mg/kg/day in 2 divided doses	200 mg/kg/day in 3 divided doses	200 - 300 mg/kg/day in 4 divided doses	12g
Ceftriaxone		80 – 100 mg/kg/day twice daily / once daily	80 -100 mg/kg/day twice daily/once daily	4g
Penicillin	1 – 1.5 lakh/kg/day in 2 divided doses	1.5 – 2 lakh/kg/day in 4 divided doses	3 – 4 lakh/kg/day in 4 divided doses	20 million
Vancomycin	20 mg/kg/day in 2 divided doses	30 mg/kg/day in 3 divided doses	40 – 60 mg/kg/day in 4 divided doses	2g
Rifampin	10 mg/kg/day in 2 divided doses	20 mg/kg/day in 2 divided doses	20mg/kg/day in 2 divided doses	600 mg

electrolytes, urine culture, coagulation profile if the child is ill or has a petechial rash, X-ray chest, PCR test for viruses in throat or nasopharyngeal swab. CRP may be low or normal early in severe infection.[9] Meningococci can be isolated from the throat in about half the patients with meningococcal disease and is not affected by antibiotic treatment.[17] Similarly aspiration of the petechiae may yield the organism in two thirds of the patients even if the child has received antibiotics.[18] These investigations are particularly useful in that a definitive diagnosis of meningococcal disease can be made when clinical status precludes lumbar puncture.

WHO has suggested working diagnosis based on clinical features and lab investigations (Box 1).

Management

The choice of empirical antibiotics depends on the age of the child, immunization status and the local resistance pattern of the organisms to antibiotics. Empirical antibiotics to be started at various age groups are given in Table V. Once the culture and sensitivity pattern is received, the antibiotics should be modified according to the sensitivity pattern. The first line antibiotics and the alternate regimen for each organism is described in Table VI.[4,19] The most recent antibiotic treatment guidelines for pneumococcal meningitis recommend the use of vancomycin along with cefotaxime or ceftriaxone in view of the increasing non-susceptibility of the isolates to both penicillin and cefotaxime. Penicillin resistance amongst pneumococcal meningeal isolates increased from 9.5% in 2008 to 42.8% in 2016, whereas cefotaxime non-susceptibility increased from 4.7% in 2008 to 28.5% in 2016. Hence, it would be prudent to add vancomycin to ceftriaxone for the initial treatment of acute bacterial meningitis till culture reports become available.[20] Antibiotics and their doses to be used in various age groups are given in Table VII.[4] Once appropriate antibiotics are given, Gram stain becomes negative and CSF culture becomes sterile in 24 hours. CSF sugar becomes normal in 3 days, CSF protein remains elevated for 10 or more

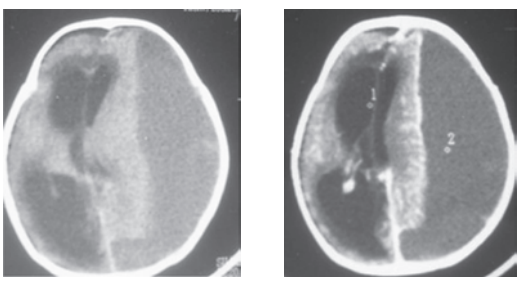

Fig.1. Subdural empyema causing midline shift

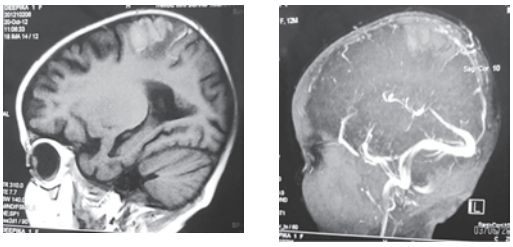

Fig.2. Superior sagittal sinus thrombosis

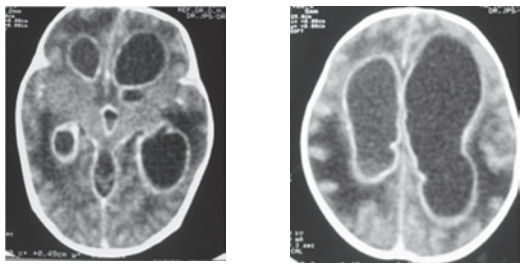

Fig.3. Ventriculitis

days while cell count status increased for a week. Prior antibiotic therapy will not alter cell count, protein or glucose. However it reduces the yield of culture by 30% and Gram stain by 20%.

Indications for repeat lumbar puncture

Repeat lumbar puncture is not necessary routinely but is indicated in the following situations: i) No improvement in 24-72 hours of antibiotic therapy, ii) Neonatal meningitis and iii) Gram negative meningitis.[13]

Role of steroids

Intravenous dexamethasone is indicated in the dose of 0.15 mg/kg/dose 6th hourly for 4 days in infants above 6 weeks of age in the management of bacterial meningitis. A dose of 0.4 mg/kg given every 12 hours for a total duration of two days has proved to be safe and efficacious as the dose of 0.15 mg/kg given every six hours for four days. The short course may perhaps help to reduce the risk of gastric hemorrhage.[21] The probable mechanism by which it exerts its action include - inhibition of the production of inflammatory cytokines (TNF α, interleukins) and minimizing alteration in the permeability of blood brain barrier. It decreases the incidence of deafness in H. influenza meningitis. The best evidence for benefit is for H. influenza meningitis and less certain for pneumococcal meningitis.[13]

Supportive care

Supportive care includes maintenance of blood pressure to ensure adequate cerebral perfusion, correction of electrolyte disturbances, control of seizures, management of raised intracranial pressure and careful fluid

management. There is no evidence that fluid restriction reduces cerebral edema in bacterial meningitis. Hence, fluid restriction is advised only if there is evidence of SIADH.[13]

Complications

Complications that can occur when managing a child with bacterial meningitis include subdural effusion, subdural empyema (Fig.1), hydrocephalus, pyocephalus, cerebral venous sinus thrombosis (Fig.2), ventriculitis (Fig.3) and cerebral abscess especially in neonates, seizures, SIADH.

Prognosis

The mortality rate is 10 - 20%.[6,22] About 15-25% of children with bacterial meningitis develop sequelae including developmental delay, cognitive impairment, seizure disorder, focal deficits, optic atrophy and hearing loss. Persistent bilateral or unilateral deafness can occur in pneumococcal (31%), meningococcal (10.5%) and H. influenza *b* (6%) meningitis. Neonatal meningitis carries a higher morbidity where in 35-45% develop sequelae such as hearing loss, blindness, hydrocephalus and cerebral palsy.

Prevention

After the introduction of H.influenzae *b* vaccine in universal immunization program, there has been a marked reduction in the incidence of H. influenzae *b* meningitis in children. Similarly incorporation of pneumococcal vaccine especially pneumococcal conjugate vaccine 13 (PCV-13) can provide protection against nearly 79% of serotypes responsible for invasive pneumococcal diseases in India.[6]

The recommendations for prevention of secondary cases among close contacts is given below.

H influenzae b infection:

- All home contacts should be given rifampicin 20 mg/kg/day (max. 600 mg/day) for four days.
- Any unvaccinated children aged 12-48 months, should be given one dose of the vaccine.
- Unvaccinated children aged 2-11 months should be given three doses of the vaccine.

Meningococcal infection:

- Rifampicin 10 mg/kg (under 1 year, 5 mg/kg) every 12 hours for two days orally (OR)
- Ceftriaxone 125 mg intramuscularly as a single dose (OR)
- Ciprofloxacin 500 mg orally as a single dose in children aged >12 years

Pneumococcal meningitis:

- Chemoprophylaxis is not normally indicated for close contacts.

Points to Remember

- ***Bacterial meningitis is a medical emergency.***
- ***High index of suspicion is necessary to diagnose bacterial meningitis especially in infants as the symptoms are quite nonspecific.***
- ***Bacterial confirmation in CSF remains the gold standard for diagnosis.***
- ***Prompt diagnosis and aggressive management is essential to prevent mortality and morbidity.***

References

1. Kabra SK, Kumar P, Verma IC, Mukherjee D, Chowdhary BH, Sengupta S, et al. Bacterial meningitis in India: An IJP survey. Indian J Pediatr. 1991; 58(4):505-511.
2. Chinchankar N, Mane M, Bhave S, Bapat S, Bavdekar A, Pandit A, et al. Diagnosis and outcome of acute bacterial meningitis in early childhood. Indian Pediatr 2002; 39(10):914-921.
3. Van de Beek D, Cabellos C, Dzupova O, Esposito S, Klein M, Kloek AT, et al. ESCMID guideline: diagnosis and treatment of acute bacterial meningitis. Clin Microbiol Infect 2016; 22:S37-S62.
4. Weinberg GA, Thompson-stone R. Bacterial infections of nervous system. In: Swaiman KF, Ashwal S, Ferriero DM, Schor NF, Finkel RS, Gropman AL, Pearl PL, Shevell M eds, Swaimans pediatric neurology: Principles and Practice 6th edn, Elsevier, Canada 2018; pp883-889.
5. Newton CRJC. Central nervous system infections (Bacterial and parasitic). Sejersen &Wang: Acute pediatr Neurol 2014; 243-270.
6. Mehendale S, JayaramanY, VeeraraghavanB. Hospital based sentinel surveillance of bacterial meningitis in India. International J Infect Dis 2016; 45: 299-300.
7. John TJ, Gupta S, Chitkara AJ, Dutta AK, Borrow R. An overview of meningococcal disease in India: Knowledge gaps and potential solutions. Vaccine 2013; 31(25):2731–2737.
8. El Bashir H, Laundy M, Booy R. Diagnosis and treatment of bacterial meningitis: Arch Dis Child 2003; 88:615-620.
9. Kanegaye JT, Soliemanzadeh P, Bradley JS. Lumbar puncture in pediatric bacterial meningitis: defining the time interval for recovery of cerebrospinal fluid pathogens after parenteral antibiotic pretreatment. Pediatrics 2001; 108:1169-1174.
10. Negrini B, Kelleher KJ, Wald ER. Cerebrospinal fluid findings in aseptic versus bacterial meningitis. Pediatrics 2000; 105:316-319.

11. Spanos A, Harrell FE Jr, Durack DT. Differential diagnosis of acute meningitis: an analysis of the predictive value of initial observations. JAMA 1989; 262:2700-2707.
12. Tunkel AR, Scheld WM. Bacterial meningitis. Philadelphia: Lippincott Williams & Wilkins; 2001 Jun.
13. Allan R. Tunkel,1 Barry J. Hartman, Sheldon L. Kaplan, Bruce A. Kaufman, Karen L. Roos, W. Michael Scheld, Whitley :Practice Guidelines for the Management of Bacterial Meningitis: Clin Infect Dis 2004; 39:1267-1284.
14. Schuurman T, De Boer RF, Kooistra-Smid AM, Van Zwet AA. Prospective Study of Use of PCR Amplification and Sequencing of 16S Ribosomal DNA from Cerebrospinal Fluid for Diagnosis of Bacterial Meningitis in a Clinical Setting. J Clin Microbiol 2004; 42:734-740.
15. Seth R, Murthy PSR, Sistla S, Subramanian M, Tamilarasu K. Rapid and Accurate Diagnosis of Acute Pyogenic Meningitis Due to Streptococcus Pneumoniae, Haemophilus influenzae Type b and Neisseria meningitidis Using A Multiplex PCR Assay. J Clin Diagn Res 2017; 11(9): FC01-FC04.
16. Kennedy W, Chang S-J, Purdy K, Le T, Kilgore PE, Kim JS, et al. Incidence of bacterial meningitis in Asia using enhanced CSF testing: polymerase chain reaction, latex agglutination and culture. Epidemiol Infect 2007; 135:1217-1226.
17. Cartwright K, Kroll S. Optimising the investigation of meningococcal disease. Br Med J 1997; 315: 757-758.
18. Van Deuren M, van Dijke BJ, Koopman RJ, Horrevorts AM, Meis JF, Santman FW, et al. Rapid diagnosis of acute meningococcal infections by needle aspiration or biopsy of skin lesions. Brit Med J 1993; 306:1229-1232.
19. Swanson D. Meningitis. Pediatr Rev 2015; 36:514-526.
20. Verghese VP, Veeraraghavan B, Jeyaraman R, Varghese R, Neeravi A, Jayaraman Y, et al. Increasing incidence of penicillin- and cefotaxime resistant Streptococcus pneumoniae causing meningitis in India: Time for revision of treatment guidelines? Indian J Med Microbiol 2017; 35(2):228-236.
21. Tunkel AR, Hartman BJ, Kaplan SL, Kaufman BA, Roos KL, Scheld WM, et al. Practice guidelines for the management of bacterial meningitis. Clinical infectious diseases 2004; 39(9):1267-1284.
22. Mohanty N, Biswas TK, Satapathy S, Meher SK, Patro D. Etioclinical profile and outcome of acute bacterial meningitis in post neo natal U-5 children: a study from tertiary care center of coastal Odisha, India. Int J Res Med Sci 2017; 5(6):2519-2523.

CLIPPINGS

Initial serum level of IL-10 as an outcome predictor in children with sepsis.

Role of IL-10 as an outcome predictor in pediatric sepsis patient were studied. Plasma specimens were collected at admission, then the patients were followed until the patients get shock or not. The initial serum levels of IL-10 was significantly decreased in both groups, but lower in the septic shock group.Cut of point <255 pg/ml was obtained through the ROC, with the sensitivity 100%, specificity 100%, positive predictive value 100%, negative predictive value 100% Conclusions: Serum IL-10 can be used as an outcome predictor in children with sepsis with a level of255 mg/ml as a cutoff for prognostic value.

Idham Jaya Ganda, Milda, Sitti Aizah Lawang, Dasril Daud. Initial serum level of IL-10 as an outcome predictor in children with sepsis. Current Pediatr Res 2018; 22(2):152-156.

NEWS AND NOTES

PAED ENDO 2019

Date: 6th January, 2019 Venue: Seminar Hall, II Floor, College Building, SRMC

Conference Secretariat

PAED ENDO 2019

Dept of Endocrinology

Sri Ramachandra Institute of Higher Education and Research (DU)

No.1, Ramachandra Nagar, Porur, Chennai.

Mobile: 9003882906, 9841184748

IAP - IJPP CME 2018

VASOACTIVE AGENTS - PRACTICAL ASPECTS

Karthik Narayanan R

Abstract: *Vasoactives are agents that are used to modulate hemodynamics in a patient. They can work by increasing the heart rate, contractility, dilating the blood vessels to improve tissue perfusion or constricting them to divert blood flow to important organs. Commonly used vasoactive agents are dopamine, dobutamine, epinephrine, nor-epinephrine, milrinone and vasopressin. Each of these agents have unique properties and knowledge about them is essential to titrate their doses in the critically ill child. While nor-epinephrine and vasopressin are dominant vasopressors, dobutamine and milrinone are dominant inodilators. Epinephrine and dopamine have varied actions based on the dose of infusion. Choosing appropriate vasoactive agent depends upon the hemodynamic status of the child. Inappropriate vasoactive selection may compromise tissue perfusion and result in more hemodynamic instability.*

Keywords: *Vasoactives, Inotropes, Vasopressor, Shock, Hemodynamics, Drugs.*

Drugs that are used to maintain hemodynamic stability are integral to pediatric emergency and intensive care. The aim of these drugs is to improve tissue perfusion by increasing cardiac output (CO) and modulating the vascular tone.

Cardiac output is a product of stroke volume (SV) and heart rate (HR). SV is the volume of blood pumped out of the heart per beat. This depends on the preload, afterload and cardiac contractility. Cardiac output can be increased either by a) optimizing the preload (with adequate fluid resuscitation), b) increasing the contractility (inotropy), c) enhancing diastolic relaxation (lusitropy - to improve coronary circulation) and d) increasing the heart rate (chronotropy) depending upon the existing pathology.[1]

* Senior Consultant - Pediatric Intensive Care, Rainbow Childrens Hospital, Chennai.

email: drkarthik.r@rainbowhospitals.in

Vascular tone or systemic vascular resistance (SVR) on the other hand influences the mean arterial pressure (or the perfusion pressure). Ensuring optimal vascular tone is essential to maintain tissue perfusion. Low SVR as well as high SVR can impair tissue perfusion and result in tissue hypoxia. Vasoactive drugs can be pure inotropes, inodilators, pure vasodilators, vasopressors or inopressors.

Physiologic considerations

It is important to understand the physiology of major receptors that regulate cardiovascular homeostasis in the body. It is by activating these receptors vasoactive drugs bring about the change in hemodynamics. The various receptors and its physiological actions have been summarized in Table I.[2]

Pharmacology of individual therapeutic agents

The commonly used vasoactive drugs and their mechanism of action are enumerated in Table II.[2]

Catecholaminergic agents: Catecholaminergic agents are the drugs of choice in circulatory shock as they are easy to titrate and have a short half-life (dopamine and dobutamine have half-life of 22- 25 minutes while epinephrine and nor-epinephrine have a half life of 2 - 2.5 minutes).[2] They act directly on various adrenergic receptors assummarized in with dose-dependent activity (Table II). Commonly used catecholamines are epinephrine, norepinephrine, dopamine and dobutamine. In view of their short half-life, they need to be given through continuous infusions only.

Dopamine: Dopamine acts on dopaminergic receptors (D1, D2) and adrenergic receptors making its action somewhat complex. At lower doses dopamine is claimed to be inotropic and vasodilatory (<5-10 μg/kg/min), however at higher doses (>10 μg/kg/min) it is a potent vasopressor.[2] Maximum dosage of dopamine is 20 μg/kg/min and can be started through a peripheral line, without requiring a central line. Higher doses may lead to receptor desensitization. Dopamine has been observed to cause immune suppression when used in patients with sepsis.[3] Recent small-randomized controlled trials have observed increased mortality, organ dysfunction and delay in achieving reversal of shock with dopamine when compared

Table I. Physiological actions of various receptors responsible for hemodynamic stability

Receptor	Distribution	Inotropy and chrontropy	Vascular action
Alpha 1	Vascular smooth muscle, sphincters of GIT and urinary tract, muscles of iris	-	Vasoconstriction
Alpha 2	CNS, blood vessels, GIT	-	-
Beta 1	Heart and kidney	++++	Vasodilatation
Beta 2	Smooth muscles of airway, blood vessels, uterus, detrusor muscles of urinary bladder and liver	++	Vasodilatiation
Dopaminergic	D1 like (D1 and D5); D2 like (D2,3 and 4)	D1 and D4 ++	D1-vasodilation D2-Vasoconstriction
Vasopressin	V1 - Smooth muscle cells of blood vessels V2 - Renal collecting ducts V3 - Pituitary (ADH release)	-	V1- Intense vasoconstriction

Table II. Commonly used vasoactive agents and its mechanism of action

	Receptor type			Effect on CVS		
Agent	**Alpha - 1**	**Beta - 1**	**Beta - 2**	**Chrontropy**	**Inotropy**	**Vaso Constriction**
Dopamine (< 10 mcg/kg/min)	+	++++	++	+++	+++	-
Dopamine (10 - 20 mcg/kg/min)	+++	++++	++	+++	+++	+++
Dobutamine	+	++++	+++	++	+++	-
Nor-epinephrine	++++	++	-	+	++	++++
Epinephrine (<0.2 mcg/kg/min)	++	++++	+	+++	+++	+
Epinephrine (0.2-1.0 mcg/kg/min)	++++	++++	+	++++	+++	++++

with epinephrine in pediatric septic shock.[4,5,6] However, dopamine continues to be used by various centers around the world, for the ease of administration through the peripheral line and potent vasopressor action.

Epinephrine: Epinephrine (adrenaline) stimulates beta-adrenergic receptors at lower doses, thereby increasing heart rate and contractility. However at higher doses >0.3μg/kg/min, due to its alpha action, it increases the systemic vascular resistance. Theoretically the beta action is more than the alpha-receptor action and it increases the blood pressure by increasing cardiac rate and contractility. Dopamine and dobutamine are less potent and have less peak effect than epinephrine or nor-epinephrine. Epinephrine increases myocardial oxygen demand (due to increased chronotropic action), impairs splanchnic circulation and increases lactate production.[7] However, the lactate production due to epinephrine infusion is not associated with adverse outcome.[8] Dosage is 0.05μg/kg/min titrated upto 1.5μg/kg/min. Epinephrine requires a central line, when infused for longer durations, as it may lead to vasoconstriction and extravasation when administered peripherally. However, it can be initiated through peripheral line to begin with.[6]

Norepinephrine: Norepinephrine has proportionally greater action on alpha as compared to beta adrenergic receptors. Hence it is a potent vasopressor when compared with epinephrine or dopamine and increases mean arterial pressure (MAP) by increasing systemic vascular resistance. It has some positive inotropic effect and chronotropic effect. At very high dose it can compromise perfusion of mesenteric, renal and cutaneous vasculature, which has always been a concern, but studies are lacking to support the claim.[9] Cerebral and coronary circulation are relatively spared. It requires a central line for infusion, as peripheral venous infusion leads to vasoconstriction. Dosage is 0.05 μg/kg/min upto 1μg/kg/min.

Dobutamine: Dobutamine is a synthetic compound that mostly stimulates beta receptors causing inotropy and vasodilatation with weaker chronotropic effects. So, dobutamine improves cardiac output and perfusion, but might not increase the blood pressure. It is a good option for those situations where perfusion is poor due to high SVR and poor myocardial contractility. Dobutamine is less effective when used in patients previously treated with beta blockers.[10] Tolerance to dobutamine develops as early as 48 hours necessitating the need to change to other inotrope. The dosage range is 5 to 20 μg/kg/min.

Phosphodiesterase III inhibitors (PDI)

Phosphodiesterases (PD) are a group of enzymes that breakdown Cyclic adenosine monophosphate (Camp) to AMP. PD-III is predominantly found in myocardium and vascular smooth muscle. PD III inhibitors increase the levels of cAMP in myocardium and vascular smooth mucle, thereby improving cardiac contractility and peripheral vascular perfusion (by causing vasodilation). They also reduce diastolic dysfunction and relaxes the ventricles during diastole, thereby reducing preload - which is called lusitropy. The overall effect is increase in cardiac output and perfusion with very minimal rise in myocardial oxygen consumption compared with other catecholamines. This effect is receptor independent and therefore desensitization will not occur. The reduced SVR may lead to hypotension if the BP is borderline. So, there are not to be used in hypotensive children. It can be considered in situations where BP is normal, cardiac output is low and SVR is high. Unlike catecholamines, PDIs have a longer half-life and therefore the effects are long-standing.

Milrinone is most commonly used PDI in children. Its commonly excreted in urine and hence dosage needed to be adjusted in renal impairment. It has a half-life of 2.3 hours. Milrinone is known to cause supraventricular, junctional and ventricular tachyarrhythmias, which is more likely with underlying hypokalemia. Dosage: Recommended to start as a bolus with 50 - 75 μg/kg/min over 1 hour and then run as an infusion at 0.5-0.75 μg/Kg/min. The bolus dose is avoided in children with greater concern of hypotension (in situations like septic shock).[11]

Natural hormones

Vasopressin: Vasopressin known as anti-diuretic hormone (ADH) is secreted from posterior pituitary. It acts through the V1 receptors in the vascular smooth muscle causing intense vasoconstriction. In times of stress, the levels of vasopressin go up, and there is a relative vasopressin insufficiency. This is the physiological basis behind using vasopressin in shock. However, unlike adults who present with high CO and low SVR shock, in children low CO and high SVR mostly characterize shock. Hence, children might not be candidates to exclusive vasopressors (no chronotropy and inotropy) like vasopressin. Vasopressin has a short half-life (10-20 mins) and should be given as infusion. However, vasopressin has some unique advantages when compared to its counterpart norepinephrine. It does not increase the heart rate like nor-epinephrine and therefore myocardial oxygen demand is reduced, especially in children when the heart rate is already 180-190/min. Since it is not dependent on adrenergic receptors, it remains effective even when the adrenergic receptors are down-regulated. Acidosis does not affect its action unlike norepinephrine. The dosage range is 0.0003-0.09 units/kg/min (extrapolated from adult studies).[12]

Newer inotropes

Levosimendan: Levosimendan is a calcium-sensitizing agent. It exerts its action by binding to cardiac troponin C in a calcium-dependent process, thereby changing the configuration of tropomyosin, which leads to increased contractility. It also helps in improving lusitropy (diastolic relaxation) by not increasing the intracellular calcium concentration in myocardium. It causes decrease in SVR and coronary vasodilatation by opening up potassium channels in sarcolemmal membranes. Overall, there is an increase in cardiac output while MAP and pulmonary arterial pressure decrease. Like all other agents, levosimendan is also arrhythmogenic.[11] The half-life is 1.5 to 2 hours, but its active metabolite OR-1896 has an elimination half-life of 70-80 hours. This leads to persistent hemodynamic effects of levosimendan days after stopping the infusion. Dosage: loading dose of 12 μg/kg/min over 10 minutes followed by a continuous infusion of 0.1 - 0.2 μg/kg/min. Mostly levosimendan has been used in post-operative low cardiac output state situations and has shown benefit in improving cardiac contractility.

Practical aspects in management of pediatric shock states

The initiation and titration of vasoactive therapy is based on the pathophysiology behind the hemodynamic disturbance. It is known that in certain shock states like septic shock, the pathophysiologic state varies from time to time and hence frequent monitoring and titration of vasoactive drugs is needed. The commonly used monitoring parameters are a) clinical - heart rate (HR), mean arterial pressure (MAP), pulse volume, capillary refill time (CRT), urine output and sensorium b) Invasive monitoring parameters – invasive arterial blood pressure (IABP), mixed venous oxygen saturation (SvO2) and central venous pressure (CVP) c) Non-invasive monitoring - Echocardiographic monitoring of respirophasic variation of inferior vena cava (IVC collapsibility/ distensibility), ejection fraction (EF) and cardiac output (CO).

The therapeutic end-points of any shock are to normalize HR, MAP-CVP >5th centile, CRT <2 sec, urine output > 1 ml/kg/hr, GCS > 13, SvO2 >70%, EF: 40 - 60% and CO: 3.3 - 6 L/min/M^2. 13 In order to attain these, vasoactive should be titrated as summarized in Fig.1 after categorizing based on the stepwise approach below.

Stepwise approach is enumerated below:[14]

Step 1: Vasodilatory or vasoconstricted shock (warm or cold shock).

Step 2: Assess cardiac function (EF) - Normal, hyperdynamic or decreased.

Step 3: Assess intravascular fluid volume (CVP, respirophasic variation of IVC, IABP) - Underfilled, normal/full.

Vasoactive-inotropic scores

The amount of cardiovascular support given by using multiple vasoactives are measured objectively using the Vasoactive-inotropic score (VIS). This index has been

	Cold shock		Warm shock	
	Normal BP	**Low BP**	**Normal BP**	**Low BP**
Initial therapy	Dopamine upto 10µg OR dobutamine upto 10µg	Dopamine upto 10µg OR adrenaline 0.05-0.2µg	Fluid boluses + dopamine 10µg	Fluid boluses + dopamine 10µg Or noradrenaline 0.05-0.2µg
No response to the above therapy / Worsening of shock / changing clinical signs from warm shock to cold Shock				
Focused ECHO + arterial monitoring and change in therapy				

Monitoring findings		
IVC status	IVC collapsed or >50% respirophasic variation	Continue fluid bolus
	IVC normal / full with minimal respirophasic variation	Discontinue fluid bolus and restrict fluids (<70% maintenance)
Cardiac function	EF<50% with normal BP	Dobutamine upto 10µg ± milrinone 0.25-0.5µg or adrenaline 0.05-0.3µg
	EF <50% with low BP	Adrenaline 0.05-0.5µg ± dobutamine upto 10µg
	EF >70% (hyperdynamic LV) with normal BP and volume (IVC)	Decrease inotropes
	EF > 70% with low BP or wide pulse pressure in IBP	Vasopressor (N.E – 0.05- to 0.5µg) or Vasopressin

Fig.1. Titration of vasoactives based on fluid status, cardiac contractility and perfusion (adapted from Ranjit et al).[14]

Table III. Preparation of infusions of Vasoactive medications

Drug	Dose	Dilution to volume	Infusion rate	Equivalent dose range
Epinephrine (central)	0.3 mg/Kg	50 ml D5 or NS	0.1 - 10 ml/hr	0.01 - 1 mcg/Kg/min
Dobutamine (Central)	30 mg/Kg	50 ml D5 or D10 or NS	0.5 - 2 ml/hr	5 - 20 mcg/Kg/min
Dobutamine (Peripheral)	3 mg/Kg	50 ml D5 or D10 or NS	5 - 20 ml/hr	5 - 20 mcg/Kg/min
Dopamine (Central)	30 mg/Kg	50 ml D5 or D10 or NS	0.5 - 2 ml/hr	5 - 20 mcg/Kg/min
Dopamine (Peripheral)	3 mg/Kg	50 ml D5 or D10 or NS	0.5 - 2 ml/hr	5 - 20 mcg/Kg/min
Milrinone	1.5 mg/Kg	50 ml D5 or NS	0.6 - 1.5 ml/hr	0.3 - 0.75 mcg/Kg/min
Nor-epinephrine (Central)	0.3 mg/Kg	50 ml D5 or NS	0.1 - 10 ml/hr	0.01 - 1 mcg/Kg/min
Vasopressin	1.5 IU/Kg	50 ml D5 or NS	0.2 - 0.5 ml/hr	0.0001 - 0.00025 IU/kg/min

D5 = 5% Dextrose; D10 = 10% Dextrose; NS = Normal Saline

proposed from the Wernovsky Inotropic index (IS) which is used to measure the cumulative dosages of inotropic agents used in post-operative cardiac surgery children.

a) Wernovsky IS = dopamine dose (μg/kg/min) + dobutamine (μg/kg/min) + 100 X epinephrine dose (μg/kg/min)15

b) VIS = IS + 10 x milrinone dose (μg/kg/min) + 10,000 X vasopressin dose (U/kg/min) + 100 x norepinephrine dose (μg/kg/min).[15]

Preparation of infusion of vasoactive medications

Adapting the universal rule of six for infusion calculations can help in preparation of stock solution and determine the infusion rates of vasoactives is peripheral line.

6 X body weight (kg) = Amount (in mg) to mix in 100 ml of solvent to give 1 ml/hr = 1 microgram/kg/min.

Based upon the volume status of the child and availability of central line, the concentration of these solutions can be modified based on rule of six, to determine sui infusion rates. A standard chart is presented in Table III.

Conclusion

Dopamine, dobutamine, epinephrine, nor-epinephrine, vasopressin, milrinone and levosimendan are the commonly used vasoactive agents in children. Before initiating any vasoactive, it is imperative to optimise preload and rule out obstructive shock as a cause of shock. There is no strong evidence to suggest superiority of one vasoactive over another in children. The choice of the vasoactive is individualized based on the hemodynamic status of the patient, which is determined by using various monitoring parameters.

Points to Remember

- ***All vasoactive drugs should be given as infusion due to their short half-life.***
- ***Accurate hemodynamic assessment is important in choosing the appropriate vasoactive agent.***
- ***Dopamine (>10mg/kg/min), norepinephrine, epinephrine (<0.2 μg/kg/min) and vasopressin are predominant vasopressors.***
- ***Dopamine (<10μg/kg/min), epinephrine (<0.2 μg/kg/min), dobutamine and milrinone are inotropes and vasodilators.***
- ***All vasoactive agents are arrhythmogenic.***

References

1. Zaritsky AL. Catecholamines, inotropic medications, and vasopressor agents. In: The pharmacologic approach to the critically ill patient. Chernow B, ed. Baltimore: Williams and Wilkins, 1994; 387-404.
2. Overgaard CB, Dzavik V. Inotropes and vasopressors: review of physiology and clinical use in cardiovascular disease. Circulation. 2008; 118:1047-1056.
3. Van den Berghe G, de Zegher F. Anterior pituitary function during critical illness and dopamine treatment. Crit Care Med 1996; 24:1580-1590.
4. Sakr Y, Reinhart K, Vincent JL, Sprung CL, Moreno R, Ranieri VM, et al. Does dopamine administration in shock influence outcome? Results of the Sepsis Occurrence in Acutely Ill Patients (SOAP) Study. Crit Care Med 2006; 34:589-597.
5. Ventura AM, Shieh HH, Bousso A, Góes PF, de Cássia F O Fernandes I, de Souza DC, et al. Double-Blind Prospective Randomized Controlled Trial of Dopamine Versus Epinephrine as First-Line Vasoactive Drugs in Pediatric Septic Shock. Crit Care Med 2015; 43:2292-2302.
6. Ramaswamy KN, Singhi S, Jayashree M, Bansal A, Nallasamy K. Double-Blind Randomized Clinical Trial Comparing Dopamine and Epinephrine in PediatricFluid-Refractory Hypotensive Septic Shock. Pediatr Crit Care Med 2016; 17:e502-e512.
7. Levy B, Bollaert PE, Charpentier C, Nace L, Audibert G, Bauer P, et al. Comparison of norepinephrine and dobutamine to epinephrine for hemodynamics, lactate metabolism,and gastric tonometric variables in septic shock: a prospective, randomized study. Intensive Care Med 1997; 23:282-287.
8. Day NP, Phu NH, Bethell DP, Mai NT, Chau TT, Hien TT, et al. The effects of dopamine and adrenaline infusions on acid-base balance and systemic haemodynamics in severe infection. Lancet 1996; 348:219-223.
9. Müllner M, Urbanek B, Havel C, Losert H, Waechter F, Gamper G. Vasopressors for shock. Cochrane Database Syst Rev 2004:CD003709.
10. Metra M, Nodari S, D'Aloia A, Muneretto C, Robertson AD, Bristow MR, et al. Beta-blocker therapy influences the hemodynamic response to inotropic agents in patients with heart failure: a randomized comparison of dobutamine and enoximone before and after chronic treatment with metoprolol or carvedilol. J Am Coll Cardiol 2002; 40:1248–1258.
11. Bistola.V, Chioncel.O. Inotropes in acute heart failure. Continuing Cardiology Education. 2017; 3:107-116.
12. Russell JA. Bench-to-bedside review: Vasopressin in the management of septic shock. Crit Care 2011; 15(4):226.
13. Davis AL, Carcillo JA, Aneja RK, Deymann AJ, Lin JC, Nguyen TC, et al. American College of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock. Crit Care Med 2017; 45:1061-1093.
14. Ranjit S, Aram G, Kissoon N, Ali MK, Natraj R, Shresti S, et al. Multimodal monitoring for hemodynamic categorization and management of pediatric septic shock: a pilot observational study. Pediatr Crit Care Med 2014; 15:e17-26.
15. Gaies MG, Gurney JG, Yen AH, Napoli ML, Gajarski RJ, Ohye RG, et al. Vasoactive inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonarybypass. Pediatr Crit Care Med 2010; 11:234-238.

NEWS AND NOTES

MADRAS PEDICON 2019

44th Annual Conference of Indian Academy of Pediatrics - Tamilnadu State Chapter

Organised by Indian Academy of Pediatrics – Chennai City Branch

Date: 15th to 18th August, 2019

Contact

Dr.Janani Sankar, Organising Secretary, MADRAS PEDICON 2019

Dr.N.Suresh, Treasurer, Chennai Pedicon 2019

IAP-CCB House, Third Floor, Flat No.9, Halls Towers,

56, Halls Road, Egmore, Chennai-600 008. Tamilnadu. India.

Mobile: 9841078101, 9444288174

Email: madraspedicon2019@gmail.com

IAP - IJPP CME 2018

HIGH FLOW NASAL CANNULA OXYGEN THERAPY - DOES IT CHANGE OUR PRACTICE?

Priyavarthini Venkatachalapathy

Abstract: *High flow nasal cannula oxygen therapy is a relatively new form of respiratory support in children that provides high flows of heated, humidified blended air and oxygen non-invasively. It is well studied in acute viral bronchiolitis and is found to reduce the need for escalation of respiratory support. Though evidence is very sparse, it is also increasingly used in other conditions of respiratory distress like pneumonia, asthma, cardiac failure, etc. Remarkable patient comfort, coupled with good safety profile, ease of use and efficacy has made high flow nasal cannula oxygen therapy a popular initial choice of respiratory support in children with moderate to severe respiratory distress, both within and outside the intensive care environment.*

Keywords: *High flow nasal cannula, Bronchiolitis, Respiratory distress, Respiratory support.*

High Flow Nasal Cannula (HFNC) oxygen therapy is a form of non-invasive respiratory support which provides high flows of a mixture of air and oxygen which is heated and humidified, directly into the nares via a non-sealing nasal cannula.[1] It is more appropriately termed, "Heated Humidified High Flow Nasal Cannula Oxygen Therapy (HHHFNC)". Standard nasal cannulas allow only limited gas flow rates that are much lower than the patient's peak inspiratory flow demand, whereas those across HFNC meet or exceed the same.[2] Also, standard nasal cannulas are poorly tolerated when gas flows exceed 2 L/min since it causes dryness and irritation of the nasal mucosa. The definition of "High Flow" is quite variable, but usually refers to a flow rate of >2 L/min in infants and >6 L/min in children.[1] The level of respiratory support offered by HFNC can be placed in between low flow oxygen devices and continuous positive airway pressure (CPAP). This review does not cover the usage of HFNC in neonates.

* Consultant, PICU and ER ,
Apollo Children's Hospital, Chennai.
email: priyavarthiniv@gmail.com

Setting up HFNC

The basic unit consists of a gas flow generator (usually an oxygen and air blender/ turbine/ conventional ventilator), heated humidifier, heated circuit and a nasal cannula (Fig.1).[3] Gas flow generator produces a mixture of air and oxygen (FiO_2 from 0.21 to 1) which is heated and humidified subsequently. This mixture is delivered through heated circuits to prevent condensation, into the nostrils via prongs, the diameter of which should not exceed half that of the nostril. This is to allow leak and avoid excessive pressure build up in the airways.[1,4] Different sized cannulas are available for neonates, infants, children and adults.

Mechanisms by which HFNC works[1,4,5,6]

Multiple mechanisms have been postulated and can be grouped as respiratory support and airway hydration.

Respiratory support: High gas flow provides flows above patient's peak inspiratory demand (Fig.2), washes out CO_2 in oropharyngeal dead space and enriches with O_2 resulting in better oxygenation and ventilation.[7]

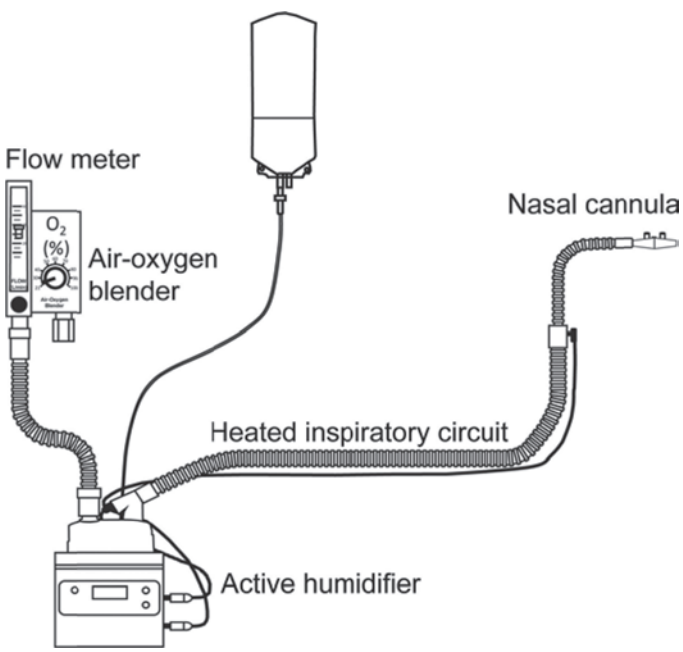

Fig.1. High flow nasal cannula oxygen therapy-setup

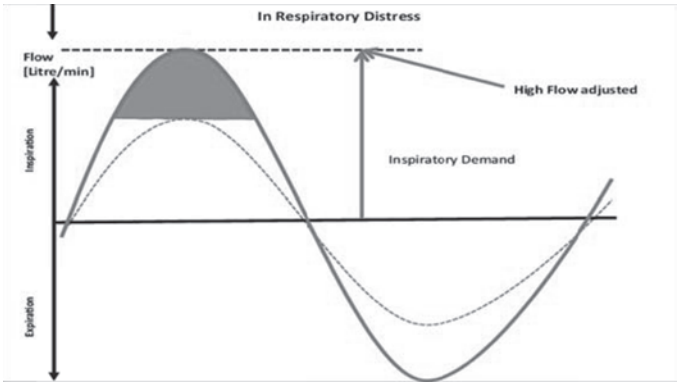

Fig.2.Respiratory distress – Increased peak inspiratory flow demand met with by HFNC[7]

Also the commonly used flow rates produce an average CPAP of about 4-6 cm H_2O which helps in splinting the airways open and preventing the alveoli from collapsing by maintaining functional residual capacity (FRC). Both these mechanisms result in reduced work of breathing.

Airway hydration: Conditioning of inspired gases (heated to 34-37^0 C and humidified to a relative humidity of 100%) facilitates comfortable delivery of high gas flows, improves mucociliary clearance, prevents drying and desiccation of airway epithelium and decreases airway resistance. This, effectively, results in improved tolerance and comfort.

Initial settings, monitoring, escalation, weaning

HFNC is usually started when a child with respiratory distress or hypoxemia needs respiratory support more than low flow oxygen but does not qualify for immediate invasive mechanical ventilation (IMV).[4] Practices and protocols for initial settings, escalation and weaning vary considerably between different units.[4,8]

Initial settings

Flows: There is no consensus on the dosing of flows. The choice of flow rate depends on the size of the patient and the degree of respiratory distress. Recent evidence is in favour of weight based dosing rather than age based protocols. It may be prudent to start with 0.5-1 L/kg/min and gradually build to a max of 2 L/kg/min (Max: 50 L/min) to improve patient tolerance. Flows above 2L/kg/min have not been shown to benefit additionally.[4]

FiO_2: FiO_2 can be set at 0.6 and titrated rapidly to achieve the target SpO_2.[4]

Monitoring

As with any form of non-invasive ventilation (NIV), monitoring is crucial. Responders show improvement in heart rate, respiratory rate, work of breathing, gas exchange and decrease in FiO_2 requirements to < 0.4, usually within 60 minutes of initiation of HFNC.[4,6] Those who remain static or worsen further (HFNC failure) require escalation to higher forms of non-invasive or invasive ventilation.[4]

Complications

Although HFNC is by and large safe, overreliance without frequent clinical assessment can potentially delay escalation to invasive therapeutic options and can increase morbidity and mortality akin to any modality of NIV.[1] Other reported, but infrequent complications include abdominal distension (hence, relatively contraindicated in post abdominal surgeries), nasal bleed and ulcers, blocked HFNC due to secretions and rarely, pneumothorax and pneumomediastinum.[4,6] If abdominal distension develops, it necessitates prompt placement of orogastric tube to prevent aspiration.

Weaning

In general, there is no need for a prolonged weaning process. Once stable with FiO2 < 0.4 and the indication for which the child was placed on HFNC has resolved or is resolving, flows can be decreased rapidly, as tolerated, every few hours. Subsequently, the child can be transitioned to low flow oxygen, if needed.

Conditions where HFNC potentially works

HFNC potentially has its applicability in a range of conditions with varied pathophysiological processes like infection, inflammation, airway obstruction, hypoventilation etc. due to its ability to work on different parts of the airway and give positive pressure.[9,10] It was originally introduced as a form of respiratory support for preterm infants with respiratory distress, as an alternative to CPAP. However, the last decade has seen an abrupt increase in its usage in both pediatric and adult population.[6]

HFNC in bronchiolitis: HFNC has found its utility in many clinical conditions; the most well studied being acute bronchiolitis where there is inflammation of small airways, altered mucociliary clearance, mucus plugging and atelectasis resulting in increased airway resistance, impaired oxygenation and ventilation.[10] HFNC, by multiple mechanisms especially, conditioning of inhaled gases, provision of CPAP and improved oxygenation, helps in overcoming the above pathophysiological processes.

Multiple observational studies and a few randomised control trials (RCT) have proven that the use of HFNC has been associated with improvement in tachypnea, decreased work of breathing, reduced need for escalation of respiratory support and intubation rates compared with standard oxygen therapy.[11-13] But, it has not been proven conclusively to be as good as or superior to CPAP.[2,4,14] However, due to its relative safety, better comfort and patient tolerance, it may be considered as the initial choice of respiratory support in children with moderate to severe acute bronchiolitis.[4] HFNC is perceived by clinicians as a "silver lining in the dark sky" in the face of limited evidence for other medical interventions like systemic steroids, nebulised adrenaline, bronchodilators and hypertonic saline.[6,15] It is being increasingly used for post- extubation respiratory support in many conditions including bronchiolitis, though evidence is scarce.[5] It is intuitive, to conclude that HFNC, by preventing the escalation of care to more invasive forms of ventilation and by providing post- extubation respiratory support possibly reduces the need for IMV and duration of the same.

HFNC in conditions other than bronchiolitis: A Cochrane review in 2014 on HFNC, excluding studies on bronchiolitis, concluded that there was insufficient evidence to determine the safety and effectiveness of HFNC as a form of respiratory support in children as no RCTs were available.[16] Despite paucity of literature proving effectiveness, HFNC has recently gained popularity in a variety of conditions like asthma, pneumonia, upper airway obstruction, cardiac failure, neuromuscular weakness etc.[4,7] A positive clinical response has been observed in physiological parameters like heart rate, respiratory rate and gas exchange with its use in these conditions.[6] However, conflicting reports are noted with regard to the need for intubation, admission to pediatric intensive care units (PICU) and length of stay.[4,6] Few studies comparing HFNC and CPAP in children with respiratory distress, due to conditions other than bronchiolitis report similar efficacy and outcomes in both groups.[6] The ongoing major trials like PARIS 2 trial and FIRST-ABC trial will possibly throw light on these aspects of HFNC therapy. Box 1 gives a list of conditions that can potentially benefit from HFNC. Further studies are, however needed to ascertain if HFNC is useful in all these conditions.

Contraindications for HFNC use: Respiratory failure, inability to protect airway, severe hemodynamic instability, uncontrolled vomiting, copious upper gastrointestinal bleeding, complete upper airway obstruction, trauma or surgery to the nose and nasopharynx are contraindications to the use of HFNC as is the case with any form of NIV.[17]

Box 1. HFNC - Uses

- Acute viral bronchiolitis[1,2,4,6,10-15,19,20]
- Post extubation respiratory support[5]
- Weaning from mask CPAP or BiPAP[21]
- Post-op cardiac surgical patients[4,6,22]
- Interfacility transfer[21]
- Respiratory distress due to
  - Pneumonia[4,22]
  - Pulmonary edema[6]
  - Upper airway obstruction (e.g.Post extubation stridor, croup)[4,6]
  - Asthma[4]
  - Cardiac failure[5,22]
- Preoxygenation before intubation[23]
- Obstructive sleep apnea[24]
- Immunocompromised children with mild to moderate respiratory distress[22,25]
- Neuromuscular diseases with mild to moderate respiratory distress[4,22]

HFNC – Setting where it can be used

HFNC traditionally was used only in PICUs.[4,6] It is now being increasingly used outside PICUs - in emergency departments, post operative cardiac intensive care units, high dependency units, pediatric wards and during interfacility transfer of patients.[4,6,7,18-20]

HFNC - Does it change our office practice?

Available literature shows that there are lot of elementary questions unanswered in multiple aspects of HFNC usage including indications, dosing of flows, escalation and weaning protocols, safety in conditions other than bronchiolitis. However, there is lot of enthusiasm shown on its usage by clinicians which is not surprising given the fact that it is non invasive, simple to set up, has good safety profile, easily available, portable and effective in some common clinical scenarios encountered in day to day office practice. It also allows aerosolised medications to be delivered via the circuit, if needed. Above all, it has the advantage of being patient friendly with excellent "acceptance" as children on HFNC can talk, play and be fed while on therapy.

Hence, HFNC seems to have changed our clinical practice and will continue to do so, given its popularity. But, it is important to remember that new treatment modalities always generates lot of interest and as pediatricians, we need to know the advantages and more so, the limitations of any therapy and keep ourselves updated on the expanding body of literature.

Points to Remember

- ***Heating and humidification are the key determinants of efficacy and tolerance of HFNC.***
- ***HFNC decreases the need for invasive mechanical ventilation in bronchiolitis.***
- ***Improved patient comfort and tolerance are the principal reasons for HFNC being used in children with moderate to severe respiratory distress of any etiology, although evidence for its efficacy and safety are scanty.***
- ***HFNC is not a replacement for invasive mechanical ventilation.***
- ***Undue reliance on HFNC without repeated clinical assessments and timely escalation of care can potentially increase mortality.***

References

1. Milési C, Boubal M, Jacquot A, Baleine J, Durand S, Odena MP, et al. High-flow nasal cannula: recommendations for daily practice in paediatrics. Ann Intensive Care 2014; 4:29.
2. Lee JH, Rehder KJ, Williford L, Cheifetz IM, Turner DA. Use of high flow nasal cannula in critically ill infants, children, and adults: a critical review of the literature. Intensive Care Med 2013; 39:247-257.
3. Nishimura M. High-flow nasal cannula oxygen therapy in adults: physiological benefits, indication, clinical benefits, and adverse effects. Respir Care 2016; 61(4):529-541.
4. Slain KN, Shein SL, Rotta AT. The use of high-flow nasal cannula in the pediatric emergency department. J Pediatr (Rio J) 2017; 93(s1):36-45.
5. Rubin S, Ghuman A, Deakers T, Khemani R, Ross P, Newth CJ. Effort of breathing in children receiving high-flow nasal cannula. Pediatr Crit Care Med 2014; 15:1-6.
6. Mikalsen IB, Davis P, Oymar K. High flow nasal cannula in children: a literature review. Scand J Trauma Resusc Emerg Med 2016; 24:93.
7. Ramnarayan P, Schibler A. Glass half empty or half full? The story of high flow nasal cannula therapy in critically ill children. Intensive Care Med 2017; 43:246-249.
8. Miller AG, Gentle MA, Tyler LM, Napolitano N. High-Flow Nasal Cannula in Pediatric Patients: A Survey of Clinical Practice Respir Care 2018; 63(7):894-899.
9. Goligher EC, Slutsky AS. Not just oxygen? Mechanisms of benefit from high-flow nasal cannula in hypoxemic respiratory failure. Am J Respir Crit Care Med 2017; 195(9):1128-1131.
10. Sinha IP, McBride AKS, Smith R, Fernandes RM. CPAP and high-flow nasal cannula oxygen in bronchiolitis. Chest 2015; 148 (3):810-823.
11. Milesi C, Baleine J, Matecki S, Durand S, Combes C, Novais AR, et al. Is treatment with a high flow nasal cannula effective in acute viral bronchiolitis? A physiologic study. Intensive Care Med 2013; 39:1088-1094.
12. Franklin D, Babl FE, Schlapbach LJ, Oakley E, Craig S, Neutze J, et al. A randomized trial of high-flow oxygen therapy in infants with bronchiolitis. N Engl J Med 2018; 378:1121-1131.
13. Cambonie G, Pons-Odena M, Baleine J, Milési C. High flow nasal cannulae for acute viral bronchiolitis in young infants: evidence-based medicine is underway to define target populations and optimal flows. J Thorac Dis 2017; 9(7):1763-1766.
14. Milési C, Essouri S, Pouyau R, Liet JM, Afanetti M, Portefaix A, et al. High flow nasal cannula (HFNC) versus nasal continuous positive airway pressure (nCPAP) for the initial respiratory management of acute viral bronchiolitis in young infants: a multicenter randomized controlled trial (TRAMONTANE study). Intensive Care Med 2017; 43(2):209-216.
15. Kline J, Kalburgi S, Halley T. High flow nasal cannula therapy for bronchiolitis across the emergency department and acute care floor. Clin Pediatr Emerg Med 2018; 19(1):40-45.
16. Mayfield S, Jauncey-Cooke J, Hough JL, Schibler A, Gibbons K, Bogossian F. High-flow nasal cannula therapy for respiratory support in children. Cochrane Database Syst Rev 2014; Issue 3:CD009850.
17. Fedor KL. Noninvasive Respiratory Support in Infants and Children. Respir Care 2017; 62(6):699-717.
18. Inata Y, Takeuchi M. Complex effects of high-flow nasal cannula therapy on hemodynamics in the pediatric patient after cardiac surgery. J Intensive Care 2017; 5:30.
19. Mayfield S, Bogossian F, O'Malley L, Schibler A. High-flow nasal cannula oxygen therapy for infants with bronchiolitis: pilot study. J Paediatr Child Health 2014; 50(5):373-378.
20. Riese J, Porter T, Fierce J, Riese A, Richardson T, Alverson BK. Clinical outcomes of bronchiolitis after implementation of a general ward high flow nasal cannula guideline. Hosp Pediatr 2017; 7(4):197-203.
21. Coletti KD, Bagdure DN, Walker LK, Remy KE, Custer JW. High-flow nasal cannula utilization in pediatric critical care. Respir Care 2017; 62(8):1023-1029.
22. Ten Brink F, Duke T, Evans J. High flow nasal prong

oxygen therapy or nasopharyngeal continuous positive airway pressure for children with moderate to severe respiratory distress? Pediatr Crit Care Med 2013; 14:e326-331.

23. Papoff P, Luciani S, Barbàra C, Caresta E, Cicchetti R. High-flow nasal cannula to prevent desaturation in endotracheal intubation: a word of caution. Crit Care Med 2015; 43(8):e327-e328.
24. Joseph L, Goldberg S, Shitrit M, Picard E. High-flow nasal cannula therapy for obstructive sleep apnea in children. J Clin Sleep Med 2015; 11(9):1007-1010.
25. García-Salido A, Mastro-Martínez I, Cabeza-Martín B, Oñoro G, Nieto-Moro M, Iglesias-Bouzas MI, et al. Respiratory failure in children with hematooncological diseases admitted to the PICU: a single center experience. J Pediatr Hematol Oncol 2015~ 37(6):449-454.

CLIPPINGS

Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices-United States, 2018-19 Influenza Season.

This report updates the 2017-18 recommendations of the Advisory Committee on Immunization Practices (ACIP) regarding the use of seasonal influenza vaccines in the United States (MMWR Recomm Rep 2017;66 [No. RR-2]). Routine annual influenza vaccination is recommended for all persons aged e"6 months who do not have contraindications. A licensed, recommended, and age-appropriate vaccine should be used. Inactivated influenza vaccines (IIVs), recombinant influenza vaccine (RIV), and live attenuated influenza vaccine (LAIV) are expected to be available for the 2018-19 season. Standard-dose, unadjuvanted, inactivated influenza vaccines will be available in quadrivalent (IIV4) and trivalent (IIV3) formulations. Recombinant influenza vaccine (RIV4) and live attenuated influenza vaccine (LAIV4) will be available in quadrivalent formulations. High-dose inactivated influenza vaccine (HD-IIV3) and adjuvanted inactivated influenza vaccine (aIIV3) will be available in trivalent formulations.Updates to the recommendations described in this report reflect discussions during public meetings of ACIP held on October 25, 2017; February 21, 2018; and June 20, 2018. New and updated information in this report includes the following four items. First, vaccine viruses included in the 2018-19 U.S. trivalent influenza vaccines will be an A/Michigan/45/2015 (H1N1)pdm09-like virus, an A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus, and a B/Colorado/06/2017-like virus (Victoria lineage). Quadrivalent influenza vaccines will contain these three viruses and an additional influenza B vaccine virus, a B/Phuket/3073/2013-like virus (Yamagata lineage). Second, recommendations for the use of LAIV4 (FluMist Quadrivalent) have been updated. Following two seasons (2016-17 and 2017-18) during which ACIP recommended that LAIV4 not be used, for the 2018-19 season, vaccination providers may choose to administer any licensed, age-appropriate influenza vaccine (IIV, RIV4, or LAIV4). LAIV4 is an option for those for whom it is appropriate. Third, persons with a history of egg allergy of any severity may receive any licensed, recommended, and age-appropriate influenza vaccine (IIV, RIV4, or LAIV4). Additional recommendations concerning vaccination of egg-allergic persons are discussed. Finally, information on recent licensures and labeling changes is discussed, including expansion of the age indication for Afluria Quadrivalent (IIV4) from ≥18 years to ≥5 years and expansion of the age indication for Fluarix Quadrivalent (IIV4), previously licensed for ≥3 years, to ≥6 months.This report focuses on the recommendations for use of vaccines for the prevention and control of influenza during the 2018-19 season in the United States. A Background Document containing further information and a brief summary of these recommendations are available at https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/flu.html. These recommendations apply to U.S.-licensed influenza vaccines used within Food and Drug Administration-licensed indications. Updates and other information are available at CDC's influenza website (https://www.cdc.gov/flu). Vaccination and health care providers should check CDC's influenza website periodically for additional information.

Grohskopf LA, Sokolow LZ, Broder KR, Walter EB, Fry AM, Jernigan DB. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices-United States, 2018-19 Influenza Season. MMWR Recomm Rep. 2018 Aug 24; 67(3):1-20. doi: 10.15585/mmwr.rr6703a1.

IAP - IJPP CME 2018

SCHOLASTIC BACKWARDNESS – REMEDIAL STRATEGIES

**Poongodi Bala*

Abstract: *Scholastic backwardness is a growing concern among parents and teachers in the modern competitive world. Prior to assessing the child in detail for academic backwardness, the high expectation of the parents should be dealt with. Poor academic performance can present with somatic symptoms. Co-morbid conditions such as attention deficit hyperactivity disorder (ADHD), autism, behavioural difficulties and emotional difficulties are common in children with scholastic backwardness. It can lead to functional impairment not only to the child but also to the parents. Scholastic backwardness contributes to school dropout and mental health difficulties. Mental health professionals should work closely with pediatricians, parents and schools. Early intervention based on multidisciplinary team approach is essential for better outcomes.*

Keywords: *Scholastic backwardness, Parental counselling, Co-morbid conditions, Remedial strategies.*

Education is an essential part of human resource development. Parents and teachers tend to worry a lot about their child's academic performance from the first day of entering into the school. Scholastic backwardness is a growing concern among parents and teachers in the modern competitive world. It causes low self-esteem in the children and can lead to mental health illness in future. Hence, it is really important to identify scholastic backwardness at an early stage and provide appropriate support.

There is no accurate data on the national incidence/ prevalence of scholastic backwardness. However, local studies have showed that around 20% of the children in India have scholastic backwardness.[1,2] Despite the confounding factors such as socio-economic status and language exposure in these studies, the percentage of children with poor academic performance is significantly quite high.

* Consultant Child and Adolescent Psychiatrist, Sri Ramachandra Institute of Higher Education & Research, Chennai.
email: pooongssk@yahoo.co.uk

Definition

It is difficult to provide a specific definition for poor academic performance as the standards vary from place to place. There is no diagnosis of scholastic backwardness as per International Classification of Diseases by World Health Organisation (ICD 11)[3] or Diagnostic and Statistical Manual of Mental Disorders by American Psychiatric Association (DSM-5)[4], because poor academic performance is a symptom and not a diagnosis. Learning difficulty is mentioned as specific learning difficulties in DSM-5 and developmental learning disorder in ICD 11. Generally poor scholastic performance can be defined as academic achievement below the expected level for a given age and cognitive skills.

Presentation

In the pediatric clinic, parents could present their children with direct symptoms such as poor concentration, poor academic scores and poor writing/reading skills. Some children or adolescents present with somatic symptoms such as abdominal pain, headache, body pain, nausea, chest pain, breathlessness, urinary incontinence and abnormal movements of the limbs.

Approach and assessment

Prior to assessing the child in detail for academic backwardness, it is important to identify and deal with the high expectation of the parents. It is not unusual to see parents and teachers with extremely high expectations these days. The competitive nature of the education system has the potential to force the parents, teachers and kids to focus purely on high marks in exams. The role of clinician involves assessing the parents' expectations in the context of the child's actual abilities/skills. Detailed history taking including academic, developmental, medical history and use of language and communication abilities of the child will help to differentiate reality from heightened expectations. The list of questions which would be useful to get information from the parents is given in Box 1.

Box 1. Detailed questions for assessment

- Current grade or marks
- Recent deterioration of academic performance
- Lag in studies behind the peer group
- History of specific difficulties e.g. reading / writing / maths
- Change of school
- History of repeating school year
- Behavioural / emotional difficulties
- Concentration difficulties
- Co-morbid medical / developmental / psychiatric conditions

The child should be assessed in all areas such as physical health, nutritional deficiency, vision and hearing impairment, social and emotional status, general intelligence, academic performance, developmental milestones and their communication skills.[6] Detailed assessment for learning difficulty includes identifying factors that affect the academic performance such as lack of prior learning, cultural differences, poor educational background, age of enrolment in school, preschool exposure and educational support available at home during school years. For example urban kids have more opportunity than village kids.[3]

Parental consent should be obtained before assessing the child. A detailed interview with the child to check their level of understanding and to assess writing and reading skills will help to identify the specific difficulties. Looking at their previous grades and marks will help to identify the pattern of difficulties, e.g. dyslexia, dyscalculia.

As single source of information or single interview will not be sufficient to reach a conclusion, collated information following interview with the parents and assessment of the child is important. Gathering information from the teachers and school, school observation and review of the worksheets by professionals could also be useful (as recommended by the Rehabilitation Council of India). The diagnosis is mainly based on detailed history taking and clinical observation though screening tools have been used for initial screening and research purpose to monitor the effectiveness of treatment.

Etiology

Once the poor academic performance is confirmed, the next step is to identify the etiology as treatment depends on the underlying cause. Scholastic backwardness in children generally reflects the underlying medical, physical or social problem.

Box 2. Etiology

Child	**Family**
Intellectual disability	Conflict within the parents
Specific learning difficulties	Separation anxiety
Co-morbid conditions	High expectations/ Overprotection
Substance misuse	Ongoing abuse
Gadget addiction	
Lack of interest	
Physical disability (Hearing/Vision)	
Poor quality of diet	
Chronic medical illness	
School	**Society**
Attitude of teacher(s)	Poverty
Teaching methods	Cultural differences
Peer group influence	Gender discrimination
Lack of resources	Socio- economic status
Academic pressure	

Etiology can be divided into four categories based on the factors related to the child, family, school and society (Box 2).[5,7,8]

Neonatal complications such as low birthweight, prematurity, seizures, hypothyroidism, jaundice and intracranial bleed can lead to intellectual disability as it affects the brain growth in early development of the child. Co-morbid developmental conditions such as attention deficit hyperactivity disorder (ADHD) and autistic spectrum disorder (ASD) could also affect the child's academic performance.

Investigations

The investigations/assessments recommended for the evaluation of scholastic backwardness are shown in Box 3.

Treatment

Treatment depends on the underlying etiology. Earlier

Box 3. Scholastic backwardness - Evaluation

- Investigations to rule out nutritional deficiency, hypothyroidism and lead toxicity
- Vision and hearing assessment
- Psychometric tests for IQ assessment
- Assessment of specific learning difficulties (SLD)
- Behavioural analysis if the child has behavioural difficulties

support is essential for a better outcome. A multidisciplinary evaluation by an ophthalmologist, otorhinolaryngologist, counsellor, clinical psychologist, special educator, pediatrician, career counsellor and child psychiatrist is needed.[3]

Parent's role

The key to the management of scholastic backwardness involves helping parents to understand their child's difficulties with detailed parental counselling. For example, if the child has low IQ level, his/her academic achievement will be expectedly low and it will be important for parents to understand this and adjust their expectations accordingly. Understanding the child's difficulties will enable parents to focus on helping their child to achieve his/her best rather than comparing with the peer groups. Moreover it helps the parents to avoid blaming the child or their partners for the poor academic performance.

Parents and teachers might have a tendency of expecting the child to complete all tasks and school/home work similar to their peer group. This will not be possible if the child is a slow learner. Hence they need to concentrate on improving his or her basics in the first instance. Parents and teachers should have realistic goals regarding what child could achieve. Parents should avoid 'homework war' at home.

Treating co-morbid conditions

Physical co-morbid conditions such as epilepsy and diabetes, developmental conditions such as ASD and ADHD and psychiatric co-morbid conditions should be treated accordingly.[8]

Remedial strategies

Each child is unique in terms of their ability to learn, grasp knowledge, style of learning and their academic performance. Remedial strategies include educational assessment of the children to find their strengths and weaknesses in their academic skills and boost the self- confidence by promoting their strengths. Individual educational plan should have short term and long-term goals with an overall aim to enhance the positive skills, self-esteem and confidence. It can be offered at school or outside of the school based on the availability of appropriate resources. Parents and carers should be trained to use those skills to practice at home. The special educational plan should focus on their basic learning and life skills which can promote their positive attitudes and values, as well as prepare them to live independently in future.

Psycho-educational intervention such as teaching in a small group setting, one to one teaching, using visual and practical methods, focusing on basic reading/writing/maths, seating the child in the front rows to minimise the distraction etc., could help the child to improve their academic performance. Children with learning difficulties will benefit from simple, short and clear instructions. Applying letter and sound knowledge to word reading and writing will be useful. It is important to emphasise that the children with specific learning difficulties (e.g. dyslexia) can respond slowly even to the most effective teaching methods.

Government support

Learning disability and specific learning disability are included in the lists of disability under "The Rights of Persons with Disabilities Bill – 2016" along with other physical and mental disabilities replacing the previous Persons with Disability Act 1995. This change will help the families to get some benefits such as disability certificate.[9]

National Institute of Open Schooling (NIOS) is a central government organisation, which provides academic and vocational training for children and adults with learning difficulties. Non-Governmental Organisations (NGOs) and private schools are working with NIOS to provide educational support to the children who cannot continue normal schooling. NIOS offers the following concessions for students with Learning Difficulty(LD) - all sub-types: (a) One hour or 25% extra time in public exams, (b) No mark reduction for grammar and spelling mistakes, (c) Use of calculator in maths exam, (d) Exemption from writing one language exam, (e) Use of scribe or typing answers on a computer and (f) 20% grace marks.[10] Professionals need to inform about these available resources to the parents, as most families are unaware of the available support.

Conclusion

Poor academic performance can lead to school dropout and add stress to the children, parents and teachers. It can lead to poor self-esteem, low motivation and behavioural difficulties. The other main complication is functional impairment in their employment and relationship. Hence, it is important to identify and intervene scholastic backwardness at an early stage to get better outcomes. Each child is unique and might require specific remedial measure based on the underlying issue along with lots of encouragement and positive reinforcement. In western countries parent support groups play an important role in identifying and treating these difficulties.[8] In India such parents groups are at a developing stage but have the potential to provide immense help to the parent communities.

Points to Remember

- ***Scholastic backwardness is a growing concern among parents, children and teachers.***
- ***It can lead to functional impairment of the children and parents.***
- ***Management is based on etiology and through multimodal approach.***
- ***Management includes special education for children and regular parental counselling. Awareness and support should be offered at school level.***

References

1. Karande S, Kulkarni M. Poor school performance. Indian J Pediatr 2005; 72(11):pp961-967.
2. MogasaleVV, Patil NM. Prevalence of specific learning disabilities among primary school children in a south Indian city. Indian J Pediatr 2012; 79(3):342-347.
3. ICD10, ICD 11 (International Classification of Disease by WHO) 10th and 11th version.
4. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th Edn. Arlington, VA American Psychiatric Association 2013.
5. Haneesh K, Krishnakumar P, Sukumaran SK, Riyaz A. Risk factors for scholastic backwardness in children. Indian Pediatr 2013;50(7):pp655-658.
6. Santosh AK. Scholastic backwardness in children attending normal school. AP J Psychol Med 2014; 15(2):251-254.
7. Nair MKC, Chhaya Prasad, Jeeson Unni, Anjan Bhattacharya, Kamath SS, Samir Dalwai. Consensus Statement of the Indian Academy of Pediatrics on Evaluation and Management of Learning Disability. Indian Pediatr 2017; 54(7):574-580.
8. Galagali PM, Luiz N. Poor school Performance in adolescence. Indian J Pract Pediatr 2015; 17(2):116-121.
9. Learning disabilities. http://www.rehabcouncil.nic.in/writereaddata/ld.pdf. Accessed on 15th August, 2018.
10. Provisions for learners with disabilities during NIOS examinations. https://www.nios.ac.in/media/documents/PWD/provisionforlwd.pdf. Accessed on 18th August, 2018.

CLIPPINGS

A Study of the relationship between cystatin C and metabolic bone disease in preterm infants.

This study was to investigate serum CysC levels in osteopenia of prematurity (OP) and determine whether CysC could be safely used as a marker of renal insufficiency in infants with OP. Study included 50 preterm infants. serum cys C levels were not significantly different between infants with OP and in infants without OP. cys C which was considered as a marker of acute kidney injury based on literature evidence is not to be considered so in preterm with OP.

Korkut S, Memur Þ, Halis H, Baþtuð O, Korkmaz L, Özdemir A, et al. A Study of the Relationship Between Cystatin C and Metabolic Bone Disease in Preterm Infants. J Clin Res Pediatr Endocrinol 2018; 10(2):119-124.

NEWS AND NOTES

1st Asia Pacific Echocardiography Course on Congenital Heart Disease

Date: 8th – 10th March, 2019

Venue: Singapore City, Singapore

Email: paev15@nus.edu.sg; Website: www.nuh.com.sg

DRUG PROFILE

PHARMACOTHERAPY FOR SPASTICITY IN CEREBRAL PALSY

Jeeson C Unni

Abstract: *Management of spasticity is integral to the therapy for children with cerebral palsy. The requirements of each child is assessed and therapy appropriate for the given child at each stage of development, is instituted. Some children with cerebral palsy may benefit from additional pharmacological treatment. Common medications include benzodiazepines, dantrolene sodium, baclofen, tizanidine, phenol and alcohol. In selected cases, local botulinum toxin A injection is used for reducing local spasticity to assist other modalities of therapy. Further studies in children and adolescents are needed to routinely recommend the anti-spasticity medications for children and adolescents with cerebral palsy. A review of the evidence for the use of each of these medications is detailed in this article.*

Keywords: *Cerebral palsy, Spasticity, BoNT-A, Baclofen.*

Prevalence of cerebral palsy (CP) is reported to be 3.6 cases per 1000 in 8-year-old children, with very little variation among Western nations.[1,2] CP is the most common cause of spasticity in children and the majority of children with CP are affected by spasticity.[3] Its incidence may be increasing secondary to improved care in neonatal intensive care units including improved survival of low birth-weight infants.

The Taskforce on Childhood Motor Disorders defines spasticity as "hypertonia in which one or both of the following signs are present (i) resistance to externally imposed movement increases with increasing speed of stretch and varies with the direction of joint movement and (ii) resistance to externally imposed movement rises rapidly above a threshold speed of joint angle".[4]

Alleviation of spasticity may not always be desirable; some patients may experience a decline in function with spasticity reduction.[5] The decision to use antispasticity medications requires careful assessment of the patient's other impairments (e.g., weakness, movement disorders) and proper selection and use of the treatment. Reasons to treat spasticity include reducing pain and muscle spasms, facilitating brace use, improving posture, minimizing contractures and deformity, facilitating mobility and dexterity and improving patient ease of care as well as hygiene/self-care.[6]

Several tools such as the Ashworth scale[7] and the "Modified" Ashworth scale[8] have been used in clinical trials, with the assumption that they measure spasticity. These scales measure a broader set of neural and musculoskeletal factors of non-velocity-dependent hypertonia in addition to spasticity itself.[9] The Tardieu scale accounts for the joint angle measure of the spastic phenomenon at different velocities of joint movement.[10] Spasticity in the child should always be assessed while he or she is in a relaxed supine position.

Over the last 20 years, several antispasticity treatments - drugs [benzodiazepines, dantrolene, baclofen and tizanidine, neuromuscular blocking agents such as botulinum toxins A and B (BoNT-A and BoNT-B)], chemical denervation using phenol and alcohol, intrathecal baclofen (ITB) have been adapted for use in patients with CP.[11]

Oral medications and ITB are used when a generalized antispasticity effect is desired. Chemical denervation agents are used to treat localized (one extremity) or segmental (lower body, hemibody) spasticity. The mechanisms of action and pharmacology of these drugs have been described.[12,13] This literature review is an attempt to assess the present scenario with regard to pharmacotherapy of spasticity in children and adolescents with cerebral palsy.

Spasticity medications

They can be classified as given in Box 1. Since tolerance can occur with medications, drug dosages should regularly be reviewed and implantable devices (pumps, stimulators) should be checked. Gabapentin, clonazepam, progabide, piracetam, lamotrigine, and cyproheptadine may potentially affect spasticity. They are currently under investigation, have undergone little clinical evaluation and

* Editor-in-Chief,
IAP Drug Formulary,
Aster Medcity, Kochi.
email: jeeson1955@gmail.com

Box 1. Spasticity medications classification

- Skeletal muscle relaxants (dantrolene sodium, baclofen)
- Benzodiazepines (diazepam)
- Alpha2-adrenergic agonists (clonidine, tizanidine)
- Botulinum toxins (onabotulinumtoxinA, abobotulinumtoxinA, incobotulinumtoxinA, rimabotulinumtoxinB)
- Phenol and alcohol injections

therefore not recommended currently for management of spasticity.

Skeletal muscle relaxants

Dantrolene Sodium: Dantrolene is the only peripherally acting oral antispasticity medication approved by the US Food and Drug Administration. It is often used in the field of anesthesiology to reverse malignant hyperthermia after delivery of anesthesia. As an antispastic drug, it acts on the muscles themselves, uncoupling excitation and contraction by inhibiting calcium release at the sarcoplasmic reticulum.[11] Caution should be taken because there have been reports of liver failure with the use of the drug.[11,12] Because dantrolene does not selectively target specific muscles, it may lead to the adverse effect of general muscle weakness.[13] In some rare cases, it has been fatal in high doses and is therefore not considered a first-line drug.[14] It may be tried in cerebral-origin spasticity - traumatic brain injury (TBI), stroke and cerebral palsy, especially as an adjunct in spasticity refractory to other treatments. There is conflicting evidence regarding the effectiveness of dantrolene in reducing spasticity in children with CP. Dantrolene frequently causes side effects in children with spastic CP, such as weakness, drowsiness and irritability.

Baclofen is widely used in clinical practice to treat spasticity in children with CP. Experts recommend starting baclofen at the lowest possible dose (5-10 mg/day divided into three doses a day)[5] to minimize adverse effects like drowsiness and sedation. It works pre- and postsynaptically as a gamma-aminobutyric acid (GABA) B agonist at the spinal level and binds to its receptors, leading to membrane hyperpolarization.[14] This restricts calcium influx, which subsequently restricts endogenous excitatory neurotransmitters from being released and inhibits mono and polysynaptic spinal reflexes.[15,16] Adverse effects include systemic muscle relaxation, sedation, and fatigue.[17,18,19] Because of potential hepatotoxicity, there is a need to monitor liver function with baclofen use.[20] There is conflicting evidence regarding the effectiveness of oral baclofen in reducing spasticity and improving function in children with CP. Systemic toxicity was found in some patients.

Intrathecal baclofen (ITB) is used for children with weight above 15 kg.[16] However, it has been noted there are more complications seen in children using ITB than in adults.[21] Furthermore, there are mixed results in studies assessing the effectiveness of baclofen in children with cerebral palsy.[11] Further studies regarding the efficacy of ITB for children are warranted. Data are inadequate concerning the use of continuous ITB as an antispasticity treatment in children with CP. CSF leaks, seromas, catheter-related complications, and wound infection occur frequently, and other, milder complications occur less frequently.

Benzodiazepines

Diazepam works postsynaptically on $GABA_A$ receptors, depressing the action of the CNS. Along with clonazepam, another benzodiazepine, diazepam induces significant sedation. Because of this sedation, a potential benefit is the reduction of spasticity at night, permitting uninterrupted sleep. Diazepam has a tendency to act primarily on flexor refexes, but it can work on extensors in higher doses.[22] Because spinal spasticity has a propensity toward flexor reflexes, diazepam is better suited for spinal spasticity than for cerebral spasticity.[22] However, these drugs also produce tolerance and dependence, drowsiness, sedation, hypersalivation and weakness, limiting their long-term use.[23] Due to development of dependence on prolonged use, abrupt cessation of medication is not recommended. Diazepam is probably effective for the short-term treatment of spasticity in children with CP. None of the studies formally addressed whether diazepam improved motor function. Ataxia and drowsiness were identified in the side-effect profile of most studies. Diazepam should be considered as a short-term antispasticity treatment in children with CP.

Alpha2-adrenergic agonists

Tizanidine has antispasticity effect which is demonstrated in adults with multiple sclerosis and spinal cord injury. Very few studies are available regarding its effectiveness in treating spasticity in children. Because tizanidine is extensively metabolized by the liver, hepatic impairment may have a significant effect on its pharmacokinetics. Side effects related to tizanidine use in

adults include hypotension, sedation, asthenia, dry mouth, dizziness, hallucinations, and hepatotoxicity. Their incidence in pediatric patients has not been studied. One study on combined use of botulinum toxin A and a low dose of tizanidine in treating children with cerebral palsy suggested it to be more effective and has fewer side effects versus baclofen with adjuvant botulinum toxin A.[24] There are few small studies suggesting efficacy of tizanidine in decreasing the spastic hypertonia associated with cerebral palsy in children.[25,26] Tizanidine is possibly effective to treat spasticity in children with CP. No toxicity was found in the small studies available. Tizanidine may be considered for the treatment of spasticity in children with CP.

Botulinum toxin

Botulinum toxin, commonly referred to as botox, is produced by the bacteria Clostridium botulinum and was originally used to treat strabismus. It is currently the most widely used drug for the treatment of focal spasticity as it avoids the generalized weakness and sedation accompanying oral medications.[27] Botulinum works by inhibiting the release of vesicular acetylcholine from presynaptic nerve terminals at the neuromuscular junction.[28] This causes temporary calming of muscle contractions by blocking the transmission of nerve impulses. There are 8 different subtypes of botulinum toxin. The two, botulinum toxin A (BoNT-A) and botulinum toxin (B BoNT-B), which differ in their level of purification and immunogenicity are used for therapy.[16] BoNT-B has a tendency to cause more side effects, which is why BoNT-A is preferred.[29] Unlike other neurolytic drugs, the effects of botox are reversible as the toxin begins to degrade and the effects last for 3-4 months.

A thorough knowledge of muscle anatomy is required and the use of electromyography and ultrasound to localize the targeted nerve is recommended.[16] It should be administered only by those adequately trained and experienced in assessment, execution and follow up of the program. Muscles commonly treated with botox include the gastronemius-soleus complex (mostly), hamstrings, hip adductors and flexor synergy muscles of the upper extremity. Muscle relaxation is evident within 48 to 72 hours and persists for a period of 3 to 6 months and may be repeated according to the advice of the specialist/ experienced pediatric neurologist. Use of botox helps improve a child's ability to walk or use hands and allow for a better fitting orthotics by reducing spasticity. Therapists could take advantage of the time when an overly powerful muscle is weakened to work on strengthening the muscle on the opposite side of the joint (antagonist).[30] Sometimes, casting of the involved extremity is done after the injection to increase the stretch of the tight muscle.

A major side effect is possible dissemination to other areas of the body, which can lead to dysphagia if it is being used in the upper limbs or neck muscles. These effects have been reported as early as 1 day and as late as several weeks after treatment. Patients and caregivers need to be adequately counseled and educated and their informed consent be obtained before initiating therapy and they should thus be able to identify the signs and symptoms of systemic effects after receiving an injection of BoNT. Immediate medical attention should be instituted if the child or adolescent develops worsening or unexpected difficulty swallowing or talking, trouble breathing, or muscle weakness. The development of immunoresistance to the toxin can also be a potential problem. Some experts recommend using the smallest dose of BoNT-A and avoiding injecting more frequently than every 3 months to minimize the risk of resistance due to antibody.[31] As with all injections, this procedure is to be used with caution in patients receiving anticoagulation therapy.

For children with CP, BoNT-A is established as an effective treatment to reduce spasticity in the upper and lower extremities, but there is conflicting evidence regarding functional improvement. The available evidence suggests that BoNT-A is generally safe in children with CP. However, severe generalized weakness may occur. For localized/segmental spasticity in the upper and lower extremities of children with CP that warrants treatment, BoNT-A should be offered as an effective and generally safe treatment.

Phenol and alcohol injections

Phenol is injected perineurally in the selected nerves. It decreases muscle spindle activity, thereby muscle tone for several months (4-12 months). But it is technically a more demanding procedure. Most often phenol is used for easy to find nerves, such as obturator and musculocutaneous; then botulinum toxin is used elsewhere. This is an effective treatment for patients with spasticity refractory to all other therapies and should be reserved for patients with a complete loss of sensation and/or no functional movement in their lower body. Potential adverse effects are disturbances of the bladder and bowel function. In current practice, phenol injection is mostly replaced by botox. Alcohol use is similar to phenol and has a shorter duration of activity.

A summary of the available medications for use in the management of spasticity in children with CP with their dose and side effects are given in Table I.

Table I. Medications to relieve spasticity

Drug	Dose	Route	Side effects	Caution
Dantrolene sodium	0.5 mg/kg/dose twice daily. Increase gradually to 4-12 mg/kg/day	Oral	General muscle weakness, irritability, drowsiness	Hepatotoxicity reported in adult studies
Baclofen	2-7 years: 10-15mg/day div 8 hrly; increase once in 3 days by 5-15 mg/ day,max-40 mg/day >8 yrs : max-60mg/day	Oral	Systemic muscle relaxation, sedation, fatigue, potential hepatotoxicity	Gradual tapering recommended to avoid withdrawal symptoms (increased spasticity, confusion, seizures)
Intrathecal Baclofen (ITB)	Pump implanted only in children with body weight >15 kg or > 4 yrs of age; titrated to varying infusion rate based on patient activity and the effect desired	Surgically implanted pump to infuse baclofen directly into the spinal canal and around the spinal cord	Device failure, overdose, Infection at implantation site, CSF leak. Side effects more in children compared to adults	Efficacy and safety of long term use to be determined.Serious withdrawal syndrome can occur with discontinuation of ITB therapy.
Diazepam	0.12 to 0.8 mg/kg/day div 8 hrly	Oral	Tolerance, drowsiness, sedation, hypersalivation, weakness	Prolonged use can produce physical dependence Avoid abrupt discontinuation
Tizanidine	0.05 mg/kg/day	Oral	Hypotension, sedation, hepatotoxicity (adult studies)	
Botulinum toxin (BTX A)	1-4U/kg depending on muscle size. Max : 6U/kg	Into the selected muscle	Fatigue, potential dysphagia	Be alert to the possibility of systemic effects such as dysphagia, dysphonia, weakness, dyspnea, or respiratory distress.
Phenol	3-7% phenol 30 mg/kg	In the selected nerve (Perineural injection)	Poorly tolerated in children. Bowel bladder dysfunction, neuropathic pain	Reserved for patients with a complete loss of sensation and/or no functional movement in their lower body

Conclusion

None of the oral medications used to treat spasticity in children has been adequately tested for safety and efficacy. There are minimal or no data regarding the pharmacokinetics or appropriate dosing parameters to treat children. These critical questions deserve serious research efforts. Although there is sufficient evidence to recommend BoNT-A as an effective antispasticity treatment in children with CP, its beneficial effects on function, ease of care giving, activity and participation need to be established. More data about safety and long-term effects are also needed.

The efficacy and safety of BoNT-B, phenol, and alcohol chemodenervation as treatments for spasticity in children with CP need to be determined. The efficacy and safety of oral baclofen and the long-term continuous intrathecal pump administration of this medication need to be determined in children with CP. There is an urgent need to find safer and more effective treatments to help children affected by generalized spasticity due to CP.

Points to Remember

- ***Local injections of BoNT-A may be recommended for treating localized/segmental spasticity in the upper and lower extremities of children with CP. The effects are reversible and may be repeated every 3 to 6 months.***
- ***The few months of reduction in local spasticity afforded by the BoNT-A injection could be utilised to improve strength of antagonist muscle groups, fitting orthotics and for casting, if necessary.***
- ***Diazepam is probably effective for the short-term treatment of spasticity in children with CP.***
- ***Tizanidine may be considered for spasticity treatment.***
- ***There is insufficient evidence to support or refute the use of oral and intrathecal baclofen and dantrolene sodium for the treatment of spasticity in children with CP.***

References

1. Yeargin-Allsopp M, Van Naarden Braun K, Doernberg BA, Benedict RE, Kirby RS, Durkin MS. Prevalence of cerebral palsy in 8-year-old children in three areas of the United States in 2002: A multisite collaboration. Pediatrics 2008; 121:547-554.
2. Paneth N, Hong T, Korzeniewski S. The Descriptive Epidemiology of Cerebral Palsy. Clin Perinatol 2006; 33:251-267.
3. Ronan S, Gold JT. Nonoperative management of spasticity in children. Childs Nerv Syst 2007; 23:943-956.
4. Sanger TD, Delgado MR, Gaebler-Spira D, Hallett M, Mink JW. Classification and definition of disorders causing hypertonia in childhood. Pediatrics 2003; 111:e89-e97.
5. Milla PJ, Jackson AD. A controlled trial of baclofen in children with cerebral palsy. J Int Med Res 1977; 5:398-404.
6. Ward A. Long-Term modification of spasticity. J Rehabil Med 2003; 35:60-65.
7. Ashworth B. Preliminary trial of carisoprodol in multiple sclerosis. Practitioner 1964; 192:540-542.
8. Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. Phys Ther 1987; 67:206-207.
9. Nielsen JF, Sinkjaer T. A comparison of clinical and laboratory measures of spasticity. Mult Scler 1996; 1:296-301.
10. Haugh AB, Pandyan AD, Johnson GR. A systematic review of the Tardieu Scale for the measurement of spasticity. Disabil Rehabil 2006; 28(15):899-907.
11. Tilton A, Vargus-Adams J, Delgado MR. Pharmacologic treatment of spasticity in children. Semin Pediatr Neurol 2010; 17:261-267.
12. Chou R, Peterson K, Helfand M. Comparative efficacy and safety of skeletal muscle relaxants for spasticity and musculoskeletal conditions: a systematic review. J Pain Symptom Manage 2004; 28:140-175.
13. Keenan E. Spasticity management, part 2: choosing the right medication to suit the individual. Br J Neurosci Nurs 2009; 5:419-424.
14. Kischka U. Neurological rehabilitation and management of spasticity. Medicine 2008; 36:616-619.
15. Awaad Y, Rizk T, Siddiqui I, Roosen N, Mcintosh K, Waines GM. Complications of intrathecal baclofen pump: prevention and cure. ISRN Neurol 2012; 2012:575168.
16. Simon O, Yelnik AP. Managing spasticity with drugs. Eur J Phys Rehabil Med 2010; 46:401-410.
17. Chou R, Peterson K, Helfand M. Comparative efficacy and safety of skeletal muscle relaxants for spasticity and musculoskeletal conditions: a systematic review. J Pain Symptom Manage 2004; 28:140-147.
18. Abbruzzese G. The medical management of spasticity. Eur J Neurol 2002; 9:30-34.
19. Keenan E. Spasticity management, part 2: choosing the right medication to suit the individual. Br J Neurosci Nurs 2009; 5:419-424.
20. Brashear A, Lambeth K. Spasticity. Curr Treat Options Neurol 2009; 11:153-561.
21. Kolaski K, Logan LR. A review of the complications of intrathecal baclofen in patients with cerebral palsy. Neuro Rehabilitation 2007; 22:383-395.
22. Lapeyre E, Kuks JBM, Meijler WJ. Spasticity: revisiting the role and the individual value of several pharmacological treatments. Neuro Rehabilitation 2010; 27:193-200.
23. Verrotti A, Greco R, Spalice A, Chiarelli F, Iannetti P. Pharmacotherapy of spasticity in children with cerebral palsy. Pediatr Neurol 2006; 34:1-6.
24. Dai AI, Aksoy SN, Demiryürek AT. Comparison of Efficacy and Side Effects of Oral Baclofen Versus Tizanidine Therapy with Adjuvant Botulinum Toxin Type A in Children With Cerebral Palsy and Spastic Equinus Foot Deformity. J Child Neurol 2016; 31(2):184-189.
25. Vasquez-Briceno A, Arellano-Saldana ME, Leon-Hernandez SR, Morales-Osorio MG. [The usefulness of tizanidine. A one-year follow-up of the treatment of

spasticity in infantile cerebral palsy]. Rev Neurol 2006; 43:132-136.

26. Nikkhah A, Mohammadi M, Ashrafi MR, Zamani G. The Efficacy and Safety of Tizanidine in Treating Spasticity in Children with Cerebral Palsy. Iranian Journal of Child Neurology 2011; 5(3):19-22.
27. Kheder A, Nair KP. Spasticity: pathophysiology, evaluation and management. Pract Neurol 2012; 12:289-298.
28. Burchiel KJ, Hsu FP. Pain and spasticity after spinal cord injury: mechanisms and treatment. Spine (Phila Pa 1976) 2001; 26(24 Suppl):S146-160.
29. Dressler D, Eleopra R. Clinical use of non-A botulinum toxins: botulinum toxin type B. Neurotox Res 2006; 9: 121-125.
30. Wallen M, O'Flaherty SJ, Waugh MC. Functional outcomes of intramuscular botulinum toxin type a and occupational therapy in the upper limbs of children with cerebral palsy: a randomized controlled trial. Arch Phys Med Rehabil 2007; 88:1-10.
31. Tilton AH. Management of spasticity in children with cerebral palsy. Semin Pediatr Neurol 2004; 11: 58-65.

CLIPPINGS

Clinical Practice Guideline: Maintenance Intravenous Fluids in Children.

This guideline is intended to assist clinicians by providing a framework for clinical decision-making.The use of this guideline differentiates the applicability to 2 subgroups of children: (1) The guideline applies to surgical (postoperative) medical patients in a critical care setting and the general inpatient ward. (2) The guideline does not apply to patients with neurosurgical disorders, congenital or acquired cardiac disease, hepatic disease, cancer, renal dysfunction, diabetes insipidus, voluminous watery diarrhea, or severe burns; neonates who are younger than 28 days old or in the NICU; or adolescents older than 18 years of age.The Key Action Statement is as follows:

1A: The AAP recommends that patients 28 days to 18 years of age requiring maintenance IVFs should receive isotonic solutions with appropriate KCl and dextrose because they significantly decrease the risk of developing hyponatremia (evidence quality: A; recommendation strength: strong).

In the 17 RCTs included in the meta-analysis, researchers in most of the studies obtained serial plasma sodium values, with the first plasma sodium being measured between 6 hours and 12 hours. The incidence of hyponatremia in patients receiving isotonic fluids ranged from 0% to 23%, whereas that of hypotonic fluids ranged from 5% to 100%. This large variability was likely related to the different study designs. Many patients who were hospitalized and received isotonic IVFs will be at risk for hyponatremia if they are receiving IV medications containing free water or are consuming additional free water via the enteral route. For these reasons, clinicians should be aware that even patients receiving isotonic maintenance IVFs are at sufficient risk for developing hyponatremia. If an electrolyte abnormality is discovered, this could provide useful information to adjust maintenance fluid therapy. If patients receiving isotonic maintenance IVFs develop hyponatremia, they should be evaluated to determine if they are receiving other sources of free water or if they may have SIAD and/or an adrenal insufficiency. If hypernatremia develops (plasma sodium >144 mEq/L), patients should be evaluated for renal dysfunction or extrarenal free-water losses.

In patients at high risk for developing electrolyte abnormalities frequent laboratory monitoring may be necessary. If neurologic symptoms that could be consistent with hyponatremic encephalopathy are present, such as unexplained nausea, vomiting, headache, confusion, or lethargy, electrolytes should be measured.

Feld LG, Neuspiel DR, Foster BA, Leu MG, Garber MD , Austin K, Basu RK, Conway EE, Fehr JJ, Hawkins C, Kaplan RL, Rowe EV, Waseem M, Moritz ML, SUBCOMMITTEE ON FLUID AND ELECTROLYTE THERAPY. Clinical Practice Guideline: Maintenance Intravenous Fluids in Children. Pediatrics Dec 2018, 142 (6) e20183083; DOI: 10.1542/peds.2018-3083.

PEDIATRIC SURGERY

AN APPROACH TO PEDIATRIC TRAUMA

*Vivek S
**Senthilnathan R
***Hariharan G

Abstract: *Trauma is one of the common preventable causes of mortality and morbidity in children. The systematic evaluation of an injured child is an integral part of the curriculum in the training of emergency care pediatricians and pediatric surgeons. The management protocol starts with the primary survey and resuscitation, followed by secondary survey and re-evaluation. This protocol based step by step evaluation ensures that the life threatening complications are promptly identified and addressed without the risk of being overlooked. This article provides a comprehensive overview of the initial assessment and the subsequent management of pediatric trauma including the current guidelines in the initial evaluation of pediatric head trauma.*

Keywords: *Cervical spine, Tension pneumothorax, Fast scan.*

Pediatric trauma is the major cause of death and disability in children worldwide. An estimated five million children die due to trauma all over the world each year.[1]

Epidemiology

In India as per National Crime Records Bureau (NCRB) report of 2006, there were 22,766 deaths (<14 years) due to injuries among children. Boys were more commonly injured than the girls. Home is the most common place of injury, followed by road/street. The most common causes of injury in children are falls, motor vehicle accidents, pedestrian accidents, bicycle accidents and child abuse. In those under 12 months of age, non-accidental injury should be considered.

Head injury remains the most common cause of morbidity and mortality in paediatric trauma. It is because of the large head size and decreased neck control. A significant extracranial injury in a child with head injury doubles the morbidity and mortality. With severe traumatic injuries, multisystem trauma is typical. This is because of the small body mass, to which energy is imparted, resulting in a greater force applied per unit body area. This intense energy leads to more multisystem injuries.

Pediatric trauma system

The pediatric trauma system should function as a part of inclusive emergency medical services (EMS), trauma and disaster response system for the region. The inclusive trauma system is defined as one in which all hospitals participate in the care of injured patients. The regional pediatric trauma center is the central component of a pediatric trauma system.

Protocols for triage, treatment, and transfer of victims of pediatric trauma are an important part of the trauma system. It has been shown that younger and more seriously injured children have better outcomes at a dedicated pediatric trauma center. The facility to provide an inclusive pediatric service, including the presence of specialist in pediatric emergency medicine, pediatric surgery and pediatric anesthesiology, is important. A well-equipped pediatric intensive care unit (PICU) is an important component of a pediatric trauma center. Data indicate that the availability of a PICU within a region improves survival in pediatric trauma.

Approach to major trauma

Child with a major injury can be hemodynamically unpredictable. Injuries cross the anatomical boundaries typically causing more than one injury. Knowledge of the potential pathophysiology allows for better prediction of outcome. Children with diffuse head injury are more prone to develop cerebral edema and intracranial hypertension that can produce unexpected apnoea. Despite these features, and often a very low Glasgow Coma Scale (GCS) score on presentation, they often have a favourable outcome.[2]

* Assistant Professor
** Professor of Pediatric Surgery,
Department of Pediatric Surgery,
Institute of Child Health and Hospital for Children,
Madras Medical College, Chennai.
email: shanmugam.vivek@gmail.com
*** Deputy Director of Medical Education,
Directorate of Medical Education, Chennai.

The primary survey and resuscitation

The highest priority in the approach to an injured child is ruling out the presence of life- or limb-threatening injury and to detect and correct abnormal physiology, hence avoiding a secondary insult. Treatment of these injuries must occur before proceeding with the rest of the physical examination. This initial assessment (the primary survey) and necessary initial resuscitation efforts must occur simultaneously. In general, they should be addressed within the first 5 to 10 minutes of evaluation.

The primary survey constitutes the ABC's of trauma care (Table I).

A. Airway maintenance with cervical spine stabilisation

B. Breathing and ventilation

C. Circulation with hemorrhage control

D. Disability with neurologic status

E. Exposure/Environment control-hypothermia

Airway with cervical spine control

In children, the airway is smaller and floppier and the disproportion between the cranium and mid-face makes it more likely that the airway will obstruct when the child is lying flat. Establishment of an open airway should be initially attempted by using standard simple airway manoeuvres. In the event of trauma and a possible cervical spine injury, this should involve a jaw thrust with cervical spine immobilization and suction.

Intubation is not immediately necessary if a patent airway and adequate ventilation are achieved. Airway obstruction in children is rarely complete, the exception being facial burns, facial trauma and laryngeal injury.

Indications for endotracheal intubation of the pediatric trauma patient include,

(1) Inability to ventilate by bag-valve-mask (BVM) methods or the need for prolonged control of the airway.

Table I. Trauma resuscitation guidelines

Immediate life-threatening injuries	Life-saving procedures
Airway	
Obstructed airway	Oxygen; simple airway positioning manoeuvres
Laryngeal/tracheal trauma	Oropharyngeal airway
Faciomaxillary trauma	Endotracheal intubation
	Cricothyrotomy, tracheostomy
Breathing	
Tension pneumothorax	Intercostal cannula
Flail chest	Intercostal tube
Hemothorax	Endotracheal intubation
Sucking chest wound (open pneumothorax)	Cover sucking chest wound on three sides
Central depression of respiration	
Circulation	
Hemorrhage	Pressure over bleeding sites
Internal	Two large-bore IV cannulas
External	Intra-osseous infusion
Cardiac tamponade/rupture	Pericardiocentesis
	Emergency thoracotomy
	(penetrating trauma only)
Disability	
Neurological dysfunction	Avoid secondary brain insult by optimizing ABC
Exposure	
Hypothermia	Warming of patient
	Warming of all fluids
Hypoglycemia	IV 10% glucose and - IV fluids

(2) Glasgow Coma Scale (GCS) score of < 8

(3) Respiratory failure from hypoxemia (e.g., flail chest, pulmonary contusions) or hypoventilation (injury to airway structures)

(4) Fluid refractory shock

(5) Loss of protective laryngeal reflexes

(6) Neurogenic hyperventilation - Sign of raised ICP

In an obtunded child, the insertion of a laryngeal mask airway (LMA) can provide an adequate airway. If airway obstruction is complete and LMA insertion is not possible, a needle cricothyrotomy should be considered. This is performed using a 14-18 gauge cannula connected to a three-way and oxygen at 15 L/min. Needle cricothyrotomy is a temporizing measure only and a definitive surgical tracheostomy should be completed within 2 hours. Surgical cricothyrotomy is contraindicated in children under 11 years of age.

Cervical spine

Children with possible cervical spine injury should be immobilized appropriately using in-line axial bimanual immobilization or a hard cervical collar of appropriate size, sandbags and adhesive tape strapping the head and trunk to a spinal board (Fig.1a and 1b). In young infants, a rolled up towel under the shoulder can overcome spinal malalignment due the protrusion of the occiput. X-rays of the cervical spine in the awake child under 5 years of age consist of two static cervical spine X-rays (anteroposterior and lateral) and if necessary, a fine-cut axial computed tomography (CT) scan.

Breathing

High flow supplemental oxygen (12 L/min) via a non rebreathing mask is given to all children with significant injury. Assess for adequacy of chest rise. In a young child this will occur in the lower chest and upper abdomen.

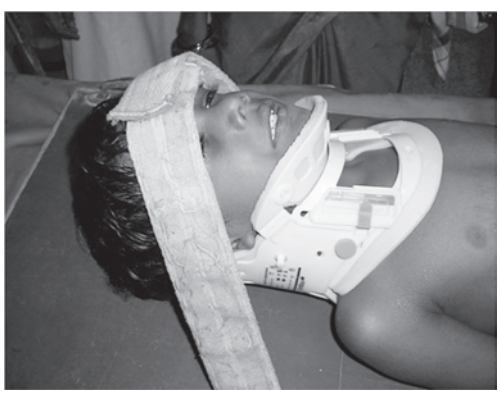

Fig.1a. Hard cervical collar

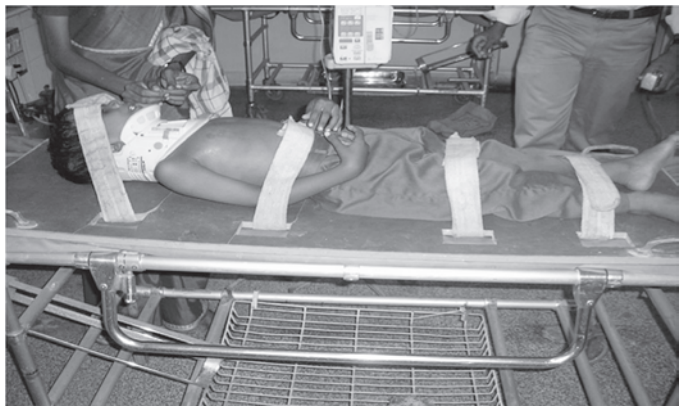

Fig.1b. Spine board

Also assess respiratory rate. Rates that are too fast or slow can indicate impending respiratory failure and the treatment is assisted ventilation. Assisted ventilation with a bag–valve–mask device is required if spontaneous ventilation is inadequate.

Tension pneumothorax (Fig.2) is relieved by inserting a 14-18 gauge over-the-needle catheter into the affected side. In children, use the second intercostal space, mid-clavicular line, while in the small infant use the fourth intercostal space, anterior axillary line, thus avoiding complications due to limited space during resuscitation due to small body size. The pneumothorax must then be definitively treated by inserting a chest tube.

Traumatic asphyxia is a syndrome of cervicofacial cyanosis, subconjunctival hemorrhage, venous engorgement and petechiae of the head and neck. Albeit rare, traumatic asphyxia is commonly associated with other injuries, such as blunt pulmonary injury, and may result in unexpected clinical deterioration if not diagnosed early in the primary survey.

Circulation

Shock is a syndrome that results from tissue perfusion that is inadequate to meet metabolic needs. In children, it may exist with normal blood pressure. In general, a palpable

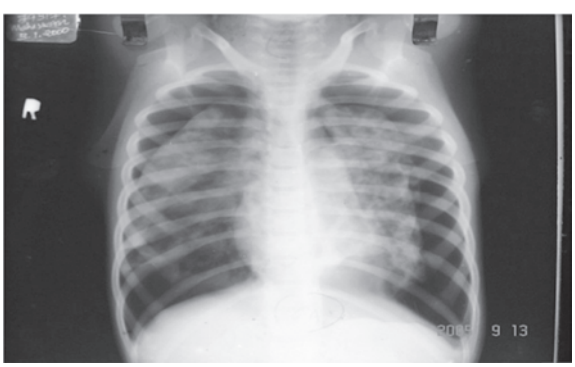

Fig.2. Tension pneumothorax

peripheral pulse correlates with a systolic blood pressure greater than 80 mm Hg and a palpable central pulse with a pressure greater than 50 to 60 mm Hg. If the child is in hypovolemia, fluid bolus of 20 ml/kg should be initiated. If a patient fails to improve after two fluid boluses of 20 mL/kg each, then blood (whole blood 20 mL/kg or packed cells 10 mL/kg) is required.

Aggressive control of hemorrhage (direct pressure to external bleeding sites) is indicated. In children with multisystem trauma, stabilizing fractures of the femur may be crucial for pain relief and control of bleeding. Where hemodynamic instability is of concern, a medical anti-shock trousers (MAST) suit of appropriate size should be used. A hemodynamically unstable child should never be sent to CT scan to define the site of bleeding. The only option is surgical intervention.

In children, blunt trauma is the rule and the liberal use of fluids is the current accepted practice, titrating to the clinical response of the child. Mortality in injured children is associated with an Injury Severity Scale ≥25, a pediatric GCS score <7 (Table I) or a Pediatric Trauma Scale <4. The amount of emergency blood transfusion required is singularly the most important independent predictive factor of outcome in children because blood transfusion of ≥20 mL/kg significantly increases the risk of coagulopathy and multisystem organ failure.

Traditionally, normal pulse rate, systolic blood pressure for age and urine output >1 mL/kg per hour usually denote the adequacy fluid resuscitation. Metabolic endpoints, such as base excess and lactate, can augment traditional signs of successful resuscitation and may be useful measures in the injured child. Pediatricians must be aware that the excessive use of chloride-containing fluids can cause hyperchloremic acidosis, resulting in persistently abnormal base excess.

Intravenous fluids must be carefully titrated in the management of traumatic brain injury (TBI) in children. Systemic hypotension, hypoxia and intracranial hypertension can cause secondary insult. Cerebral perfusion pressure (CPP), the difference between mean arterial pressure (MAP) and intracranial pressure (ICP) must be maintained within the physiological limits because the neurological outcome improves if the CPP is maintained at levels of 60-70 mm H_2O. Hypotension is a correctable cause of secondary brain injury with a direct effect on CPP. Appropriate use of fluids and low threshold for starting inotropes in maintaining MAP of at least 70 mmHg is recommended.[3]

Box 1. AVPU

A - Alert,

V - Responsive to **V**erbal stimuli,

P - Responsive to **P**ainful stimuli or

U - Unresponsive.

Disability or attention to central nervous system disorder

Assess cortical function by GCS/AVPU scale and brainstem function by pupillary size, equality, response to light and breathing pattern (Box 1).

The AVPU mnemonic is commonly used to assess the disability in the primary survey. 'P' or 'U' indicates a GCS score of less than 8 and requires emergency attention and further assessment. Capillary blood glucose (CBG) measurement by dextrostix has to be done. If CBG <60 mg/dl give 2-5 ml/kg of 10% dextrose and followed by glucose infusion at the rate of 6-8 mg/kg/minute to maintain euglycemia.

Exposure and other important considerations

Carefully examine the whole body by completely undressing the child. Children are at risk for hypothermia. Exposure for physical examination should be limited to a short time to prevent hypothermia. Pre-warmed IV fluids, warm blankets and overhead heating lamps may help in maintaining normothermia. Management of pain needs to be prioritised. Adequate analgesia should be provided early using intravenous opiates. Adequate monitoring of childrens' respiratory rate, blood pressure, oxygen saturation, heart rate and peripheral perfusion should be ensured. The primary survey and trauma resuscitation guidelines is summarised in Table I.

Secondary survey

The essential aspects of the secondary survey in pediatric trauma are: Continuous resuscitation and monitoring, history, head to toe examination and investigations.

Continuing resuscitation and monitoring: Any further deterioration while on close observation necessitates immediate return to the airway, breathing and circulation (ABC). After airway problems, blunt injury abdomen is the second-most common cause of preventable death in paediatric major trauma.

History: A complete history must be elicited from the patient, family, or the accompanying personnel using the

mnemonic 'SAMPLE' -S Signs and symptoms; **A:** Allergies; **M**: Medication; **P**: Past history; **L:** Last ate; Last tetanus and **E**: Event

Head-to-toe examination: **A** systematic head-to-toe, front-and-back examination to identify injuries not noted in the primary survey is done. A formal neurological assessment of the child should now be performed.

Investigations: Blood samples should be collected during the initial resuscitation phase. A bedside blood sugar level must be done to rule out hypoglycemia. In the radiological investigations, a standard trauma X-ray series is ordered (i.e. chest X-ray, lateral cervical spine X-ray and pelvic X-ray). Further radiological investigation will be determined by clinical need. An electrocardiogram must be done in blunt thoracic injury with suspected myocardial contusion.

Observation and re-evaluation

Abdominal trauma

Abdominal trauma is the commonest cause of initially missed fatal injury in children. Abdominal signs of injury may be minimal or absent. If abdominal trauma is considered likely in a stable child, close observation and serial evaluation looking for increasing tenderness and distension is recommended. Diagnostic peritoneal lavage is not advocated in pediatric trauma. A focused assessment with sonography in trauma (FAST) scan and contrast enhanced CT (CECT) abdomen are next in line to rule out solid organ injury.

Urgent laparotomy in the child with an abdominal injury should be considered if:

1) The child remains hypotensive despite 40 mL/kg IV fluid resuscitation over a 6 hours period
2) A hollow viscus injury is suspected (e.g. pneumoperitoneum in abdominal X-ray)
3) A traumatic diaphragmatic rupture diagnosed on chest X-ray or abdominal CT
4) Significant gastrointestinal hemorrhage is detected by bleeding via a nasogastric tube or in rectal examination

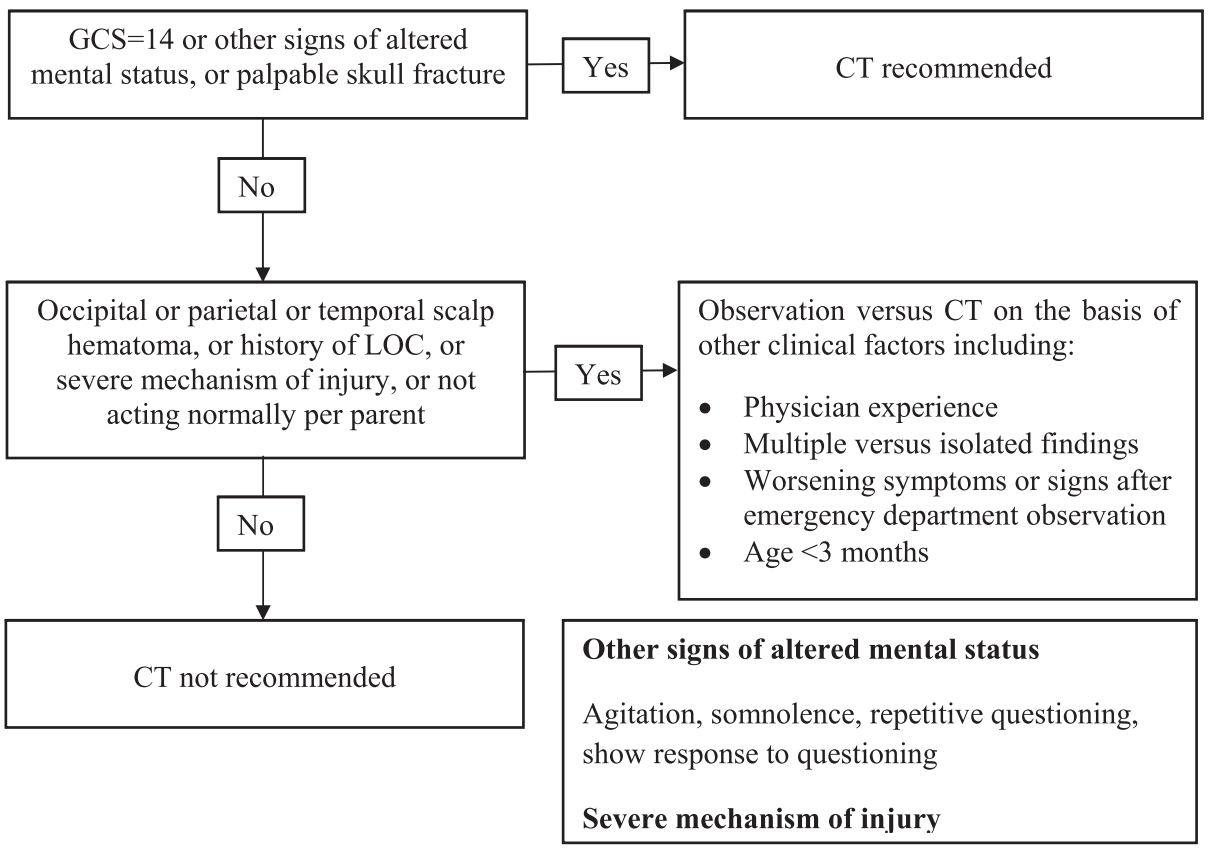

Fig.3. PECARN pediatric head injury / trauma algorithm – For age less than 2 years

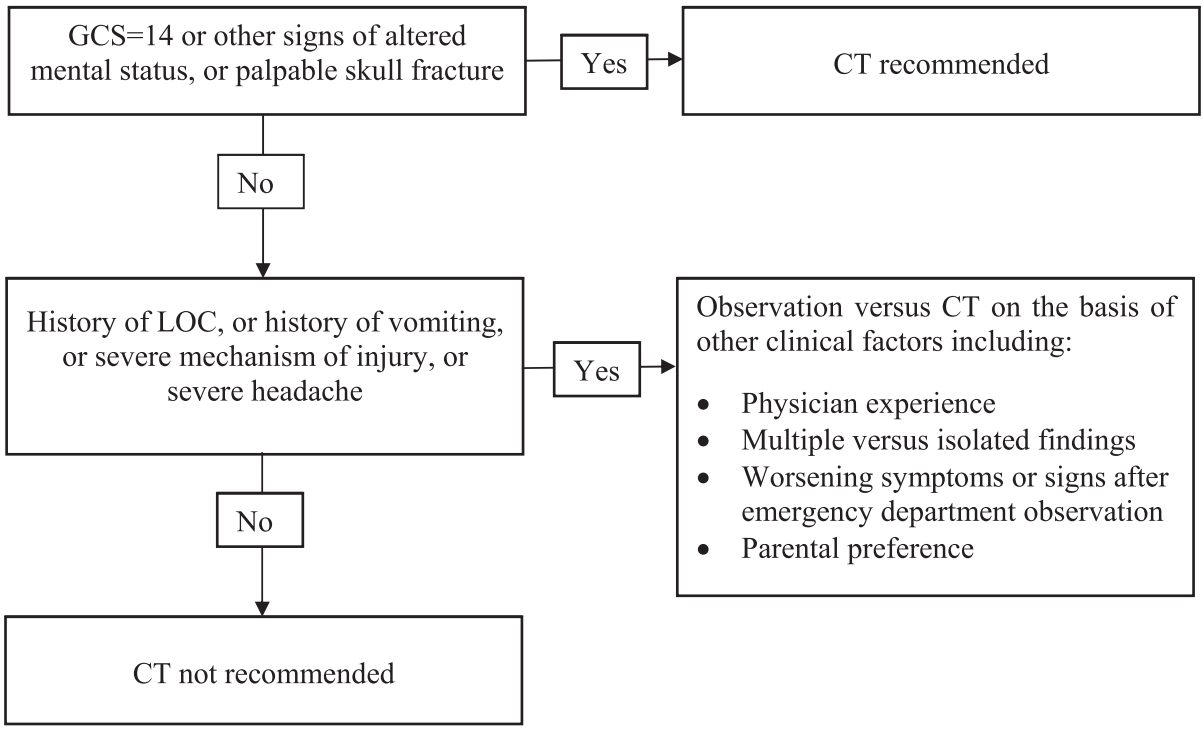

Fig.4. PECARN pediatric head injury / trauma algorithm – For age above 2 years

Table II. Pediatric Glasgow Coma Scale scores

Response	score	Response	score
Eye opening (all ages)		**Best verbal response**	
Spontaneously	4	**> 5 years**	
Response to voice	3	Oriented and appropriate	5
Response to pain	2	Disoriented conversation	4
No response	1	Inappropriate words	3
Best motor response		Incomprehensible sounds	2
> 1 year		No response	1
Obeys commands	6		
Localizes pain	5	**2–5 years**	
Flexion withdrawal	4	Appropriate words	5
Decorticate posturing	3	Inappropriate words	4
Decerebrate posturing	2	Cries and/or screams	3
No response	1	Grunts	2
< 1 year		No response	1
Spontaneously	6		
Localizes pain	5	**0–23 months**	
Flexion withdrawal	4	Smiles, coos	5
Decorticate posturing	3	Cries but consolable	4
Decerebrate posturing	2	Persistent cries and/or screams	3
No response	1	Grunts	2
		No response	1

Head trauma

The most common cause of death in injured children is head trauma. A GCS score greater than or equal to 6 is associated with a favourable outcome and neurologic status. The important message is that no matter how the patient presents neurologically, all efforts should be generated to ensure survival and maintain stable neurologic status.

PECARN guidelines for decision making on CT Brain

The Pediatric Head Injury/Trauma Algorithm (PECARN)[4] was developed by the Pediatric Emergency Care Applied Research Network (PECARN). It applies to patients with a Glasgow Coma Scale of 14 or higher.

1. Use the Glasgow Coma Scale (GCS) to determine if the child satisfies the required criteria for evaluation using the PECARN algorithm (Table II).
2. Determine the GCS : This number categorizes the following

   Mild = GCS Score of 13-15:

   Moderate Disability = GCS Score of 9-12:

   Severe Disability = GCS Score of 3-8:

   Apply the PECARN Pediatric Head Injury/Trauma algorithm (Fig.3 & Fig.4).[4]

Injury prevention

Injury prevention is an important aspect in pediatric trauma. The injury prevention initiatives are often not promoted because of factors like limited resources. There are methods to identify and refine the approach to the injury prevention initiatives that are specific for the region and it should incorporate injury-prevention activities into staff and patient education and community-based intervention.

The management of major pediatric trauma requires a multidisciplinary approach and the medical care is tailored to meet the specific needs of the injured child. An understanding of the different pathophysiology and the unique way in which children can present with major trauma will allow this multidisciplinary team to achieve the best possible patient outcome.

Points to Remember

- ***Remember mnemonic SAMPLE - Signs and symptoms, allergy, medication, past history, last meal, last tetanus and event in pediatric trauma history taking.***
- ***Triage, treatment and transfer are important in the trauma care of children.***
- ***Primary survey in recognising life threatening injuries.***
- ***GCS less than 8, flail chest, loss of laryngeal reflex are signs of imminent death.***

References

1. Holder Y, Peden M, Krug E, Lund J, Gururaj G, Kobusingye O. Injury Surveillance Guidelines. Geneva: World Health Organization; 2001. Available from: http://www.who.int/violence_injury_prevention/media/en/136.pdf .
2. Lieh-Lai MW, Theodorou AA, Sarnaik AP, Meert KL, Moylan PM, Canady AI. Limitations of the Glasgow Coma Scale in predicting outcome in children with traumatic brain injury J Pediatr 1992; 120:195-199.
3. Barlow KM, Minns RA. The relation between intracranial pressure and outcome in non-accidental head injury. Dev Med Child Neurol 1999; 41:220-225.
4. Kuppermann N, Holmes JF, Dayan PS, Hoyle JD Jr, Atabaki SM, Holubkov R, et al. Identification of children at very low risk of clinically-important brain injuries after head trauma: a prospective cohort study. Lancet. 2009; 374(9696):1160-1170. doi: 10.1016/S0140-6736(09)61558-0. Epub 2009 Sep 14.

NEWS AND NOTES

4th Annual Surgical Conference (Global Surgery)

Dates: 1st – 4th February, 2019

Venue: Department of Surgery, Aga Khan University, Karachi, Pakistan

Email: sheriff.charania@aku.edu

Phone: +92 21 34864374 / 34864759

RADIOLOGY

SHORT STATURE

*Vijayalakshmi G
**Natarajan B
**Kasi Visalakshi K P
**Abirami K
***Thangalakshmi A
***Raveendran J

We saw precocious puberty in the previous issue and the x-ray evaluation to establish bone age. In this issue we will see the radiological findings in children with delay in growth and short stature with special emphasis on growth hormone deficiency. The skeletal age is appropriate for chronological age in a child with familial short stature while it is delayed in constitutional growth delay. However, if bone age is delayed by more than two years, then the child has to be further evaluated. Chronic illness, malabsorption and malnutrition, chronic inflammation, heart and renal disease, skeletal dysplasia, genetic and endocrine abnormalities can lead to short stature. After a clinical review, bone age is established by radiological evaluation and laboratory investigations should follow.

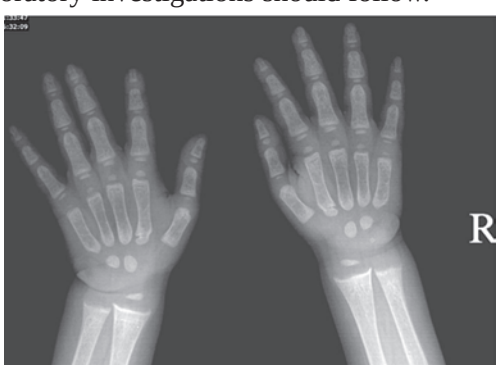

Fig.1. Rickets with delayed bone age

Fig 1 is that of a 7 year old child who presented with short stature. The hand x-ray shows the distal radius centre which appears at one and half years. The first metacarpal centre which should have appeared at two and half years has not appeared. Note also the increased distance between the epiphysis and metaphysis of the distal radius- the hallmark of rickets. Rickets along with delay in skeletal maturation is suggestive of renal cause of short stature which needs confirmation by biochemistry.

* Professor
** Associate Professor
*** Assistant Professor,
Department of Pediatric Radiology,
Institute of Child Health and Hospital for Children,
Chennai
email: drviji.rad@gmail.com

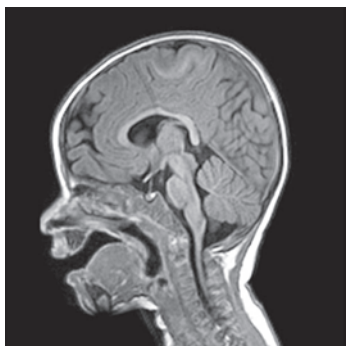

Fig.2. Normal pituitary- Note the bright spot of the posterior pituitary

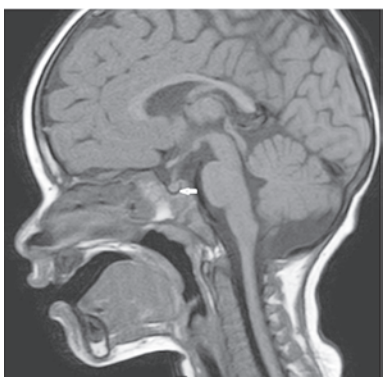

Fig.3. Absent bright spot of posterior pituitary (arrow points to pituitary in sella) - histiocytosis

Hypothyroidism and growth hormone deficiency are common endocrine causes for short stature and delayed bone age. The cause for growth hormone deficiency is sometimes revealed in MRI of brain. The normal anterior pituitary is isointense in T1 and T2 weighted images while the posterior pituitary is bright on T1 and hypointense on T2 images due to its high lipid concentrations (Fig.2).

In Fig.3 you can see that the posterior pituitary bright spot is missing. This is a case of histiocytosis with loss of

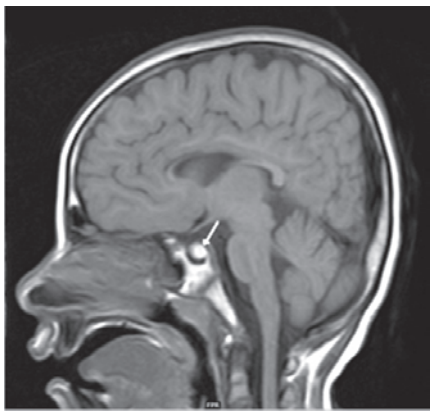

Fig.4. Rathke's cleft cyst

the bright spot due to histiocytic infiltration leading to growth hormone deficiency.

Fig 4 shows a hyperintense round lesion in the sella. This is a Rathke's cleft cyst that arises in the pituitary gland. The pituitary has a dual ectodermal origin. The posterior part arises from a diverticulum from the developing brain, that grows downwards into the pituitary fossa. Here it meets another outpouching from the roof of the primitive mouth, called the Rathke' pouch. This folds on itself as it unites with the future posterior pituitary and the cleft in between,

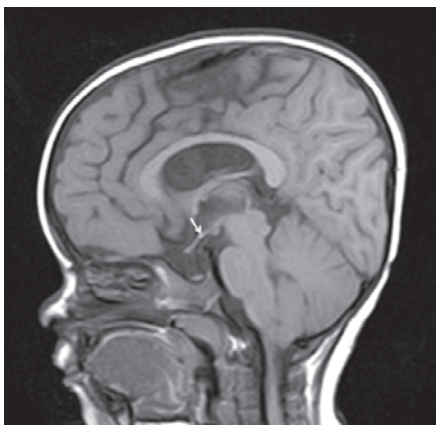

Fig.5. Ectopic posterior pituitary (arrow) sagittal section

sometimes fails to obliterate. Small cysts then develop in the cleft and are usually of no consequence. Cysts greater than 3 mm need to be followed for growth. Operative removal is indicated when the cyst exceeds 1 cm as they can cause headache or pituitary hormone deficiency. These cysts can also get infected or may rupture its content into the anterior pituitary causing inflammation and profound hypopituitarism.

Defective embryonal migration of the posterior pituitary from the diencephalon may halt its progress into

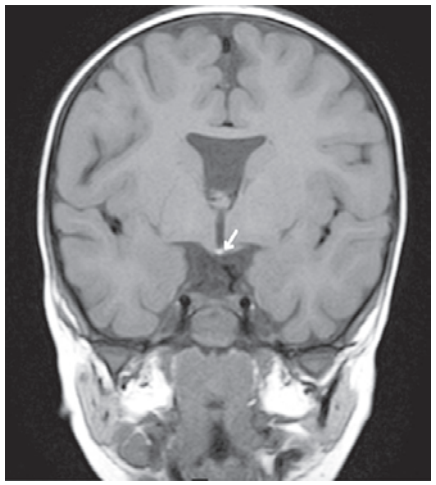

Fig.6. Ectopic posterior pituitary (arrow) – coronal section

the sella. In Fig.5 and Fig.6 the posterior pituitary bright spot is not seen in the sella, but is situated posteriorly at the median eminence. The pituitary stalk may be thin, absent or attenuated which explains the poor functioning of the anterior pituitary due to inadequate flow or disruption of the pituitary-hypophyseal portal system. The ectopic posterior pituitary has normal function.

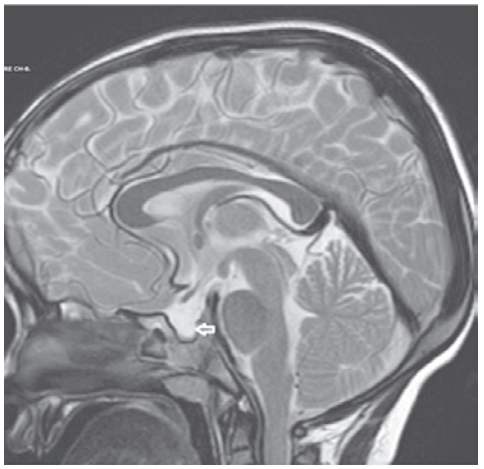

Fig.7. Empty sella - bright CSF in the sella

Sometimes the pituitary gland is compressed and atrophied by CSF entering the sella through the dural sellar diaphragm and collecting there (Fig.7). This is referred to as empty sella as the pituitary is not visualised. Arachnoid cysts and craniopharyngiomas can also compress the pituitary gland. Epidermoid cysts are rare cysts that can occur near the sella. They are formed due to trapping of skin cells during embryological development. They are usually associated with inflammation of the pituitary and hypopituitarism. Cyst content can also leak causing sterile meningitis. MRI has thus made imaging of the pituitary and evaluation for growth hormone deficiency possible.

CASE REPORT

A RARE CASE OF BRUTON AGAMMAGLOBULINEMIA

*Hemachitra J
*Senthilkumar P
*Durai Arasan G
**Sathya J
***Shanthi S

Abstract: *Of all the primary immunodeficiency disorders, those affecting antibody production are more frequent. These patients usually have recurrent infections with encapsulated bacteria. Patients with X linked agammaglobulinemia have profound defect in the B cell development resulting in severe hypogammaglobulinemia and absence of circulating B cells.*

Keywords: *Agammaglobulinemia, B lymphocytes.*

A high index of suspicion is needed to diagnose the defects of the immune system early enough so that appropriate treatment can be instituted before irreversible damage occurs. Diagnosis is difficult because of masking of classical presentation due to extensive use of antibiotics. Of all the primary immunodeficiency diseases, those affecting antibody production are the most frequent. Selective absence of serum and secretory immunoglobulin (IgA) is the most common defect, with rates ranging from 1 in 333 to 1 in 18,000 persons among different races and ethnicities. By contrast, agammaglobulinemia estimated to occur with a frequency of only 1 in 10,000 to 1 in 50,000 persons.[1] Children with defects in antibody production, phagocytic cells, or complement proteins have recurrent infections with encapsulated bacteria and may grow and develop normally despite their recurrent infections.

Case Report

A 2 ½ year old male child, first born of non-consanguineous marriage was admitted with fever, cough, tachypnea, cellulitis of the left hand and purulent discharge from left ear of one week duration. He was born as a term, small for gestational age child, with a birth weight of 1.8 kgs and was admitted in NICU for 11 days for low birth weight care. The child was previously treated for recurrent skin and respiratory tract infections as outpatient but there was no inpatient treatment. His immunization status was appropriate for age and height and weight were both within minus two 'z' scores. On examination, the child was febrile, had multiple small abscesses in both lower limbs, impetigenous lesions on the trunk, a big draining perianal abscess and hepatomegaly with a liver span of 9 cm. There was no significant lymphadenopathy and tonsils were hypoplastic. A provisional diagnosis of pneumonia with acute suppurative otitis media and multiple abscesses was made and the child was started on appropriate antibiotics.

Investigations showed neutrophilic leucocytosis, anemia and elevated ESR. Liver and renal function tests were normal. Chest x-ray showed bronchopneumonia. Pus culture from the draining perianal abscess and ear swab grew Pseudomonas aeruginosa but his blood culture was negative. In view of the clinical findings and history of recurrent skin and respiratory infections, immunodeficiency was suspected. HIV screening was negative and hence investigations for primary immunodeficiency disorders were done.

His immunoglobulin profile showed very low levels of IgE - 1 IU/mL (0.4-351.6), Ig A - 24.6 mg/dL, (17-318), IgG - 156 mg/dL (350-1620) and IgM - 30.3 mg/dL (30 -265). Flow cytometry showed the following values. CD3-/CD19+ (Bcells) 0.13, (6 – 23%) and CD3-CD19+ (Absolute count) 8, (91 – 610) cells/μL, suggesting absolute B cell deficiency. In view of the clinical picture and investigations a diagnosis of Bruton's agammaglobulinemia was made. This was further confirmed by genetic analysis which revealed BTK gene mutation (p. Ser572fs). Genetic analysis in the mother was done and she was a heterozygous carrier for the same mutation. The child was treated with antibiotics and intravenous immunoglobulin. He was discharged with advice to continue monthly immunoglobulin therapy with appropriate treatment of infections. The child is on regular follow up.

* Associate Professor of Pediatrics
** Professor of Pediatrics,
Chengalpattu Medical College, Chengalpattu
*** Professor of Pediatric Hematology,
Institute of Child Health and Hospital for Children, Chennai
email: hemachitramkumar@gmail.com

Discussion

Children with X linked agammaglobulinemia (XLA) or Bruton agammaglobulinemia, have a profound defect in B lymphocyte development resulting in severe hypogammaglobulinemia, absence of circulating B cells, small to absent tonsils and no palpable lymph nodes. The abnormal gene in XLA maps to q22 on the long arm of the X chromosome and encodes the B cell protein tyrosine kinase (BTK). BTK is necessary for pre B cell expansion, maturation and probably has a role in all stages of B cell development.[2] Most boys affected with XLA remain well during the first 6-9 months of life by virtue of maternally transmitted IgG antibodies. Thereafter they acquire infections with extracellular pyogenic organisms, such as Streptococcus pneumonia and Hemophilus influenzae, unless they are given prophylactic antibiotics immunoglobulin therapy. Infections include sinusitis, otitis media, pneumonia or less often sepsis or meningitis. Infections with Mycoplasma and fungal infections are also seen. Diagnosis should be suspected if lymphoid hypoplasia is found on clinical examination and serum concentrations of IgG, IgA, IgM and IgE are low. Flow cytometry is an important test to demonstrate the absence of circulating B cells, which will distinguish this disorder from common variable immunodeficiency, hyper IgM syndrome and transient hypogammaglobunemia of infancy.[1] Complications include chronic sinopulmonary infections, enteroviral infections of the central nervous system, increased occurrence of autoimmune diseases and lymphoma.[3] Patients with XLA have survived into their late 40s. If the mother is a carrier for the disease, chorionic villus sampling or amniocentesis can be performed to collect fetal lymphocytes. At birth, cord blood samples can be tested for a decrease in CD 19+ B cells. The prognosis is good if they are diagnosed and treated early with regular intravenous immunoglobulin therapy before the sequelae of recurrent infections appear.[4]

References

1. Rebecca H. Buckley. Primary defects of antibody production. In: Nelson Text book of pediatrics. Robert M Kleigman, Bonita F Stanton, Joseph W St Geme III, Nina F Schor, Richard E Behrman (Eds), First South Asian Edition, Reed Elsevier India Pvt Ltd, New Delhi, 2016; pp1012-1018.
2. Khan WN. Regulation of B lymphocyte development and activation by Bruton's tyrosine kinase. Immunol Res 2001; 23(2-3):147-156.
3. Park JY, Kim YS, Shin DH, Choi JS. Primary cutaneous peripheral T cell lymphoma in a patient with X linked agammaglobulinemia, Br J Dermatol 2011; 164(3):677-679.
4. Chun KJ, Lee TJ, Song JW, Linton JA. Analysis of clinical presentations of Bruton disease, a review of 20 years of accumulated data from pediatric patients at Severence Hospital. Yonsei Med J 2008; 49(1):28-36.

AUTHOR INDEX

SUBJECT INDEX