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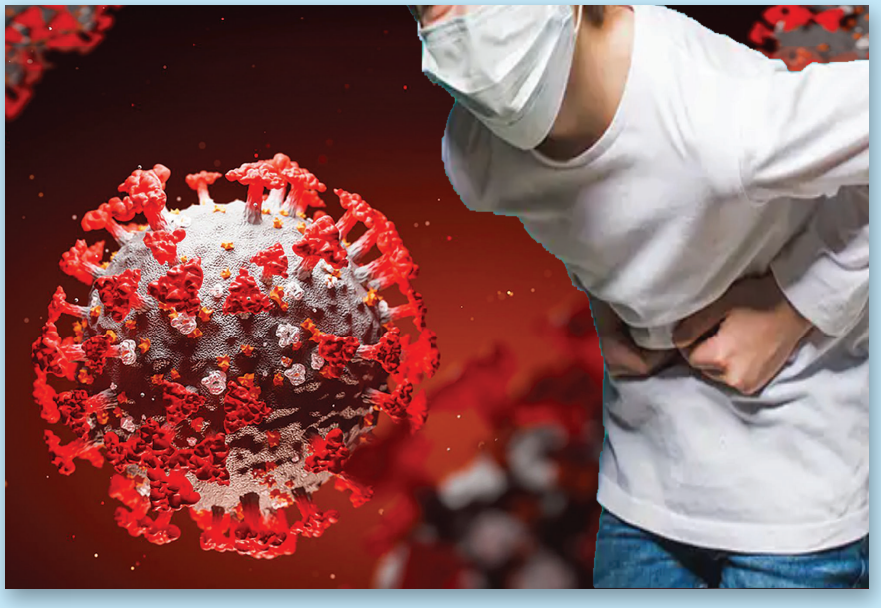

**Editorial**

*"Gastrointestinal Manifestations of COVID-19: Are They Associated with Severe Disease in Children"*

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## EDITORIAL BOARD




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EDITORIAL

# Gastrointestinal Manifestations of COVID-19: Are They Associated with Severe Disease in Children

**Syed Shafi Ahmed Muaz**

COVID-19 is a highly contagious disease that was first reported in Wuhan, Hubei Province, China in December 2019.[1] Ever since the COVID-19 pandemic has hit the world the landscape of its clinical manifestations has been changing and its gastrointestinal (GI) features are now being recognised more frequently.[2,3]

Similar to the respiratory tract, SARS-CoV-2 binds to GI tract cells via the ACE-2 and TMPRSS2 cell receptors in the intestine causing release of cytokines. Fecal shedding of the virus has been demonstrated, which may continue even after nasopharyngeal swabs become negative. Recently, GI symptoms have come to the fore with the recognition of multisystem inflammatory syndrome (MIS-C), a manifestation of COVID-19 with systemic hyperinflammation and multi-organ failure. In the largest series of MIS-C, 84.1% had GI symptoms [abdominal pain (75%), vomiting (56%), diarrhea (40%)].[4]

The exact mechanism of GI involvement in COVID-19 is unknown. The probable mechanism may be due to the interaction between ACE2 and the COVID-19 virus, as these receptors are abundantly present in small and large intestines.[5] Other possible mechanisms include inflammatory responses such as cytokine storms, drug side effects and finally, the dysregulation of intestinal flora through immune mechanisms.[6] COVID-19 leads to various degrees of liver injury, presenting with abnormal levels of alanine aminotransferase (ALT), aspartate amino-transferase (AST) and albumin accompanied by slightly elevated bilirubin levels as well as elevated gamma-glutamyltransferase and alkaline phosphatase levels (ALP). Liver injury may be due to the cytopathic effects of the virus. Virus binding to ACE2 receptors in hepatocytes especially, cholangiocytes, and there occurs an immune-mediated inflammation. Another possible factor may be the high positive end-expiratory pressure level that can cause hepatic congestion by increasing right atrial pressure. Indeed, drug-induced liver injury caused by COVID-19 treatment should be carefully considered.[7]

Among the COVID-19 patients, a wide range of GI symptoms have been reported. A recent research work in China confirmed that more than 80% of the patients experienced digestive symptoms to some extent, including diarrhea, diminished appetite, nausea, vomiting, abdominal pain and gastrointestinal bleeding during their hospitalization.[8,9] Lu et al[10] reported that diarrhea and vomiting were observed in 8.8% and 6.4% in a cohort study of children with COVID-19 infection.

A systemic review and meta-analysis showed that gastrointestinal symptoms are common in children with COVID-19 with nearly a quarter of patients exhibiting at least one gastrointestinal symptom. The most common gastrointestinal symptom was diarrhoea, followed by vomiting and then abdominal pain.[11]

Another intriguing GI manifestation is a "surgical" abdomen clinically mimicking appendicitis. Imaging showed features of terminal ileitis, ileo-colitis and/or mesenteric lymphadenitis, all patients improving with conservative management.[12] In a cohort study in Hong Kong, 15 COVID-19 patients out of 59 presented gastrointestinal (GI) symptoms. The presence of the RNA molecules of the virus in the patient's stool was tested, and 48% had positive results. In some patients, the stool result remained positive even after the

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respiratory samples became negative. This study recommended that health care workers should take extra precautions during sampling from GI secretion and conducting endoscopic procedures in COVID-19 patients.[13]

A systematic review showed that the gastrointestinal tract was the system more frequently associated to the multisystem inflammatory syndrome in children (MIS-C), a severe spectrum of disease in children.[14] Laboratory-confirmed COVID-19 pediatric patients with gastrointestinal manifestations, particularly vomiting, had a severe systemic involvement and high mortality rate. Moreover, cardiac abnormalities were a relevant finding in this setting. Pediatric COVID-19 patients, mainly in those with underlying conditions and gastrointestinal manifestations, may have a severe and systemic involvement, with high mortality rate.

Gastrointestinal involvement had high levels of serum biomarkers, indicating acute inflammation, predominantly with increase of fibrinogen and D-dimer parameters. The elevated levels of these parameters have been also correlated with cytokine storm, multi-organ dysfunction and unfavorable outcome in severe patients with COVID-19.[15] de Paula et al[16] evaluated 83 patients with laboratory-confirmed COVID-19, both by real-time RT-PCR exam and serological test and aimed to compare demographic and anthropometric data, underlying conditions, clinical characteristics, exams, treatments, and outcomes in laboratory-confirmed pediatric COVID-19 patients with and without gastrointestinal signs and symptoms. Therefore, they suggested that laboratory-confirmed COVID-19 pediatric patients with digestive signs/symptoms require attention for hyperinflammation condition and cardiac abnormalities. Multicenter study conducted in 15 hospitals including 101 COVID-19 pediatric inpatients showed that GI symptoms were present in 57% and were the first manifestation in 14%. Adjusted by confounding factors, those with GI symptoms had higher risk of pediatric intensive care unit admission. GI symptoms are predictive of severity in COVID-19 children admitted to hospitals.[17]

So gastrointestinal symptoms are frequent in COVID-19 pediatric patients admitted to hospital. The spectrum of GI manifestations of pediatric COVID-19 may range from mild non-specific symptoms to severe symptoms mimicking a "surgical" abdomen, which may occur even in the absence of respiratory symptoms. These symptoms are also predictive of severity, regardless to other confounding factors and associated with severe systemic involvement and high mortality rate. GI symptoms had higher risk of pediatric intensive care unit admission. It is important for pediatricians to be aware of these clinical presentations and maintain a high index of suspicion for COVID-19, especially in those who have been exposed to a COVID-19 patient.

**References**


1. Bedford J, Enria D, Giesecke J, Heymann DL, Ihekweazu C, Kobinger G, et al. COVID-19: towards controlling of a pandemic. *Lancet* 2020; **395**:1015-18.
2. Chang TH, Wu JL, Chang LY. Clinical characteristics and diagnostic challenges of pediatric COVID-19: A systematic review and metaanalysis. *J Formos Med Assoc* 2020;**119**:982-89.
3. Tian Y, Rong L, Nian W, He Y. Review article: gastrointestinal features in COVID-19 and the possibility of faecal transmission. *Aliment Pharmacol Ther* 2020;**51**:843-51.
4. Miller J, Cantor A, Zachariah P, Ahn D, Martinez M, Margolis K. Gastrointestinal symptoms as a major presentation component of a novel multisystem inflammatory syndrome in children (MIS-C) that is related to COVID-19: A single center experience of 44 cases. *Gastroenterology* 2020;**159**:1571-74.
5. Musa S. Hepatic and gastrointestinal involvement in coronavirus disease 2019 (COVID-19): What do we know till now? *Arab J Gastroenterol* 2020;**21**:3-8.
6. Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for Gastrointestinal Infection of SARS-CoV-2. *Gastroenterology* 2020;**158**:1831-33.
7. Matthai J, Shanmugam N, Sobhan P. Coronavirus Disease (COVID-19) and the Gastrointestinal System in Children. *Indian Pediatr* 2020;57:533-35.
8. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;**395**:497-506.
9. Wang D, Ju XL, Xie F, Lu Y, Li FY, Huang HH, et al. Clinical analysis of 31 cases of 2019 novel coronavirus

infection in children from six provinces (autonomous region) of northern China. *Zhonghua Er Ke Za Zhi* 2020;**58**:269-74.

10. Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, et al. SARS-CoV-2 Infection in Children. *N Engl J Med* 2020;**382**:1663-65.

11. Akobeng AK, Clarke CG, Abdelgadir I, Barimah ET, Gordon M. Gastrointestinal manifestations of COVID-19 in children: a systematic review and meta-analysis. *Frontline Gastroenterology* 2021;**12**:332-37.

12. Tullie L, Ford K, Bisharat M, Watson T, Thakkar H, Mullassery D, et al. Gastrointestinal features in children with COVID-19: an observation of varied presentation in eight children. *Lancet Child Adolesc Health* 2020;**4**:e19-20.

13. Cheung KS, Hung IFN, Chan PPY, Lung KC, Tso E, Liu R, et al. Gastrointestinal Manifestations of SARS-CoV-2 Infection and Virus Load in Fecal Samples From a Hong Kong Cohort: Systematic Review and Meta-analysis. *Gastroenterology* 2020;**159**:81-95.

14. Abrams JY, Godfred-Cato SE, Oster ME. Multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2: a systematic review. *J Pediatr* 2020;**226**:45-54.

15. Akbari H, Tabrizi R, Lankarani KB. The role of cytokine profile and lymphocyte subsets in the severity of coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. *Life Sci* 2020. doi: 10.1016/j.lfs.2020.118167.

16. de Paula CSY, Palandri GG, Fonseca TS, Vendramini TCA, Farhat SCL, Pereira MFB. Gastrointestinal manifestations are associated with severe pediatric COVID-19: A study in tertiary hospital. *J Infect* 2021;83:e22-e25**.**

17. Jimenez G, Rodríguez-Belvís V, Gonzalez F, Ortega D, Segarra O, Benitez M, et al. COVID-19 Gastrointestinal Manifestations Are Independent Predictors of PICU Admission in Hospitalized Pediatric Patients. *The Pediatric Infectious Disease Journal* 2020;39:e459-e462.

DS (Child) H J 2021; 37(1): 5-8

LEADING ARTICLE

# Care of Neonates and Children During Corona Crisis and Importance of Continuation of Essential Services

**Farhana Rahat[1], Ahmed Murtaza Choudhury[2]**

***Abstract***

*The corona virus disease (SARS-CoV-2) has rapidly spread across the world and global population including children are facing unprecedented health crisis. The chance of vertical and perinatal transmission of SARS-CoV-2 virus in children is not proven yet. The effect of the virus on neonate and infant appears to be small. On the other hand, pregnant women suffering from corona virus disease may give birth to premature or IUGR babies who will need extra care. Breast feeding is considered as gold standard in almost all situation. Continuation of breast feeding along with other essential services have reduced the risk of transmission of corona virus.*

***Keywords:*** *SARS-CoV-2, feeding recommendation, essential services.*

## Introduction

The recent pandemic caused by the novel Coronavirus 2019 (COVID-19) has exposed global population to an unprecedented health crisis.[1] The World Health Organization declared the disease as a global pandemic in March 2020.[2] Since then the disease has been causing significant mortality and morbidity all over the world.

COVID-19 has affected predominantly adults or older age group.[3] Pregnant women have the same risk of infection like general population.[4] But due to changes to the immune system pregnant women may be more vulnerable to severe infection.[5] Some evidences suggest that risk of serious illness like pre-eclampsia, fetal distress etc. may be greatest in the later part of pregnancy.[6] The most noted fetal complications were prematurity and intrauterine growth restrictions.[7] These preterm babies may develop respiratory distress syndrome, severe sepsis etc. The care of neonate and infant born to COVID-19 infected or suspected mother has become a concern and sometimes matter of controversy. This review focuses on newborn and children care, feeding and handling of children during COVID-19 situation according to the recommendations of expert committee.

## The effect of SARS-CoV-2 virus on children

The effect of SARS-CoV-2 virus on infants and neonates appear to be small.[8] They are also at lower risk of developing COVID-19. Among the confirmed cases of COVID-19 children, most have experienced mild or asymptomatic illness.[9,10] Reasons for the disparity in occurring serious disease between newborn, infant and adults are not fully understood; differences in immune mechanism may be the cause.[11] Decreased angiotensin converting enzyme activity in nasopharyngeal epithelium and less vigorous interleukin-6 responses during SARS-CoV-2 infection may contribute to the less severe clinical profiles.[12] However older children may develop serious disease like Multi-system Inflammatory Syndrome (MIS-C).[13]

## Perinatal transmission of SARS-CoV-2 virus

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an RNA virus which predominantly

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affect the respiratory system.[14] Respiratory viruses rarely result in intrauterine transmission of infection to fetuses. Therefore, intrauterine transmission of SARS-CoV-2 is anticipated to be low.[15] Only few reports suggest the isolation of novel coronavirus from amniotic fluid and placenta.[16]

**Breast feeding of neonate and infant**

Breast feeding is the cornerstone for nutrition and survival of infant and young child. So, World Health Organization recommends exclusive breast feeding for the first 6 month of life, followed by continuous breast feeding with appropriate complementary foods up to 2 years and beyond.[17] However questions have been raised whether mothers with COVID-19 can transmit the virus to their neonate or infant through breast feeding.

The transmission of COVID-19 through breast milk has not been proven yet. At present, data are not sufficient to conclude transmission of COVID-19 through breast feeding. In a study of 46 COVID-19 positive mothers, the breast milk samples of 43 mothers were negative and only 3 were positive for COVID-19 virus by RT-PCR. The viral particles were not alive and not the same like infective viruses. Transmission of COVID-19 would need replicating the viruses to overcome the defense mechanism in the infants and cause clinical infection.[18]

Recommendations was that, for neonates or infants born to a COVID-19 positive or suspected mother should be based on a full consideration of not only the potential risk of COVID-19 infection of the infant, but also the risk of morbidity and mortality associated with not breast feeding or the inappropriate use of formula milk.

In infants, the risk of COVID-19 infection is low and is typically mild or asymptomatic. Infected mother can breast feed her child because consequences of not breast feeding and separation between mother and children can be significant.[19] Since March 18$^{th}$, 2020, WHO recommended that women with COVID-19 can breastfeed if they wish to do so, based on the idea that babies would get antibodies and anti-infective factors through breast milk which can protect the newborn from getting infections.[20] Mothers with suspected or confirmed COVID-19 should be encouraged to initiate or continue to breast feed. Mothers should be counseled that the benefits of breast feeding substantially outweigh the potential risk of transmission.[21] Mother can breast feed her child with hygienic precautions.[20]

**Breast feeding with hygiene**

These include wearing of masks, washing of hands with soap and water or with an alcohol-based hand rub before and after touching the baby. Chest only needs to be washed if just coughing up on it. Breasts are not required to washed before every feeding.[21]

**Feeding and handling of neonate**

In response to the sudden pandemic, most recommendations suggested that asymptomatic newborn should not be separated from their mothers and should breast fed with hygienic precautions.[22]

Mother and infant should be allowed to remain together while rooming-in including kangaroo mother care. Kangaroo mother care can help the preterm and low birth weight babies to maintain their temperature, establishment of breast feeding, prevention of sepsis and avoid hospital admission.[23,24] Perinatal transmission is unlikely to occur if correct hygienic precautions are undertaken along with effective parental education. In the earlier days of the pandemic, neonate and infant were separated from mother and those created psychological stress to mother, child and other caregivers. Restriction to parent visiting has potentially significant impact on parental attachment and well-being with secondary effect on infants' physical and mental health.[25] Now WHO recommends that mother and newborn should not be separated. The dyad may practice KMC even in cases of suspected or confirmed COVID-19 infection by using personal protective equipment and disinfection of used surfaces.[26]

When maternal general health impedes direct breastfeeding or in case of separation of mother and neonate, mothers should be encouraged and supported to express milk. Milk should be expressed with proper hygiene like appropriate hand washing and wearing masks. A caregiver can help the mother in the procedure. Expressed milk should provide freshly to the child. Expressed breast milk should not be pasteurized because it reduces the biological and immunological value of human milk.[23, 27]

**Feeding sick children[28, 29]**

When a child becomes sick due to COVID-19 infection with symptoms like cough or difficult breathing or

diarrhea, feeding becomes a problem. They can lose weight and become sicker. They should seek for medical care as well as feeding should be cared of.

1. **Frequent breast feeding:** Breast feeding frequently can help the sick child to fight sickness as it will give energy. It will enable them to prevent weight loss and recover quickly. It will also give them comfort. If the child is unwell or too weak to suckle, expressed breast milk can be given from a clean cup or cup-spoon. When mother is COVID-19 positive, she can express breast milk with proper hand washing and wearing masks.
2. **Continue feeding:** Children need more food and liquids when they are sick. As appetite is usually lost, they are encouraged to take small frequent meals. Food should be easily digestible and not fatty. They should also take oral rehydration salt (ORS) and Zinc supplementations when they suffer from diarrhea.
3. **Extra meal during recovery:** Child should take an additional meal of solid food each day to make up lost weight for 2 weeks after recovery or regaining appetite.
4. **Supplementation:** If the mother is unwell or unable to feed the child supplementation with donor milk can be a choice. If that is not available infant formula can be given. In this case safe preparation of milk should be ensured. Child should be fed from a cup or cup-spoon.

**The role of continuation of essential services**

Bangladesh has successfully achieved the MDG goals and is approaching to fulfill the SDG targets. All the achievements in child health sector are dependent on continuous availability of health services to mother and children around the globe.[30] Due to the recent pandemic, the utilization of maternal and newborn health services has decreased approximately by 19 percent.[31] Lack of health facilities could cause death of over 28,000 children under the age of 5 years within 6 months.[32] Reduction of routine immunization coverage will put a number of children at risk of mortality and morbidity from preventable diseases like diphtheria, measles, polio, pneumonia, meningitis etc. Disrupted essential services could increase child mortality by 37 percent and maternal mortality by 19 percent over the next year.[33] Comparing to adults, so far the direct effects of COVID19 on child and adolescent appears not significant. But, the indirect effect could be horrifying. Essential health care services should be preserved to prevent avoidable losses of child lives during the COVID-19 pandemic and to protect progress in reducing child mortality achieved over recent years.[34]

**Conclusion**

The global pandemic caused by SARS-CoV-2 virus is one of the most distressing global health crises of our time. After weighing carefully the risks and benefits of essential care, most international organizations recommend to continue the life saving measures for the survival of preterm and low birth weight babies. Essential care should be continued with hygienic precautions. The message is to ensure that mother, newborn and children will continue to receive all the essential services while remaining as safe as possible.

**References**


1. Zaigham M, Andersson O. Maternal and Perinatal Outcome with COVID-19, A Systematic Review of 108 Pregnancies. *Acta Obstet Gynecol Scand* 2020;**99**:823-29.
2. World Health Organization. Rolling update on coronavirus disease (Covid-19). 2020. Available from https://www.who.int/emergencies/diseases/novelcoronavirus-2019/events-as-they-happen.
3. Neonates in the COVID-19 pandemic. *Pediatric Research* 2020. https://doi.org/10.1038/s41390-020-1096-y.
4. Chen Y, Li Z, Zhang YY, Zhao WH, Yu ZY. Maternal Health Care Management During the Outbreak of Coronavirus Disease 2019. *J Med Virol* 2020;**92**:731-39.
5. Favre G, Pomar L, Musso D, Baud D. 2019-nCoV Epidemic: What About Pregnancies? *Lancet* 2020; **395**:e40.
6. Knight M, Bunch K, Vousden N, Morris E, Simpson N, Gale C. Charecteristics and Outcomes of Pregnant Women Admitted to Hospital with Confirmed SARS-CoV-2 Infection in UK: National Population-based Cohort Study. *BMJ* 2020;**369**:m2107.
7. Nessa A, Momtaj KR, Parvin S, Salma U, Sarker MAS, Shahi MS, et al. Study on COVID-19 Positive Pregnant Women and Pregnancy Outcome. *Sir Salimullah Med Coll J* 2020;**28**:83-87.
8. Lopes de Sousa. Effects of COVID-19 Pregnancy and Neonatal Prognosis: What is the Evidence. *Int J Environ Res Public Health* 2020;17:E4176.
9. Zimmermann P, Cutis N. COVID-19 in Children, Pregnancy and Neonates. *The Pediatric Infectious Disease Journal* 2020;**39**:469-77.
10. Zimmermann P, Cutis N. Coronavirus Infections in Children Including COVID-19: An Overview of the Epidmiology, Clinical Features, Diagnosis, Treatment and Prevention Options in Children. *Pediatr Infect Dis J* 2020;**39**:355-68.

11. Molloy EJ, Bearer CF. COVID-19 in Children and Altered Inflammatory Responses. *Pediatr Res* 2020. https://doi.org/10.1038/s41390-020-0881-y.

12. Soraya GV, Ulhaq ZS. Interleukin-6 Levels in Children Developing SARS-CoV-2. *Infect Pediatr Neonatol* 2020;**61**:253-54.

13. Whittaker E, Bamford A, Kenny J. Clinical charecteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. *JAMA* 2020;**324**:259-69.

14. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A Pneumonia Outbreak Associated with A New Coronavirus of Probable Bat Origin. *Nature* 2020;**579**:270-73.

15. Salvatore CM, Young- Han J, Acker KP, Tiwari P, Jin J, Brandler M, et al. Neonatal Management and Outcomes during the Covid-19 Pandemic: An Observational Cohort Study. *Lancet Child Adolesc Health* 2020;**4**:721-27.

16. Zamaniyan M, Ebadi A, Aghajanpoor Mir S, Rahmani Z, Haghshenas M, Azizi S. Preterm Delivary in Pregnant Woman with Critical Covid-19 Pneumonia and Vertical Transmission. *Prenat Diagn* 2020; **40**:1759-61.

17. World Health Organization, UNICEF. Global Strategy for Infant and Young Child Feeding. Geneva, Switzerland: World Health Organization; 2020. Available from: https://www.who.int.nutrition.

18. Centeno-Tablante E, Medina-Rivera M, Finkelstein JL, Rayco-Solon P, Garcia-Casal MN, Rogers L, et al. Transmission of novel coronavirus-19 through breast milk and breast feeding. A living systematic review of the evidence. *Ann N Y Acad Sci* 2021;**1484**:32-54.

19. Wu Z, Mc Googn JM. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of A Report of 72314 Cases From the Chinese Centre for Disease Control and Prevention. *JAMA* 2020:**323**:1239-42.

20. Breastfeeding advice during the COVID-19 outbreak. Available from: https://www.emro.who.int/non-communicable-diseases/campaigns/breastfeeding-advice-during-the-covid-19-outbreak.html.

21. World Health Organization. Clinical management of COVID-19: Interim guidance (27 May 2020). Geneva, Switzerland: World Health Organization; 2020.

22. Lavizzari A, Klingenberg C, Profit J, Zupancic JAF, Davis AS, Mosca F, et al. International Comparison of Guidelines for Managing Neonates at the Early Phase of the SARS-CoV-2 Pandemic. *Pediatr Res* 2021:**89**:940-51.

23. World Health Organization, UNICEF: Protecting, promoting and supporting breast feeding in facilities providing maternity and newborn services: the revised baby-friendly hospital initiative 2018. Implementation guidance. Available from: https://www.who.int/nutrition/publications/infantfeeding/bfhi-implementation/en/.

24. Tran HT, Nguyen PTK, Huynh LT, Le CHM, Giang HTN, Nguyen PTT, et al. Appropriate Care for Neonates Born to Mothers with COVID-19 Disease. *Acta Pediatr* 2020;**109**:1713-16.

25. Tscherning C, Sizun J, Khun P. Promoting Attachment Between Parents and Neonate Despite the COVID-19 Pandemic. *Acta Pediatr* 2020. https:// doi.org/10.1111/apa.15455.

26. Hoque MM. KMC Practices During COVID-19 Pandemic: *Dhaka Shishu (Children) Hospital Journal* 2020;**36**:85-86.

27. UNICEF. Coronavirus disease (COVID-19): What parents should know. Available from: https://www.unicef.org/stories/novel-coronavirus-outbreak-what-parents-should-know.

28. WHO. Home care for patients with COVID-19 presenting with mild symptom and management of their contacts. Interim Guidance. March 17, 2020. Available from: https://www. who.int/publications-detail/home-care-for-patients-with-suspected-novel-coronavirs-(ncov)-infection-and-management-of –coronavirus-of –contacts.

29. UNICEF. Community Infant and Young Child Feeding(C-IYCF) counseling package. Available from: https://www.unicef.org/nutrition/index58362. html.

30. Hussain M. Effect of COVID 19 Pandemic on Child Health and Post Pandemic Scenario in Bangladesh. *Bangladesh J of Child Health* 2020;**44**:4-7.

31. UNICEF. As covid-19 devastates already fragile health system, over 6000 additional children under 5 could die a day, without urgent action. Available from: https://www.unicef.org/bangladesh/en/press releases/covid-19-devastates-already-fragile-healthsystems.

32. COVID-19: Over 28,000 children could die in 6 months without urgent action. Available from: https://unb.com.bd/ category/Bangladesh/covid-19-over-28000-children could-die-in-6-months-without-urgent-action/51543

33. Preserve essential health services during the COVID-19 pandemic: Bangladesh. Available from: https:www.globalfinancingfacility.org/sites/gff_new/files/documents/Bangladesh-Covid-Brief_GFF.pdf

34. Hussain M, Mamun MAA, Anwar S, Begum N, Chowdhury AS, Kamrul K. Paediatric COVID-19: Review of Hospital Experience and Impact on Child Health Services in Bangladesh. *Malaysian Journal of Paediatric and Child Health* 2021;**27**:46-56.

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ORIGINAL ARTICLE

# Status of Red Blood Cell Indices in Iron Deficiency Anemia and β Thalassaemia Trait: A Comparative Study

**Biva Mondal[1], Mashud Parvez[2], Md Masud Rana[3], Lotifur Rahman[4], Rowshan Zahan[5], Kishor Chandra Pal[6], Waqer Ahmed Khan[7]**

**Abstract**

***Background:*** *Iron deficiency anemia (IDA) and β thalassemia trait (β -TT) are the two important differential diagnosis of microcytic hypochromic anaemia. It is important to distinguish between the above two conditions to avoid unnecessary iron therapy. Red blood cell (RBCs) indices are simple, easy, and cost effective method to get a primary and valuable information regarding the diagnosis of IDA and β -TT.*

***Objectives:*** *This study was aimed to compare the RBC count, hemoglobin (Hb), hematocrit (Hct%), RBC indices, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW) and redcell distribution width index (RDWI) in Iron deficiency anemia and β thalassemia trait.*

***Methods:*** *This cross-sectional comparative study was conducted in the department of clinical pathology, Dhaka Shishu Hospital, Dhaka from July 2019 to March 2020. Total 107 patients with microcytic hypochromic anaemia (64 subjects of IDA and 43 subjects of β -TT were tested for RBC count, Hb%, MCV, MCH, MCHC, RDW, and PCV from venous blood by haematology analyser. Serum ferritin was measured by Enzyme Linked Immunosorbent Assays (ELISA). Statistical analysis was performed by SPSS version 22. Statistical significance was set at p value less than 0.05.*

***Results:*** *RBC count, Hb, and Hct,MCV, MCH and MCHC were significantly lower and RDW and RDWI was significantly higher in IDA group than in β- TT group ($p< 0.001$). Similar result was observed in male and female participants when compared them in separate group.*

***Conclusion:*** *The study showed that RBC count, Hb, Hct, MCV, MCH, and MCHC were significantly lower in IDA group than in β-TT group, whereas RDW and RDWI were significantly higher in IDA group than in β-TT group.*

***Keywords:*** *Iron deficiency anemia, β thalassemia trait, red blood cell indices.*

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## Introduction

Anemia may be defined as a reduction in the concentration of Hb which leads to reduced oxygen carriage and delivery to the tissues.[1,2] The global prevalence of anemia in children aged 6-59 months is 43%.[3-5] Anemia is considered a public health problem in developing countries, and it has been estimated that 2 billion people suffer from anemia worldwide. The underlying causes of anemia are many, varied and preventable, such as nutritional deficiencies, infections, and hemoglobin (Hb) disorders.[6] Microcytic hypochromic anaemia is a very common haematological abnormality in clinical practice.[7] Two most common causes of microcytic hypochromic anaemia are iron deficiency anemia (IDA) and β thalassemia trait (β -TT), which are sometimes difficult to differentiate clinically.[8,9] IDA in young children is recognized as a major public health issue and the most prevalent form of micronutrient deficiency worldwide.[3] IDA may occur as a result of an iron-deficient diet, intestinal iron malabsorption, and chronic blood loss due to many factors like hemorrhage or hemoglobinuria because of intravascular hemolysis.[10-12]

Thalassemias are defined as a heterogeneous group of genetic disorders of Hb synthesis due to the reduction of one or more of the globin chains production.[13] Thalassemia is a growing global public health problem as it was expected that about 900,000 births of clinically significant thalassemia disorders would occur in the year 2020.[14] It is estimated that about 1.5% of world population are carriers of the associated genetic mutation.[15,16]

IDA and β-TT should be differentiated to avoid unnecessary iron therapy, because iron treatment is indicated in IDA and contraindicated β-TT.[17] Hb electrophoresis is a reliable, rapid, reproducible and easy method to separate various Hb fractions depending on their charge and these fractions are then quantitated.[18] A definitive differential diagnosis between between IDA and β-TT is based on the result of HbA2 percentage, serum iron, and ferritin concentration. Electronic cell counters have been used to determine red cells indices as the first indicator of anemia. To reduce unnecessary investigation, blood indices are used to detect subjects who have a high probability of anemia. To differentiate these two conditions several rapid and inexpensive discriminating indicators have been proposed in large-scale research since 1973. These indices are obtained from automated cell counters that traditionally give parameters like Hemoglobin (Hb), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Red Blood Cell Distribution Width (RDW), Mean Corpuscular Hemoglobin Concentration (MCHC), and Red Blood Cell Count (RBC).[19-23] The modern hematology laboratory uses the automated blood cells analyzed. It gives rapid, cost-effective and accurate analysis of red cell indices which have an important diagnostic utility. Most of these analyzers measure the RBC count, MCV, and Hb concentration. The other indices such as the hematocrit (Hct), MCH, and MCHC are derived from the primary measurements.[24] The MCV is either directly measured by the instrument, or it is calculated by certain formula. The red cell distribution width (RDW) is calculated as standard deviation (SD) of RBC or as a coefficient of variation.[25] This study will describe and compare the RBC indices of IDA group with those of â- TT group to have detail information about the behavior of the RBC indices in the above two different conditions.

## Materials and Methods

This cross sectional comparative study was conducted in the department of clinical pathology, Dhaka Shishu Hospital, Dhaka from July 2019 to March 2020. Total 107 children of both sexes with microcytic hypochromic anaemia (64 children with IDA and 43 children with β-TT) age ranged from 1 year to 18 years were included in this study. Patients already on nutritional supplements, having long standing illness or on medication interfering with micronutrient metabolism (e.g. antiepileptic drugs such as acetazolamide, carbamazepine and clobazam, aspirin and antacids containing magnesium hydroxide) and patients who were diagnosed and was having a family history of haematological disorders other than thalassemia were excluded from the study. A questionnaire was used to obtain the data including age and sex. Two ml peripheral venous blood were collected under sterile conditions in an EDTA tubes and another 2 ml venous blood were collected in the other tubes without anticoagulant for serum separation. Serum was separated within 3 hours of collection. The RBC count, the measurements of Hb, MCV, MCH, MCHC, RDW, and packed cell volume (PCV/Haematocrit) were obtained by haematology analyser: Mythic -22 using reagent Kits (Diluent, Cleaner, Lytic). Serum ferritin was

measured by Enzyme Linked Immunosorbent Assays (ELISA) using reagent kits (IMMULITE and IMMULITE 1000 system). According to the WHO guidelines, anemia is defined as Hb <11g/dl; and iron deficiency as Serum Ferritin <12 μg/l in children <5 years old and <15 μg/l in children older than 5 years in both male and female group.[26] Statistical analysis was performed using statistical package for social science (SPSS) software version 22 (SPSS Inc. Chicago, IL). The RBC count, concentrations of Hb, Hct, MCV, MCH, MCHC, RDW and RDWI were expressed in mean ±SD. Descriptive statistics were applied to describe the value derived from tests. The mean concentration of Hb, Hct, RBC count and red cell indices were compared using independent sample Student *t* test between IDA group and β TT group. Statistical significance was set at *p* value less than 0.05.

**Result**

Total 107 patients with microcytic hypochromic anaemia were included in the study. Among them 64 subjects were IDA and 43 subjects were β-TT. The age of patients were from 1 year to 18 years, both male and female children were included in the study. The mean ± age of IDA group and β -TT group was 4.31±4.58 (range 1-18 years) and 5.07±4.72 (range 1-17) years. There was no significant difference in age between two groups (p=0.409) (Table I).

There were 36 males and 28 females in IDA group and 22 males and 21 females in β-TT group. There were no significant difference between two group (p=0.605). So, IDA group and β-TT group was age and sex matched (Table II).

The comparison between IDA group and β-TT group in regards to RBC count, Hb concentration, hematocrit and red cell indices is shown in Table III. The mean± RBC count (4.42±0.52 vs 5.35±0.74) x $10^{12}$/L, p<0.001, 95% CI, -1.075,-0.506) Hb concentration (7.25±1.30 vs 10.49±1.62 g/dl, p<0.001, 95% CI, -3.705,-2.308) and hematocrit (24.36±2.99 vs 32.62±4.81%, p<0.001, 95% CI, -5.832,-5.760) were significantly higher in β -TT group than IDA group. The mean± MCV (55.31±5.36 vs 61.08±5.38, p<0.001, 95% CI, -3.747,-3.703), MCH (16.47±2.81 vs 19.68±2.26, p<0.001, 95% CI, -1.992,-2.036), MCHC (29.38±2.18 vs 32.27±1.57, p<0.001, 95% CI, -2.289,-2.314) were significantly higher in β -TT group than IDA group (Table III). However, the mean± RDW (20.53±1.93 vs 16.68±1.88, p<0.001, 95% CI, 4.678, 4.683), RDWI (254.95±51.68 vs 198.95±55.39, p<0.001, 95% CI, 82.178, 82.411) were significantly higher in IDA group than β -TT group (Table III).

**Table I**
*Age distribution of IDA group and β-TT group*

| Group | Total number | Age range (years) | Mean ±SD (years) | p value |
|---|---|---|---|---|
| IDA | 64 | 1.0-18.0 | 4.31±4.58 | 0.409 |
| β-TT | 43 | 1.0-17.0 | 5.07±4.72 | |

**Table II**
*Sex distribution of IDA group and β-TT group.*

| Group | Total number | Gender | | p value |
|---|---|---|---|---|
| | | Male | Female | |
| IDA | 64 | 36 | 28 | 0.605 |
| β-TT | 43 | 22 | 21 | |

**Table III**
*Comparison of RBC count, Hb, Haematocrit and red cell indices between IDA and β-TT group*

| Variable | Iron deficiency anaemia (IDA) (n=64) Mean ±SD | β-thalassemia trait (β-TT) (n=43) Mean ±SD | p value | 95% Confidence interval |
|---|---|---|---|---|
| RBC count (x$10^{12}$/L) | 4.42±0.52 | 5.35±0.74 | <0.001 | -1.075,-0.506 |
| Hb (g/dl) | 7.25±1.30 | 10.49±1.62 | <0.001 | -3.705,-2.308 |
| Hematocrit (%) | 24.36±2.99 | 32.62±4.81 | <0.001 | -5.832,-5.760 |
| MCV (fl) | 55.31±5.36 | 61.08±5.38 | <0.001 | -3.747,-3.703 |
| MCH(pg) | 16.47±2.81 | 19.68±2.26 | <0.001 | -1.992,-2.036 |
| MCHC(g/dl) | 29.38±2.18 | 32.27±1.57 | <0.001 | -2.289,-2.314 |
| RDW% | 20.53±1.93 | 16.68±1.88 | <0.001 | 4.678, 4.683 |
| RDWI | 254.95±51.68 | 198.95±55.39 | <0.001 | 82.178, 82.411 |

**Discussion**

The most commonly encountered disorders with mild microcytic anemia are IDA and β-TT. Differentiation of this two condition is very important because their prognosis and treatment are different. The first step to diagnose microcytic anemias is to analyze blood samples and to determine the erythrocyte indexes using cell counters.[26]

In our study we found that RBC count, Hb and Hct values were higher in β-TT group than IDA group (Table III). Our findings were similar to the findings of Vehapoglu et al.[19] They considered RBC count a valuable index and found higher RBC count in 64.1% of 290 children with microcytic anemia at the time of diagnosis. However, the frequency of high RBC count was 29.4% in children with IDA. Which indicates that more number of patients with β-TT have higher RBC counts than patients with IDA. The authors also observed that the RBC count was increased at the initiation of iron therapy in patients with iron deficiency anemia and decreased by the end of therapy.

In our study we found that the Hb concentration was more in β-TT than iron deficiency anemia (10.49±1.62 g/dl vs 7.25±1.30 g/dl, p<0.001).and RDW is greater in IDA than beta thalassemia trait patients (20.53±1.93 vs 16.68±1.88, p<0.001). These findings were consistent with findings of Miri-Moghaddam et al[27], Belisario et al[28] and Urrechaga et al[29]. They observed that erythrocytosis (increased RBC) and mild anemia are characteristics of β-thalassemia trait, and the erythrocytes are usually more microcytic (reduced MCV) than in with iron deficiency anemia; whereas in with iron deficiency anemia, the level of anisocytosis (RDW) is greater, along with lower Hb levels when compared with those of β-thalassemia.[27-29] These higher values are related to the disease pathophysiology as excess globin chain leads to an ineffective erythropoiesis, resulting in increased RBC production trying to compensate for anemia.[30] RDW and RDWI were significantly higher in IDA group than in β-TT group (Table III) and that agrees with other studies. RDW showed a highly significant difference between β-TT and IDA (p <0.001). The highest RDW was found in IDA followed by the β-TT reflecting more anisocytosis in IDA than β-TT. Rahim et al[31] also found that RDW was higher in IDA than in β-TT patients. In β-thalassemia trait, almost all RBC are microcytic because deficient synthesis of globin chains resulting from thalassemia mutations expresses itself in all of the RBC precursors. Consequently, RDW values are relatively constant.[32] IDA is progressive rather than stable and if the patient suffers from chronic blood loss. Furthermore, IDA leads to abnormal erythropoiesis those results in increased variation in shape and size: Poikilocytosis and anisocytosis.[33]

**Conclusion**

The study showed that RBC count, Hb, Hct, MCV, MCH, and MCHC were significantly lower in IDA group than β-TT group, whereas RDW and RDWI was significantly higher in IDA group than β-TT group.

## References


1. Mehta AB, Hoffbrand AV. Haematology at a Glance. 4th ed. UK: Wiley Black Well;2014. pp. 25-6.
2. Bekele A, Tilahun M, Mekuria A. Prevalence of Anemia and Its Associated Factors among Pregnant Women Attending Antenatal Care in Health Institutions of Arba Minch Town, Gamo Gofa Zone, Ethiopia: A cross-sectional study. *Anemia* 2016;2016:1073192.
3. McLean E, Cogswell M, EgliI, Wojdyla D, DeBenoist B. World wide prevalence of anaemia, WHO vitamin and mineral nutrition information system, 19932005. *Public health nutrition* 2009;**12**:444-54.
4. WHOUNCF, UNU (2001) Iron deficiency anemia assessment, prevention, and control: A guide for program managers. Geneva.
5. WHO. MicronutrientDeficiencies-Iron Deficiency Anemia. Available from: http://www.who. int/nutrition/topics/ida/en/.Accessed28June 2020.
6. Kayode O, Adeola O, Oladunjooge A. Anemia in developing countries: Burden and prospects of prevention and control. In: Silverberg D, editor. Anemia. 1st ed. Croatia: InTech-Open; 2012. P.115-6.
7. Sankar VH, Arya V, Tewari D, Gupta UR, Pradhan M, Agarwal S. Genotyping of alpha -thalassaemia in microcytic hypochromic anemia patients from North India. *J Appl Genet* 2006;**47**:391-95.
8. Wharton BA. Iron deficiency in children: detection and prevention. *Br J Haematol* 1999;**106**:270-80.
9. Olivieri NF. The beta-thalassemias. *N Engl J Med* 1999;**341**:99-109.
10. World Health Organization. Global Estimates for Health Situations Assessment and Projections. Geneva: World Health Organization, 1990. Available from:
11. Hudnall SD. Hematology: A Pathophysiologic Approach. 1st ed. USA: Mosby Elsevier; 2012.P. 18-9.
12. Hatton CS, Jones NC, Hay D, Keeling D. Haematology Lecture Notes. 9th ed. UK: Wiley Black Well; 2013.P.15-6.
13. Weatherall DJ. Haemoglobin and the inherited disorders of globin synthesis. In: Hoffbrand AV, Catovsky D, Tuddenham EG, editors. Postgraduate Haematology. 5th ed. UK: Blackwell Publishing; 2005.P.88-9.
14. Turgeon ML. Clinical Hematology Theory and Procedures. 5th ed. USA: Lippincott Williams and Wilkins; 2012.P.220-1.
15. Bordbar E, Taghipour M, Zucconi BE. Reliability of different RBC indices and formulas in discriminating between ß-thalassemia minor and other microcytic hypochromic cases. *Mediterr J Hematol Infect Dis* 2015;**7**:e2015022.
16. Soliman AR, Kamal G, Elsalakawy A, Mohamed TH. Blood indices to differentiate between b-thalassemia trait and iron deficiency anemia in adult healthy Egyptian blood donors. *Egypt J Haematol* 2014;**39**:91-92.
17. Massey AC. Microcytic anemia. Differential diagnosis and management of iron deficiency anemia. *Med Clin North Am* 1992;**76**:549-66.
18. Singh M, Gautam A. To Evaluate Anaemia by Erythrocyte Indices, Red Cell Distribution width and Haemoglobin Electrophoresis with Special Reference to Thalassemia in Paediatric Age Group. *Journal of Evolution of Medical and Dental Sciences* 2015;**4**:1755-64.
19. Vehapoglu A, Ozgurhan G, Demir AD, Uzuner S, Nursoy MA, Turkmen S, et al. Hematological indices for differential diagnosis of Beta thalassemia trait and iron deficiency anemia. *Anemia* 2014;**57**:673-78.
20. England J, Fraser P. Differentiation of iron deficiency from thalassaemia trait by routine blood-count. *The Lancet* 1973;**301**:449-52.
21. Klee GG, Fairbanks VF, Pierre RV, O'sullivan M. B. Routine erythrocyte measurements in diagnosis of iron-deficiency anemia and thalassemia minor. *American Journal of Clinical Pathology* 1976;**66**:870-77.
22. Mentzer W. Differentiation of iron deficiency from thalassaemia trait. *The Lancet* 1973;**301**:882.
24. Kaushansky K, Lichtman M, Kipps T, Seligsohn U, Prchal J. Williams Hematology. 8th ed. USA: The McGraw-Hill; 2010.P.34-8.
25. Ciesla B. Haematology in Practice. 1st ed. USA: F.A. Davis Company; 2007.P.46-7.
26. Matos JF, Dusse LM, Borges KB, Castro RL, Coura-Vital W, Carvalho M. A new index to discriminate between iron deficiency anemia and thalassemia trait. *Rev Bras Hematol Hemoter* 2016;**38**:214-19.
27. Miri-Moghaddam E, Sargolzaie N. Cut off determination of discrimination indices indifferential diagnosis between iron deficiency anemia and â-thalassemia minor. *Int J Hematol Oncol Stem Cell Res* 2014;**8**:27-32.
28. Belisário AR, Viana MB. Efeitos da talassemia alfa nas manifestações clínicas ehematológicas da anemia

falciforme: uma revisão sistemática. *Rev Med Minas Gerais* 2010;**20**:312-21.

29. Urrechaga E, Borque L, Escanero JF. The role of automated measurement of red cell subpopulations on the Sysmex XE 5000 analyzer in the differential diagnosis of microcytic anemia. *Int J Lab Hematol* 2011;**33**:30-36.
30. Matos JF, Borges G, Fernandes AS, Faria JR, Carvalho MG. RDW as differential parameter between microcytic anemias in "pure" and concomitant forms. *J Bras Patol Med Lab* 2015;**51**: 22-27.
31. Rahim F, Keikhaei B. IDA and beta-TT differentiation. *Turk J Hemaol* 2009;**26**:138-45.
32. Aslan D, Gumruk F, Gurgey A, Altay C. Importance of RDW value in differential diagnosis of hypochrome anemias. *Am J Hematol* 2002;**69**:31-33.
33. Bessman JD, Feinstein DI. Quantitative anisocytosis as a discriminant between iron deficiency and thalassemia minor. *Blood* 1979;**53**:288-93.

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ORIGINAL ARTICLE

# Neurological Complications of Intrathecal Chemotherapy in Children: Experience in A Tertiary Care Hospital in Bangladesh

**Sheikh Farjana Sonia[1], Avijeet Kumar Mishra[2], Azmeri Sultana[3], Sharmin Afroze[4]**

**Abstract**

***Background:*** *Intrathecal (IT) chemotherapeutic agents have a narrow therapeutic index and high potential for toxicity. Though severe side effects are rare, but sometime consequences of IT chemotherapy can be catastrophic.*

***Objectives:*** *The objective of the study was to observe the neurological complications of intrathecal chemotherapy administrations in patients getting treatment for childhood malignancy.*

***Methods:*** *This prospective study included 33 patients who received IT chemotherapy on 76 occasions from July 2020 to December 2020 at Dr. M R Khan Shishu Hospital and ICH. We documented all the neurological complications within two weeks of IT chemotherapy. We defined minor neurological complications as headache, backache, fever, nausea, or vomiting. Major neurological complications were defined as nuchal rigidity, paresthesia, paralysis, or chemical arachnoiditis. All the cases were managed according to the internationally standard protocol.*

***Results:*** *Among the patients who received IT chemotherapy 64% were male and 36% were female. The mean age of child was 7 years. The most common diagnosis was BCP (B cell precursor) ALL (75.8%), followed by T-cell ALL (15.1%), APML (Acute promyelocytic leukemia) (6.1%), and B lymphoblastic Lymphoma (3%). Therapy consisted of methotrexate alone in 73 (96.1%) occasions, and cytarabine alone in 3(3.9%) occasions. Minor events occurred in 17(22.4%) occasions but no patient developed major events after administration of IT chemotherapy. Among the side effects a total of 5 (6.6%) occasions children developed nausea, 4 (5.3%) had back pain, 3 (3.9%) had headache, 2 had (2.6%) vomiting, 2 (2.6%) had dizziness and 1(1.3%) developed fever after IT chemotherapy administration. No patient developed major neurological events like neck rigidity, paralysis and chemical arachnoiditis. About 77.6% occasions, children did not develop any side effects after IT chemotherapy administration.*

***Conclusion:*** *No major toxic neurological events occurred but only minor neurological complications developed after IT chemotherapy administration. It is important for clinicians to be aware of the adverse events and consider them when treating patients with IT chemotherapy.*

***Keywords:*** *Intrathecal chemotherapy, complications*

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## Introduction

Acute lymphoblastic leukemia and other aggressive lymphoid malignancies have high incidence of central nervous system (CNS) involvement. Various solid tumors, most notably neuroblastoma and nephroblastoma, can also metastasize in CNS as a late-stage complication causing devastating effects.[1]

Several treatment protocols have been developed targeting malignant cells in the CNS, among them the most commonly used modality of treatment is intrathecal (IT) chemotherapy. IT chemotherapy is frequently used for the prophylaxis and treatment of CNS metastasis.[1] It is introduced into the CSF after doing lumber puncture (LP). When drugs are given in this way, they are said to be given intrathecally.

The goal of IT chemotherapy is to the exposure of drugs to CNS, while reducing systemic drug toxicities.[2] The chemotherapeutic agents approved for intrathecal use include methotrexate, cytarabine, liposomal cytarabine, and thiotepa.[3,4] The scheduling and dosing of these medications varies depending on whether they are used for prophylaxis or treatment. Corticosteroids are frequently included with IT chemotherapy, most commonly hydrocortisone, to increase cytotoxicity and to decrease the risk of chemical arachnoiditis.[5] Most prophylactic regimens for leukemia and lymphomas contain methotrexate, either as a single agent or in combination with cytarabine.

The narrow therapeutic index and high potential toxicities of these agents can have potentially fatal consequences. Chemical arachnoiditis, an acute syndrome occurring hours after injection and characterized by headache, backache, vomiting, fever, meningismus and cerebral fluid pleocytosis is among the most common and potentially serious effects.[5,6] More severe symptoms also have been reported including cauda equina syndrome, encephalitis, papilledema, myelopathy, paraplegia, cranial nerve palsies, and seizures.[7,8]

Outcome of leukemia in children has shown a steady improvement, with recent trials demonstrating excellent survival in patients in the last few decades.[9,10] However, despite the advances in disease outcome, treatment related toxicity remains unacceptably high. Though severe side effects with IT chemotherapy are infrequent, outcome can sometimes be catastrophic. The true incidence of neurological complications is not well quantified. It is possible that the incidence of complications after IT chemotherapy in this setting is underestimated because cases may go unrecognized or unreported. The aim of this study was to describe the neurological side effects of IT chemotherapy administration.

## Materials and Methods

This prospective study was conducted over a period of 6 months from July 2020 to December 2020 at Dr. M R Khan Shishu (Children) Hospital & Institute of Child Health, a tertiary care hospital of Dhaka city after approval from Ethical Review Committee. All children (Age: 1-18 years) getting intrathecal chemotherapy seeking treatment at our center were included. A total of 76 intrathecal chemotherapy were administered during this study period. An informed written consent was taken from parents and assurance about confidentiality was given.

The procedure of lumber puncture (LP) was explained in simple wards to patients and parents. The Paediatric Haemato-Oncology consultant did the procedure and one experienced nurse assisted the procedure. LP was performed under strict aseptic precaution with 25G spinal needles inserted in the L2-L3 or L3-L4 interspace. Patients were placed in their lateral decubitus position with knees flexed; and intrathecal chemotherapy was administered afterwards. Patient diagnosed as ALL and Lymphoma received methotrexate and patient diagnosed as APML received cytarabine as intrathecal medication. Sedation was not used in any case. Patients were asked to drink adequate liquids and they were asked to take rest in bed for the subsequent 3-4 hours on a routine basis. Patients were also advised not to use pillow to sleep for the subsequent 24 hours.

**Table I**

*Dose of Intrathecal Methotrexate according to age*

| Age | Dose of Methotrexate (Intrathecal) |
|---|---|
| <2year | 8 mg |
| 2-3 year | 10 mg |
| >3 year | 12 mg |

We documented signs and symptoms of neurotoxicity that were not present before administration but developed acutely thereafter. Development of new symptoms indicative of neurotoxicity and/or arachnoiditis within fourteen days of administration of IT chemotherapy, specifically paralysis, paresthesia, headache, back pain, nuchal rigidity,

fever, nausea, or vomiting were recorded. We documented only new-onset symptoms because the systemic changes like fever, nausea, vomiting, and asthenia, which may be associated with chemical arachnoiditis may also occur for other reasons in this patient population. We defined minor neurological complications as headache, backache, fever, nausea, or vomiting. Major neurological complications were defined as nuchal rigidity, paresthesia, cranial nerve palsy, paralysis, or chemical arachnoiditis. This division was to allow distinction between more serious neurologic toxicities associated with IT chemotherapy from events with less impact on quality of life.

All data were recorded systematically in preformed data collection form and quantitative data was expressed as mean and standard deviation and as numbers (%) for categorical data. Statistical analysis of the results was obtained by using window-based computer software devised with Statistical Packages for Social Sciences (SPSS-20).

**Results**

During the study period, 76 intrathecal chemotherapy administrations were performed in 33 patients, of whom 21 (64%) were male and 12 (36%) were female. The mean age of child was 7 years (range 2 to 15 years). The most common diagnosis was BCP (B cell precursor) ALL (75.8%), followed by T-cell ALL (15.1%), APML (Acute promyelocytic leukemia) (6.1%), and B Lymphoblastic Lymphoma (3%) which is shown in table II. Therapy consisted of methotrexate alone in 73 (96.1%) occasions, and cytarabine alone in 3 (3.9%) occasions.

**Table II**
*Demographic characteristics of patients received IT chemotherapy (N=33)*

| Characteristics | Parameter |
|---|---|
| Age in years (mean ±SD) | 7.7 ±7 |
| Sex (%) | |
| Male | 64 |
| Female | 36 |
| Diagnosis (%) | |
| BCP ALL | 75.8 |
| T ALL | 15.1 |
| APML | 6.1 |
| B lymphoblastic lymphoma | 3 |
| Type of Chemotherapy (%) | |
| Methotrexate received | 96.1 |
| Cytarabine received | 3.9 |

The symptoms developed after administration of IT chemotherapy are shown in Figure 1. No patient developed major adverse events like neck rigidity, paresthesia, paralysis and chemical arachnoiditis. Among the side effects a total of 5 (6.6%) occasions, children developed nausea, 4 (5.3%) occasions had back pain, 3 (3.9%) had headache, 2 had (2.6%) vomiting, 2 (2.6%) had dizziness and 1 (1.3%) developed fever after IT chemotherapy administration. About 77.6% occasions, children did not develop any side effects after IT chemotherapy administration.

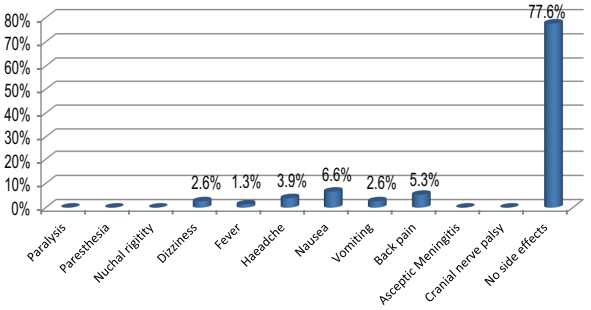


**Fig.-1** *Side effects that developed after IT chemotherapy administration*

Minor events occurred in 17 occasions (22.4%) after IT chemotherapy administration. Among the minor side effects maximum child had nausea 29.4% followed by back pain 23.5%, headache 17.6%, vomiting 11.8%, dizziness 11.8%, and fever 5.9% (Figure2). All the cases were managed conservatively on OPD basis according to unit protocol. No patient required admission for these minor events.

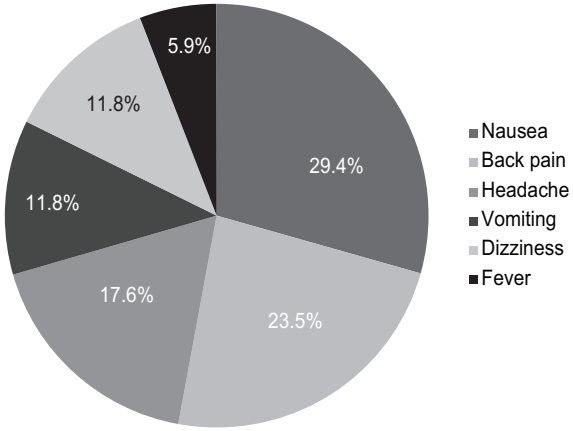


**Fig.-2** *Minor side effects that developed after IT chemotherapy*

**Discussion**

IT chemotherapy for both therapy and prophylaxis of CNS involvement has been a mainstay for medical management of leukemia and lymphoma throughout the world for several decades and for patients with leptomeningeal involvement by solid tumors.[6] We report the adverse neurologic events following IT chemotherapy used as prophylaxis for CNS involvement at our center over six months period. No child developed major neurotoxicity after IT chemotherapy administration. We found minor side effects in 17 cases (22.4%) after administration of IT chemotherapy.

Survival for patients with leptomeningeal spread of disease is low while the incidence of early and late complications associated with IT chemotherapy is high.[11-13] Several studies showed the overall incidence of acute neurotoxicity from IT MTX in children is 3-11%.[14] The incidence of minor side effects after IT chemotherapy is 26-30%.[1] In our study we found minor side effects after IT chemotherapy in 22.4% cases.

Although symptoms such as headache and back pain related to lumbar puncture are not uncommon, clinicians should also be cognizant that these symptoms may signify impending onset of more significant toxicity. Methotrexate is typically assumed to be the major cause of such neurotoxicities,[14] but cytarabine is also a known major cause.[15-17] Jabbour et al[7] evaluated neurologic complications secondary to IT liposomal cytarabine in combination with high-dose methotrexate as prophylactic treatment in patients with ALL and found the incidence of severe complications to be 16%.

Geiser et al[18] found that a toxic syndrome characterized by fever, headache, and vomiting, lasting 2-5 days, occurred in 61% of 39 children with acute leukemia in complete remission, receiving central nervous system prophylaxis with intrathecal methotrexate, and in 14% of 34 children receiving the same plus cranial radiation. The syndrome was accompanied by pleocytosis with lymphocytes, monocytes, and neutrophils. Our study did not find any serious toxic effects.

In a study done by Byrnes et al[19] found that the incidence of major neurologic adverse event was 6.8% and the rate of minor neurologic event was 38.3% for all cases of patients receiving IT chemotherapy. The adverse events encountered most frequently were headache (15.9%), nausea (13.6%), vomiting (9.6%), back pain (5.8%), and fever (5.8%). The most frequent major adverse events were asthenia (4.3%) and paresthesia (3.8%). In our study the rate of minor neurologic event was 22.4%, among them the most frequent adverse effect was nausea (6.6%) followed by back pain (5.3%), headache (3.9%), vomiting (2.6%), dizziness (2.6%) and fever (1.3%).

In the case of IT chemotherapy, there is chance of contamination of the IT methotrexate. Zeng et al[20] investigated the development of paraplegia amongst the patients who received IT methotrexate, discovering trace amounts of vincristine that contaminated intrathecal drugs produced by a manufacturing plant in China causing a large outbreak of severe neurological damage. Murata et al[21] reported a case of demyelination secondary to myelopathy attributed to an IT methotrexate dose. When there is outbreak of severe adverse reactions due to IT chemotherapy, especially when temporally related, one should suspect potential chemotherapy contamination.

Olmos-Jimenez et al[22] performed an observational and prospective study in Spain evaluating standardized triple intrathecal chemotherapy in hematology-oncology patients over an 18-months period. Adverse events occurred in 39.3% of 56 doses. The adverse event recorded most frequently was headache, followed by vomiting and vertigo. In one occasion (1.8%) there was grade 2 sensorimotor polyneuropathy. But in our study the most frequent adverse event recorded was nausea and we did not find any child with neuropathy.

Riva et al[23] found that the most common adverse effect after intrathecal chemotherapy was headache (50%). Other complications observed were lumbar pain in seven patients and transient paresthesia in the legs of one patient. Severe complications were not observed in this study which is similar to our study.

The minor adverse events that developed after IT chemotherapy administration could be due to concomitant administration of other systemic chemotherapy which we did not investigate. Future studies should be done to demonstrate whether concurrent administration of other systemic chemotherapeutic agents may cause the adverse neurological events.

## Conclusion

Our study shows that IT chemotherapy related complications are frequently mild. No major toxic events occurred after IT chemotherapy administration in our study. Oncologist should be aware of the potential complications and uncontaminated chemo-therapeutic agents as well as strict aseptic precaution should be taken to prevent the serious adverse neurological complications.

## References


1. Byrnes DM, Vargas F, Dermarkarian C, Kahn R, Kwon D, Hurley J, et al. Complications of intrathecal chemotherapy in adults: Single-institution experience in 109 consecutive patients. *Journal of oncology* 2019. Doi: 10.1155/2019/4047617.
2. Kerr JZ, Berg S, Blaney SM. Intrathecal chemotherapy. *Critical reviews in oncology/hematology* 2001;**37**:227-36.
3. Kak M, Nanda R, Ramsdale EE, Lukas RV. Treatment of leptomeningeal carcinomatosis: current challenges and future opportunities. *Journal of Clinical Neuroscience* 2015;**22**:632-37.
4. Mack F, Baumert BG, Schäfer N, Hattingen E, Scheffler B, Herrlinger U, et al. Therapy of leptomeningeal metastasis in solid tumors. *Cancer Treatment Reviews* 2016;**43**:83-91.
5. Kwong YL, Yeung DY, Chan JC. Intrathecal chemotherapy for hematologic malignancies: drugs and toxicities. *Annals of hematology* 2009;**88**:193-201.
6. Bleyer WA. The clinical pharmacology of methotrexate. New applications of an old drug. *Cancer* 1978;**41**:36-51.
7. Jabbour E, O'Brien S, Kantarjian H, Garcia-Manero G, Ferrajoli A, Ravandi F, et al. Neurologic complications associated with intrathecal liposomal cytarabine given prophylactically in combination with high-dose methotrexate and cytarabine to patients with acute lymphocytic leukemia. *Blood* 2007;**109**:3214-18.
8. Bhojwani D, Sabin ND, Pei D, Yang JJ, Khan RB, Panetta JC, et al. Methotrexate-induced neurotoxicity and leukoencephalopathy in childhood acute lymphoblastic leukemia. *Journal of clinical oncology* 2014;**32**:949.
9. Pui CH, Pei D, Sandlund JT, Ribeiro RC, Rubnitz JE, Raimondi SC, et al. Long-term results of St Jude Total Therapy Studies 11, 12, 13A, 13B, and 14 for childhood acute lymphoblastic leukemia. *Leukemia* 2010;**24**:371-82.
10. Hunger SP, Lu X, Devidas M. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children's oncology group. *J Clin Oncol* 2012;**30**:1663-69.
11. Grant R, Naylor B, Greenberg HS, Junck L. Clinical outcome in aggressively treated meningeal carcinomatosis. *Archives of Neurology* 1994;**51**:457-61.
12. Glantz MJ, Cole BF, Recht L, Akerley W, Mills P, Saris S, et al. High-dose intravenous methotrexate for patients with nonleukemic leptomeningeal cancer: is intrathecal chemotherapy necessary? *Journal of Clinical Oncology* 1998;**16**:1561-67.
13. Fizazi K, Asselain B, Vincent Salomon A, Jouve M, Dieras V, Palangie T, et al. Meningeal carcinomatosis in patients with breast carcinoma: Clinical features, prognostic factors, and results of a high dose intrathecal methotrexate regimen. Cancer: Interdisciplinary *International Journal of the American Cancer Society* 1996;**77**:1315-23.
14. Shuper A, Stark B, Kornreich L, Cohen IJ, Aviner S, Steinmetz A, et al. Methotrexate treatment protocols and the central nervous system: significant cure with significant neurotoxicity. *Journal of Child Neurology* 2000;**15**:573-80.
15. Pérez-Larraya JG, Palma JA, Carmona-Iragui M, Fernández-Torrón R, Irimia P, Rodríguez-Otero P, et al. Neurologic complications of intrathecal liposomal cytarabine administered prophylactically to patients with non-Hodgkin lymphoma. *Journal of Neuro-Oncology* 2011;**103**:603-09.
16. Ostermann K, Pels H, Kowoll A, Kuhnhenn J, Schlegel U. Neurologic complications after intrathecal liposomal cytarabine in combination with systemic polychemotherapy in primary CNS lymphoma. *Journal of Neuro-oncology* 2011;**103**:635-40.
17. Levinsen M, Harila-Saari A, Grell K, Jonsson OG, Taskinen M, Abrahamsson J, et al. Efficacy and toxicity of intrathecal liposomal cytarabine in first-line therapy of childhood acute lymphoblastic leukemia. *Journal of pediatric hematology/oncology* 2016;**38**:602-09.
18. Geiser CF, Bishop Y, Jaffe N, Furman L, Traggis D, Frei E. Adverse effects of intrathecal methotrexate in children with acute leukemia in remission. *Blood* 1975;**45**:189-95.

19. Byrnes DM, Dermarkarian CR, Kahn R, Kwon D, Vargas F, Hurley J, et al. Incidence of neurological complications secondary to intrathecal chemotherapy used as either prophylaxis or treatment of leptomeningeal carcinomatosis. *Blood* 2016;**128**:5973.

20. Zeng G, Ma H, Wang X, Yan H, Wan X, Jiang B, et al. Paraplegia and paraparesis from intrathecal methotrexate and cytarabine contaminated with trace amounts of vincristine in China during 2007. *Journal of Clinical Oncology* 2011;**29**:1765-70.

21. Murata KY, Maeba A, Yamanegi M, Nakanishi I, Ito H. Methotrexate myelopathy after intrathecal chemotherapy: a case report. *Journal of Medical Case Reports* 2015;**9**:1-4.

22. Olmos-Jiménez R, Díaz-Carrasco MS, Cabañas-Perianes V, Pulido MV, Espuny-Miró A. Evaluation of standardized triple intrathecal therapy toxicity in oncohematological adult patients. *Farmacia Hospitalaria* 2017;**41**:611-17.

23. De la Riva P, Andres-Marín N, Gonzalo-Yubero N, Tainta-Cuezva M, Caminos N, Urtasun-Ocariz MÁ, et al. Headache and other complications following intrathecal chemotherapy administration. *Cephalalgia* 2017;**37**:1109-10.

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ORIGINAL ARTICLE

# Clinico-pathological Profile of Childhood Non-hodgkin Lymphoma (NHL) in A Tertiary Care Hospital in Bangladesh

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**Abstract**

***Background:*** *Non-Hodgkin Lymphoma (NHL) is the third most common childhood malignancy. With histopathology based intensive chemotherapy and CNS-directed therapy, survival can reach more than 80%.*

***Objective:*** *The study was conducted to observe the clinico-pathological findings of NHL in Bangladeshi children.*

***Methods:*** *A prospective observational study was conducted in the Paediatric Haematology and Oncology Department of BSMMU from June 2012 to December 2012. Newly diagnosed NHL patients were included in the study. Patient's initial clinical presentations, time interval from onset of symptoms to diagnosis were recorded. Diagnostic and staging workups were done by CBC, biochemistry, radio-imaging, histopathology (FNAC/excision biopsy), serous fluids/CSF cytology (cytospin), and bone marrow aspiration.*

***Result:*** *Among the 34 patients, BL had preponderance (n=23, 68%) then LL. Median age was 7.6 years. Male: female ratio was 2.1:1. Delayed diagnosis was found in 59% patient. Primary sites were abdomen (65%), thorax (32%), and head-neck (3%). At initial presentation, 83% patients of Burkitt NHL and 100% Lymphoblastic NHL patients came with advanced disease. Bone marrow involvement was found in 23.6% patients and 12% had CNS involvement at their presentation. Irrespective to histology, most common stage was stage-III, which was 53% and then stage-IV was 35%. Median LDH was 1719 U/L. Patient with abdominal variety of NHL came with abdominal complaint like pain (66%), distension (65%), ascites (48%), mass like hepatomegaly (39%), splenomegaly (26%), intussusceptions (8%), testicular involvement (4%). B symptoms were commonly found in 74% patient. Pallor (82%), anorexia, nausea & vomiting (48%), oedema (25%), peripheral lymphadenopathy (49%) were also noticed. In case of thoracic variety of NHL, most common presentation was respiratory distress (90%), superior mediastinal syndrome (SMS) (45%), with high incidence of B symptoms (90%), peripheral lymphadenopathy (72%) with other respiratory finding like chest bulging, mediastinal mass, pleural effusion was also found.*

***Conclusions:*** *About 59% childhood NHL patients tend to present with delayed diagnosis and 88% with advanced disease. Burkitt NHL is the commonest childhood lymphoma, mostly presented with abdominal complaint. Thoracic variety is mostly Lymphoblastic lymphoma. Histopathological findings following excisional biopsy is the most significant and confirmatory for diagnosis. Serum LDH were found significantly high level in both varieties.*

***Keywords:*** *NHL, clinical picture, LDH, diagnostic investigations.*

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## Introduction

Childhood NHL is a diverse collection of lymphoid malignancies with varied pathologies, cells of origin, natural history. The history of advances in understanding and management of NHL in the last half of twentieth century is one of the modern success stories of pediatric oncology. Advances in classification, staging, treatment and supportive care have transformed a once invariably fatal disease into one of the most curable childhood cancers.[1] Lymphoma is the third most common malignant tumor in children and adolescent in precedence of leukemia and CNS tumor.[2] It accounts approximately 7% of cancers in less than 20 years of age.[3] The vast majority (70%)[4] are high grade tumors with aggressive clinical behavior.[2,5] NHL comprises a heterogeneous group of lymphoid neoplasm. The distribution of subtypes according to WHO Classification of Tumors of Haematopoetic and Lymphoid Tissues[6] is significantly different in children and adult. In children, Lymphoblastic lymphoma was (LBL/LL) 23%, Burkitt lymphoma (BL) was 60%, and Anaplastic large-cell lymphoma was (ALCL) (17%)[5] while the proportion of Diffuse large B-cell lymphoma (DLBCL) increases with increasing age.[7] Over the last two decades, various studies have shown consistent improvement in overall prognosis.[8] Event free survival (EFS) ranges between 80-90% in B-cell lymphomas,[8-10] and only slightly lowers in LL & ALCL.[11,12] Patient with BM and/or CNS involvement at diagnosis required more intensive therapy and have the worst prognosis.[10,13,14]

Despite its high cure rates in developed countries, the success is not mirrored in resource poor countries. Being a limited resource country, Bangladesh has also inferior survival rates with so many obstacles. Lack of awareness among health care providers for early symptoms of cancer is considered to be the predominant reason for delayed diagnosis with advanced disease, thus resulting inferior outcome and more disappointing treatment result. This study looks into presenting features of childhood NHL of different histopathology in patients who came to BSSMU, and thus helps to share knowledge for early diagnosis among health care professionals and ensures better outcome of our NHL children.

## Materials and Methods

This prospective observational study was conducted in the Paediatric Haematology and Oncology Department of Bangabandhu Sheikh Mujib Medical University (BSMMU). Initially total 40 newly diagnosed children with NHL were enrolled from June 2012 to December 2012 but after full filling the exclusion criteria only 34 children were observed for this study. Patients with previous history of malignancy, history receiving chemotherapy or radiotherapy, patients who abandoned treatment in early phase (<5 days), and having predisposing factors like immuno-deficiency, HIV infection, previous transplantation were excluded. For each child a semi-structured questionnaire was prepared; informed written consents were obtained from parents of patients.

All patients were divided into two groups by clinico-histopathological findings (1) Group-A Burkitt NHL (n=24) and (2) Group-B Lymphoblastic NHL (n=11). Histopathological classification was made according to WHO classification for hematological malignancies. As the immunohistochemistry was not available & affordable for all patients; abdominal localizations were included in group for Burkitt lymphoma/B-cell, while those of mediastinal or thoracic involvement were included in therapy group for Lymphoblastic lymphoma/T-cell. They were treated with intensive systemic chemotherapy protocols; LMB-96 protocol for Burkitt group and BFM-95 protocol for Lymphoblastic group.

All patients had undergone for pre-treatment evaluation which included complete history and physical examination, haematological & biochemical investigations including complete blood picture, biochemistry, and coagulation profile. Percutaneous iliac crest bone marrow aspiration for morphological studies and cytospin analyses of CSF were done in every patient to see involvement in these sites. Cytospin analyses of serous fluids were also done in cases of malignant effusions. Imaging studies included chest x-ray, ultrasonography of abdomen and, for some patients, CT-abdomen, CT-chests were done. Patient who had complete resection of tumor were considered as stage-II. But if tumor was not resected or incompletely resected, then they were considered as stage III-IV.

## Results

After discarding patients following exclusion criteria, 34 patients were analyzed. Among them 23(67.6%) had BL, 11(32.4%) had LL. Male female ratio was 2.1:1 (BL 2.8:1 and LL 1.2:1). Median age was 7.5 years (range: 2-13 years) for BL 6 years and LL 9 years. Age distribution showed 5-9 years age group was the commonest, 50% (Table I).

**Table I**
*Patients demographics and characteristics*

| Traits | Frequency | % | Burkitt Lymphoma (BL) Frequency | % | Lymphoblastic Lymphoma(LL) Frequency | % |
|---|---|---|---|---|---|---|
| No of patients | 34 | - | 23 | 67.6 | 11 | 32.4 |
| Age (years) | | | | | | |
| Median | 7.5 | | 6 | | 9 | |
| Range (years) | 2-13 | | 2-13 | | 5-13 | |
| Age group | | | | | | |
| 0-4 yrs | 7 | 20.6 | | | | |
| 5-9 yrs | 17 | 50 | | | | |
| 10-14 yrs | 10 | 29.4 | | | | |
| 15-17 yrs | 0 | | | | | |
| Sex | | | | | | |
| Male | 23 | 67.6 | 17 | 74 | 6 | 54.5 |
| Female | 11 | 32.4 | 6 | 26 | 5 | 45.5 |
| Male female ratio | 2.1:1 | | 2.8:1 | | 1.2:1 | |
| Primary site | | | | | | |
| Abdomen | 22 | 65 | | | | |
| Head neck | 1 | 32 | | | | |
| Thorax | 11 | 3 | | | | |

Most common primary site was 'Abdomen' 22 (65%), next were 'Thorax' 11 (32%) and 'Head-neck' 1(3%) (Table I). On histological basis, all this thoracic variety found LL, abdominal & head-neck region were BL. Irrespective to histology, most common stage was stage-III 53%, and stage-IV was 35%, stage-II was 12% (Fig.-1). At initial presentation, 83% patients of BL came with advanced disease. Most common group was stage-III 43.5%, next stage-IV 39.1% and stage-II 17.4% patients. No patient found in stage-I. On the other hand, 100% LL patients came with advanced disease at their initial presentation; stage-III 73% and stage-IV 27%. No patient found in stage-I, II (Fig.-2).

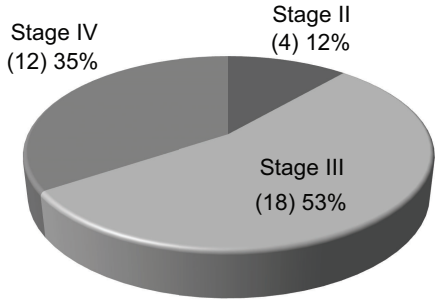


**Fig.-1** *Distribution of stage in all childhood NHL (n= 34)*

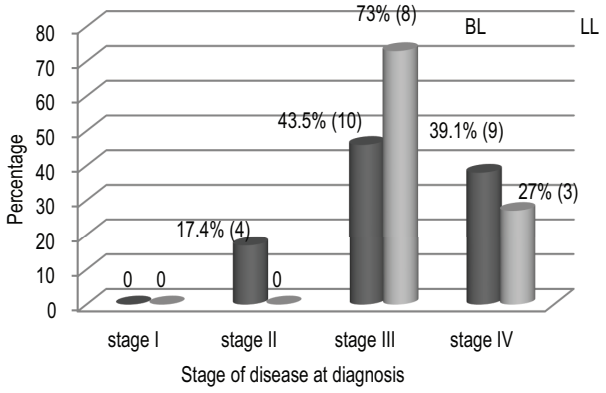


**Fig.-2** *Distribution of stage of tumor in different histological sub types of NHL (n=34)*

**Table II**
*Dissemination of childhood NHL at diagnosis (n=34)*

| Prognostic factor | All patient (n=34) | | Burkitt Lymphoma (BL) (n=23) | | Lymphoblastic (LL) (n=11) | |
|---|---|---|---|---|---|---|
| | No of patient | Percentage | No of patient | Percentage | No of patient | Percentage |
| Bone Marrow (BM) involvement | | | | | | |
| Yes | 8 | 23.6 | 6 | 26 | 2 | 18 |
| M2 =5-25% blast | 3 | 37.5 | 2 | 33 | 1 | 50 |
| M3 =>25% blast | 5 | 62.5 | 4 | 67 | 1 | 50 |
| No (M1 = <5%blast) | 26 | 76.4 | 17 | 74 | 9 | 82 |
| CNS involvement | | | | | | |
| Yes | 4 | 11.8 | 3 | 13 | 1 | 9 |
| CNP (Cranial nerve palsy) | 1 | 25 | | | 1 | 100 |
| CSF blast (cytospin) | 1 | 25 | 1 | 33 | 0 | 0 |
| CNP+CSF blast | 2 | 50 | 2 | 67 | 0 | 0 |
| No | 30 | 88.2 | 20 | 87 | 10 | 91 |

In this study, out of 34 patients, 8 (23.6%) patients had bone marrow involvement. Of them M2 (5-25% blast) was in 37.5%, M3 (>25% blast) was in 62.5% patients. According to histology, 26% of all BL & 18% of all LL had BM involvement at their diagnosis. In case of BL patient M2 found in 33%, M3 in 67% patients. In LL, 50% had M2, 50% had M3 [Table-II]. CNS involvement found in 4(11.8%) patients; of them 25% presented with cranial nerve palsy (CNP), 25% had blast in their CSF, and 50% had both findings together. According to historlogical distribution, 13% of all BL and 9% of all LL had CNS involvement at the time of their diagnosis (Table II).

In this study, definitive diagnosis had been done by histopathology, cytology of serous fluid, and immunohistochemistry. Out of 34 patients, 24 patients were diagnosed by histopathology, of them 10 had excision biopsy & 14 had fine needle aspiration (FNAC). Fifteen patients were diagnosed by cytology of serous fluid (i.e. peritoneal fluid, pericardial fluid) to see malignant cell by cytospin analysis. Immunohistochemistry were done in 8(23.5%) patients with Leucocyte Common Antigen (LCA), CD20, CD3. It revealed 4(11.8%) had B cell (LCA & CD20 positive) and 4(11.8%) had T cell (LCA, CD3 positive). One patient may had more than one method to diagnose the disease

LDH is one of the most important prognostic factors, indicating tumor load at diagnosis. In this study, most patients had high level of LDH in serum (Fig.-3); most common level group was 400-1000 U/L (>2 times above than upper limit of normal) found in 32% patient. Next common group was >4000 U/L (>10 times above than upper limit of normal) found in 21% patients. Median LDH was 1719 U/L, minimum 348 U/L and maximum 8790 U/L.

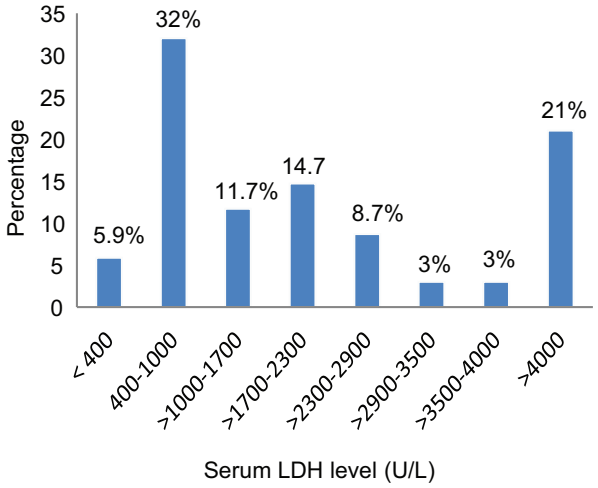


**Fig.-3** *Distribution of Serum Lactate Dehydrogenase (LDH) level at diagnosis (n=34)*

Along with abdominal complaint patient with abdominal variety of NHL came with Pallor (82%), B symptoms (74%), peripheral lymphadenopathy (49%), respiratory distress (48%), anorexia, nausea & vomiting (48%) (Fig.-4). In case of thoracic variety of NHL, most common presentation was respiratory distress (90%), with high incidence of B symptoms (90%), peripheral lymphadenopathy (72%) with superior mediastinal syndrome (SMS) (45%), and also hepatomegaly (72%) (Fig.-5).

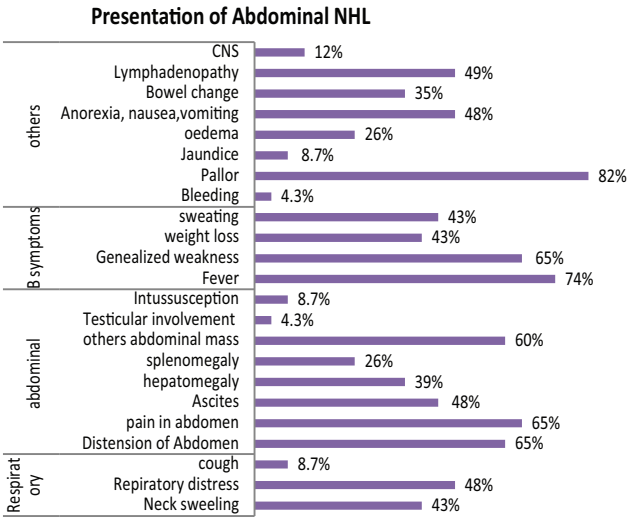


**Fig.-4** *Clinical presentation of abdominal variety of NHL*

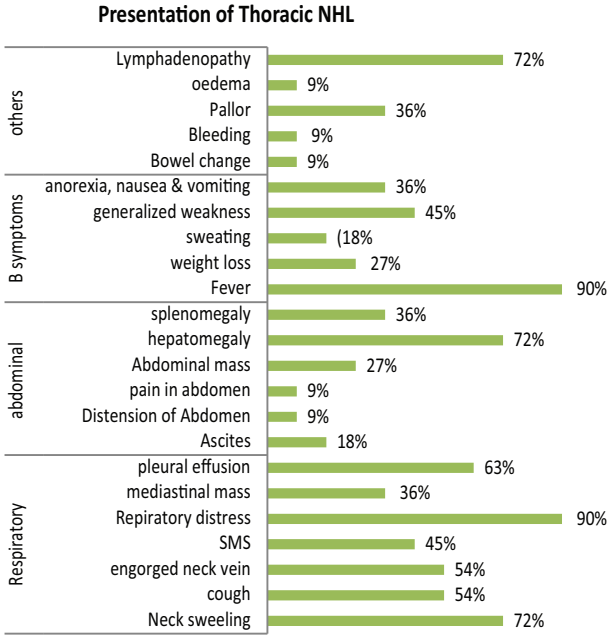


**Fig.-5** *Clinical presentation of Thoracic variety of NHL*

A good number of patients (59%) presented with delayed diagnosis (required >30 days from onset of symptoms to diagnosis), 32% came within 4 weeks, and only 9% came early (within <2 weeks) (Fig.-6).

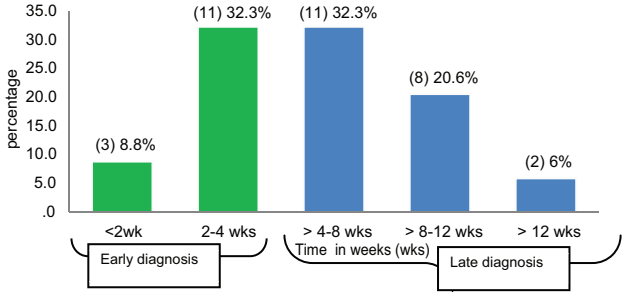


**Fig 6** *Time interval between the onsets of symptoms to diagnosis ( n=34)*

## Discussion

After analysing 34 newly diagnosed childhood NHL patient, it was observed that a good number (38%) patients had delayed diagnosis and so that had delayed start of treatment. It was as like Pedrosa et al[15] study who stated 40% patients had delayed diagnosis and duration of symptoms were on average 50 days. Median age was found 7.5 years, ranging 2-13 years. According to National Cancer Institute (NCI), NHL is rare under 5 years of age but in this study 21% patients were found less than 5 years old at the time of diagnosis. There was no patient under 2 years of age as similar to Sandlund et al[3] analysis. Male were 23 (68%) and female 11 (32%); with ratio 2.1:1.

In this study, primary site of tumor was abdomen in 65%, 32% in thorax and 3% in head-neck region. About 88% patients presented with advanced disease (stage-III, IV) and only 11% presented with localized diseases (stage-I, II). Most common stage was stage-III (53%) and next common was stage-IV(35%). In group observations, all (100%) LL patients and 83.5% of BL had advanced disease. At initial presentation, 23.6% patient came with bone marrow involvement and 11.8% patients had CNS involvement. This result was very similar with the study conducted in St. Jude research hospital by Sandlund et al[16] and Murphy et al[17]. On clinical presentation overview, 96% of BL patients presented with pre-dominantly abdominal disease and 4% in nasopharynx (head-neck region). Sandlund et al[3] also found similar result. Patient came with abdominal complaint like pain (66%), distension of abdomen (65%), ascites (48%), abdominal mass (60%), hepatomegaly (39%), splenomegaly (26%), intussusceptions (8.7%),

testicular involvement (4%). B symptoms were common 74%, respiratory distress noticed in 48% patient. Pallor (82%), anorexia & nausea-vomiting (48%), oedema (25%), peripheral lymphadenopathy (49%) were also noticed. Morsi et al[18] found most common symptom in abdominal NHL was abdominal pain (81.4%), abdominal swelling (76.7%). Martin et al[19] found that, abdominal tumors are associated with abdominal pain, constipation, masses, or ascites. On the other hand, in patient with thoracic variety of NHL most common presentation was respiratory distress (90%), superior mediastinal syndrome (SMS) (45%), mediastinal mass (36%), pleural effusion (63%), along with high incidence of B symptoms (90%), peripheral lymphadenopathy (72%), hepatomegaly (72%). Zhang et al[20] also found mediastinal mass as the most common feature in thoracic NHL.

Due to misdiagnosis, 4 patients were initially diagnosed as TB and treated with anti TB drugs, 1 had steroid therapy before coming here. Five (83%) patient had surgery due to acute condition of abdomen, intussusceptions, abdominal mass before refereeing. In this study, definitive diagnosis of NHL were done by histopathology, cytology of serous fluid and immunohistochemistry. Reiter et al[12] also suggested these investigations to diagnose NHL. With the relation to the histological subtypes, BL was observed to be predominant in this study, affecting 68% patients, rest 32% was LL as like Pedrosa et al[15] studied in Brazil. Elevated serum LDH levels were found in 94% patients, median 1719 U/L, ranges from 348-8790 U/L. Pillon et al[21] found serum LDH 1191 U/L. Although it is non-specific, but it is a good marker of tumor burden and proliferation rate, and has a prognostic value.[9,13] Patte et al[13], Reiter et al[12] studied that treatment should be based on histopathology of tumor mass, and so for this in this study chemotherapy protocol were selected according to histologic subtypes. Here, all BL patients received intensive chemotherapy with 'NHL-FAB-LMB-96' protocol according to their dissemination of disease at diagnosis,[22] all LL patients received chemotherapy with NHL-BFM-95 protocol. Radiotherapy no longer appears to have a role in treatment of primary CNS disease, and radical surgery with its potential risks, has become unnecessary.[13,23-25] So no local/cranial radiotherapy administered in any group of patients and surgery had been done with limitation. For this treatment plan, histopathology plays the most important role.

With the help of major advances in diagnosis, multimodality therapy, development of the rational use of combination chemotherapy and improved supportive care, cure rate of childhood cancer has been increased tremendously. But still now in our country one of the main lacking is delayed or improper diagnosis, this makes patient presented with advanced disease at diagnosis. More the advanced disease the treatment approach and outcome out will be worse.

## Conclusion

Childhood NHL is one of the most common malignancy of young age, median age 6 years for Burkitt and 9 years for Lymphoblastic Lymphoma. Usually tends to present with delayed diagnosis with advanced disease. Abdominal varieties were mostly Burkitt lymphoma; revealed B-cell type in immunohistochemistry. They presented with abdominal pain, abdominal mass, ascites, intussusceptions, testicular involvement. Thoracic varieties were commonly Lymphoblastic lymphoma, mostly T-cell type. They usually presented with respiratory distress, superior mediastinal syndrome (SMS), mediastinal mass, pleural effusions. B symptoms, pallor, respiratory distress, peripheral lymphadenopathy were common in both groups. Serum LDH were found significantly high level. Histopathological findings following excisional biopsy is the most significant and confirmatory for diagnosis.

## References


1. Perkins SL, Morris SW. Chapter 6, Biology and pathology of pediatric NHL. In: Weinstein JH, Hudson MM, Link MP, editors. Paediatric lymphoma. New York (NY): Springer; 2007. P91-107
2. Bakshi S. Childhood non-hodgkin lymphoma: clinical profile. *Indian J Med Paediatr Oncol* 2004;**24** (4)suppl. 2:27-29.
3. Sandlund T, Downing R, Crist WM. Non-Hodgkin's lymphoma in childhood. *N Engl J Med* 1996;9;**334**: 1238-48.
4. Kusumakumary P, Shanavas A, Priyakumari T, Chellam VG, Nair MK. Non-hodgkin's lymphoma in children: Disease pattern and survival. *Pediatric Hematology-Oncology* 1998;**15**:509-17.
5. Reiter A. Treating Non-hodgkin lymphoma in children and adolescents- current experience and future directions. Presented at: 5th St. Jude Viva Forum, session-hematological malignancies in children. 2011 March 21-23;Singapore. Available from: www.viva.sg/stjude/presentationsFromSJVF2011.html [Accessed on 28.09.20].
6. Vardiman JW, Brunning AD, Arter DA, Porwit A. Introduction and overview of the classification of the lymphoid neoplasms. In: Jaffe ES, Stein H, Swerdlow SH, editors. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. Lyon, France: International Agency for Research on Cancer (IARC), 2008;P157-66.

7. Reiter A. Diagnosis and treatment of childhood non-hodgkin's lymphoma. *Hematology American Society of Hematology Education Program* 2007;285-96.

8. Patte C, Auperin A, Michon J, Behrendt H, Leverger G, Frappaz D, et al. The Societe Francaise d'Oncologie Pediatrique LMB 89 protocol: highly effective multiagent chemotherapy tailored to the tumor burden and initial response in 561 unselected children with B-cell lymphomas and L3 leukemia. *Blood* 2001;**97**:3370-79.

9. Reiter A, Schrappe M, Tiemann M, Ludwig WD, Yakisan E, Zimmermann M, et al. Improved treatment results in childhood B-cell neoplasms with tailored intensification of therapy: A report of the Berlin-Frankfurt-Munster Group Trial NHL-BFM90. *Blood* 1999;**94**:3294-3306.

10. Atra A, Imeson JD, Hobson R, Gerrard M, Hann IM, Eden OB, et al. Improved outcome in children with advanced stage B-cell non Hodgkin's lymphoma (B-NHL): Results of the United Kingdom Children Cancer Study Group (UKCCSG) 9002 protocol. *Br J Cancer* 2000;**82**:1396-1402.

11. Reiter A, Schrappe M, Tiemann M, Ludwig WD, Parwaresch R, Zimmermann M, et al. Intensive ALL-type therapy without local radiotherapy provides a 90% event-free survival for children with T-cell lymphoblastic lymphoma: A BFM Group report. *Blood* 2000;**95**:416-21.

12. Brugieres L, Deley MC, Le Deley, Pacquement H, Meguerian BZ, Terrier-Lacombe MJ, et al. CD 30(þ) anaplastic large-cell lymphoma in children: Analysis of 82 patients enrolled in two consecutive studies of French Society of Pediatric Oncology. *Blood* 1998;**92**:3591-98.

13. Patte C, Auperin A, Gerrard M, Michon J, Pinkerton R, Sposto R, et al. Results of the randomized international FAB/LMB96 trial for intermediate risk B-cell non-Hodgkin lymphoma in children and adolescents: it is possible to reduce treatment for the early responding patients. *Blood* 2007;**109**:2773-80.

14. Cairo MS, Gerrard M, Sposto R. Poor response to initial reduction therapy (COP) and combined bone marrow and CNS disease are poor prognostic factors in children with advanced (BM+CNS) B-NHL treated on the international study FAB/LMB96 [Abstract]. *Blood* 2003;**102**:492.

15. Pedrosa MF, Pedrosa F, Lins MM, Nicodemos T, Pontes N, Falbo G. Non-hodgkin's lymphoma in childhood: clinical and epidemiological characteristics and survival analysis at a single center in Northeast Brazil. *J Pediatr (Rio J)* 2007;**83**:547-54.

16. Sandlund JT, Murphy SB, Santana VM, Behm F, Dana J, Costan WB, et al. CNS involvement in children with newly diagnosed non-hodgkin's lymphoma. *J Clin Oncol* 2000;**18**:3018-24.

17. Murphy SB. Classification, staging and end results of treatment of childhood non-Hodgkin's lymphomas: dissimilarities from lymphomas in adults. *Semin Oncol* 1980;7:332-39.

18. Morsi A, Abd El-Ghani MA, Majed ES, Fawzy M, Ismail H, Manar M. Clinico-pathological features and outcome of management of pediatric gastrointestinal lymphoma. *Journal of the Egyptian Nat Cancer Inst* 2005;**17**:251-59.

19. Johnston JM, Coppes MJ. Pediatric Non-Hodgkin Lymphoma. In: Medscape Drugs Disease & Procedures [Internet]: USA. Available from: www.emedicine,medscape.com/article/987540-overview.

20. Zhang Y, Zhang R, Jin L, Yang J, Duan Y, Zhou C, et al. Clinical outcome of 319 children with non-hodgkin lymphoma treated in a single center in China. In: fourth international symposium on childhood, adolescence and young adult non hodgkins lymphoma, 2012 Nov 1-3, New York, USA. *BJH* [Abstract no 44 on Internet] 2012;**159**(Suppl.s1):1-73.

21. Pilon M, Piglione M, Garaventa A, Conter V, Giuliano M, Arcamone G, et al. Long term results of AIEOP LNH-92 protocol for the treatment of paedatric lymphoblastic lymphoma: a report of the Italian Association of pediatric hematology and oncology. *Paediatric Blood and Cancer* 2009;**53**:953-59.

22. Cairo MS, Gerrard M, Sposto R, Auperin A, Pinkerton CR, Michon J,et al. Results of a randomized international study of high-risk central nervous system B non-Hodgkin lymphoma and B acute lymphoblastic leukemia in children and adolescents. *Blood* 2007;**109**:2736-43.

23. Patte C, Philip T, Rodary C, Bernrd A, Zuker JM, Bernard JL, et al. Improved survival rate in children with Stage III and IV B-cell non-Hodgkin's lymphoma and leukaemia using multi-agent chemotherapy: results of a study of 114 children from the French Pediatric Oncology Society. *J Clin Oncol* 1986;**4**: 1219-26.

24. Miron I, Frappaz D, Brunat MM, Combaret V, Buclon M, Bouffet E. Initial management of advanced Burkitt lymphoma in children: Is there still a place for surgery? *Ped Hem Oncol* 1997;**14**:555-56.

25. Al-Attar A, Atra A, Al-Bagdadi R, Al-Naimi M, Al-Saleem T, Pritchard J. 'Debulking' surgery is unnecessary in advanced abdominal Burkitt lymphoma in Iraq. *Br J Cancer* 1989;**59**:610-12.

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ORIGINAL ARTICLE

# Prevalence of Infection and Changing Pattern of Organisms Causing Infections in Childhood Nephrotic Syndrome

**KM Sarwar Mahmud[1], Rubina Afroz Rana[2]**

**Abstract**

***Background:*** *Infection remains an important complication of children with nephrotic syndrome. It results in significant morbidity and may also be responsible for a poor response to steroid therapy or induce relapse in child who has already attained remission.*

***Objectives:*** *This study was conducted to find out pattern of infection and type of organisms causing infections in nephrotic syndrome.*

***Methods:*** *This cross sectional study was conducted in the Paediatric Nephrology Department of Dhaka Shishu (Children) Hospital from January 2010 to November 2010. One hundred fifteen (115) cases of nephrotic syndrome, age between 1 to 13 years were enrolled according to the inclusion criteria. Along with routine investigations, urine, blood and throat swab culture and sensitivity and MT test were done. Risk factors of infection were also determined. Statistical analysis was done by SPSS version 12. Level of significance was taken as <0.05.*

***Results:*** *Prevalence of infection in nephrotic syndrome was 54.78%. Infections were more common in childhood nephrotic syndrome below 6 years of age. Infections encountered in nephrotic syndrome were UTI 51(44.34%), septicemia 4(3.47%), pneumonia 5(4.34%), peritonitis 1(0.87%), cellulitis 1(0.87%) and tuberculosis 1(0.87%). Statistically significant risk factors associated with infection were generalized edema, steroid dependence, steroid resistance, persistent proteinuria and high spot urine protein creatinine ratio. In case of UTI E. coli was the commonest 27(52.9%) organism followed by Morganella and Pseudomonas 5(9.8%).*

***Conclusion:*** *Prevalence of infection in nephrotic syndrome is very high and E. coli is the commonest organism found in this study. Generalized edema, persistent proteinuria, hypoalbuminemia, steroid dependence, steroid resistance are important risk factors for infection.*

***Keywords:*** *Prevalence, infection, organisms, childhood nephrotic syndrome.*

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## Introduction

About one third of every nephrotic syndrome admission was due to an infection. In a study the rate of infection was 38%.[1] A recent study by Moorani et al[2] points to URTI, cellulitis, diarrhoea UTI and peritonitis as the most frequent infections. In the various published results, the type of infection is variable.[3] In a study conducted by Senguttuvan et al[4] found UTI is the commonest infection followed by peritonitis, acute RTI and tuberculosis. Regarding bacteriology of UTI, 76.7% urine cultures are positive and 23.3% are culture negative. Regarding causative organisms, E.coli was the commonest organisms (36.6%) followed by Klebsiella (27.5%). This varies from the study by Gulati et al. where E. coli was responsible for 60% cases and non E. coli organisms accounted for 39% of the culture isolates in UTI.[5] In children with nephrotic syndrome serious infection may be acute and fulminate and manifest with vague or nonspecific features, which may delay an early diagnosis.[6] Because fever and physical findings may be minimal in the presence of corticosteroid therapy. A high index of suspicion, prompt evaluation and early initiation of antibiotic therapy are critical.[7] Occult infections may manifest as a steroid non response or relapse in a child who has already attained remission.

Therefore it is essential to know the current trend of prevalence of infection in children with nephrotic syndrome, the organisms prevalent in our set up to decide about appropriate antibiotics, duration of treatment, and to observe the response of treatment and how quick patients enter into remission. The knowledge of the etiological profile of infection in nephrotic children will help to raise the awareness level of treating physicians so that avoidable infectious process could be minimized. It is important to know the infectious agents and their sensitivity pattern among the nephrotic patients who are already immunocompromized and also need treatment with immunosuppressive agents. Different study conducted in both developed and developing countries showing different prevalence rate for different type of infections and changing organisms are also found. There is also a changing pattern of antibiotics sensitivity.

There is overcrowding, malnutrition, increased prevalence of infections in Bangladesh and patients with nephrotic syndrome are immunocompromised. So the study is designed to find out the type of infections and their changing pattern of sensitivity to antibiotics to reduce the morbidity and mortality.

## Materials and Methods

This cross sectional study was conducted in the Pediatric Nephrology Department of Dhaka Shishu (Children) Hospital from January 2010 to November 2010. Prior to the commencement of this study the research was approved by the Institutional Ethical Review Committee. All Nephrotic Syndrome patients admitted in hospital during study period were included in the study. Critically ill patients having respiratory distress, children with ARF/CRF/Urogenital anomalies were excluded from the study. Risk factors of infection were also determined.

Thorough history taking and elaborate clinical examination was performed and recorded on an appropriate questionnaire. Routine investigations like urine microscopy, urine culture, spot urine protein creatinine ratio, lipid profile, complete blood count (CBC) with examination of the blood film, platelet count, ESR, serum total protein (STP), serum albumin, serum electrolytes, blood urea, serum creatinine and ultra sonography of KUB region were done in all patients. Renal biopsy was done in cases where there were indications like: persistent hematuria, persistant hypertension, hypocomplementemia, impaired renal functions, frequently relapsing nephrotic syndrome (FRNS) with steroid toxicity, FRNS with steroid dependence, steroid non responders.

HBsAg and anti HCV was performed in all patients by ELISA. These children were screened for other infections by one or more of the following investigations as needed: peritoneal fluid and cerebrospinal fluid examination (Gram stain, cytology, biochemistry and culture); chest X-ray.

Along with routine investigations, urine culture and sensitivity, blood culture and sensitivity, throat swab culture and sensitivity, MT test was done. Urine specimens were collected under the direct supervision of staff nurse or doctor after proper cleaning of the genital area with soap and water thoroughly. In case of boys the glance was washed by retracting the foreskin and in case of girls urine was collected after washing the vulva with their legs and labia apart. Clean catch, freshly voided, midstream urine was collected in a sterile container and were transferred to the laboratory and was subjected to microscopy as early as possible. Urine and blood culture was done on blood agar and McConkeys agar media. A positive urine culture was defined as midstream clean voided specimens with isolation of $>10^5$ CFU/ml of a single organism. When the colony count was $<10^4$ organisms/ml, or when there was mixed growth, culture was repeated.

All investigations were done in the microbiology, pathology and biochemistry department of Dhaka Shishu (Children) Hospital. Radiological investigations i.e., chest X-ray and ultrasonography (USG) of the kidney, ureter and bladder (KUB) region was done at the Department of Radiology, Dhaka Shishu (Children) Hospital.

Data entry and analysis was done by using SPSS version 12. In addition to descriptive statistics such as frequency tabulation, mean, standard deviation, statistical test such as 't' test was applied accordingly to determine statistically significant association. Level of significance was taken as <0.05.

## Results

A total of 115 nephrotic syndrome children were included in this study and among them 63(54.78%) presented with infection (Fig.-1).

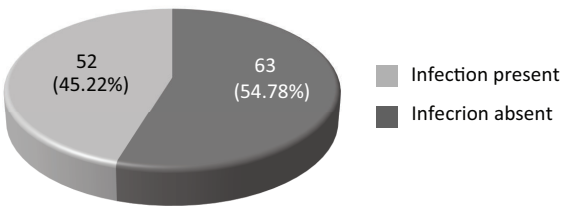


**Fig.-1** *Prevalence of infection in nephrotic syndrome (N=115)*

Infection in nephrotic syndrome was common (63.49%) in children age between 2-6 years (Table I).

**Table I**
*Age distribution of Nephrotic Syndrome patients (N=115)*

| Age in years | Number of patients (Percent) | With infection (n=63) |
|---|---|---|
| <2 yrs | 4(3.47) | 3(4.76) |
| 2-6 yrs | 61(53.04) | 40(63.49) |
| >6 yrs | 50(43.47) | 20(31.75) |

Most common infection in nephrotic syndrome is UTI. Out of 115 patients 51(44.34%) had UTI, followed by Pneumonia 5(4.34%), Septicemia 4(3.47%), Peritonitis 1(0.87%), Cellulitis1(0.87%) and Tuberculosis 1(0.87%) [Fig.-2].

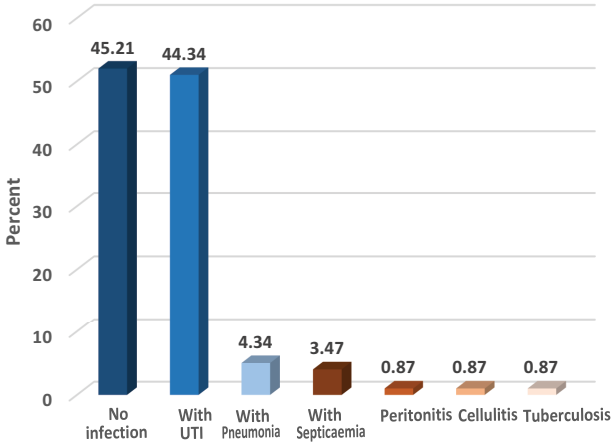


**Fig.-2** *Pattern of infections in nephrotic syndrome*

Statistically significant risk factors associated with infection were generalized edema, steroid dependence, steroid resistance, persistent proteinuria and high spot urine protein creatinine ratio (Table-II).

**Table-II**
*Risk factors of infection in nephrotic syndrome*

| Risk factors | | Infection | | $\chi^2$ | p value |
|---|---|---|---|---|---|
| | | Present | Absent | | |
| Age | <6 years | 28 | 37 | 1.351 | 0.16 |
| | >6 years | 27 | 23 | | |
| Sex | Male | 35 | 46 | 2.340 | 0.09 |
| | Female | 20 | 14 | | |
| Relapse | Present | 46 | 50 | 0.002 | 0.58 |
| | Absent | 9 | 10 | | |
| Steroid dependence | Present | 14 | 06 | 4.771 | 0.03 |
| | Absent | 41 | 54 | | |
| Steroid Resistance | Present | 15 | 3 | 10.782 | 0.001 |
| | Absent | 40 | 57 | | |
| Facial puffiness | Present | 54 | 58 | 0.259 | 0.53 |
| | Absent | 1 | 2 | | |
| Leg edema | Present | 54 | 58 | 0.259 | 0.53 |
| | Absent | 1 | 20 | | |
| Swelling of the genitalia | Present | 53 | 60 | 2.220 | 0.23 |
| | Absent | 2 | 0 | | |
| Generalized anasarca | Present | 15 | 6 | 5.736 | 0.02 |
| | Absent | 40 | 54 | | |
| Oliguria | Present | 54 | 56 | 1.622 | 0.21 |
| | Absent | 1 | 4 | | |
| Fever (Temp $>100^0$F) | Present | 41 | 44 | 0.022 | 0.53 |
| | Absent | 14 | 16 | | |
| Pain abdomen | Present | 51 | 57 | 0.259 | 0.45 |
| | Absent | 4 | 3 | | |
| Vomiting | Present | 52 | 54 | 0.822 | 0.29 |
| | Absent | 3 | 6 | | |
| Skin infection | Present | 52 | 59 | 1.226 | 0.28 |
| | Absent | 3 | 1 | | |
| Sore throat | Present | 53 | 60 | 20220 | 0.23 |
| | Absent | 2 | 0 | | |
| Immunization | Immunized | 41 | 40 | 0.855 | 0.23 |
| | Not immunized | 14 | 20 | | |
| Albumin in urine | <2.5+ | 1 | 8 | 5.275 | 0.02 |
| | >2.5+ | 54 | 52 | | |
| RBC in urine | <25 | 41 | 52 | 2.725 | 0.08 |
| | >25 | 14 | 08 | | |
| Protein creatinine ratio | <2 | 16 | 6 | 6.760 | 0.01 |
| | >2 | 39 | 54 | | |
| Pus cell | >20/HPF | 32 | 6 | 6.760 | 0.01 |
| | <20/HPF | 39 | 54 | | |

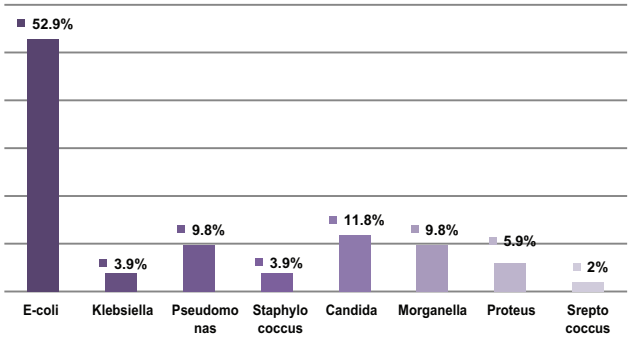


**Fig.-3** *Organisms causing UTI in patients having nephrotic syndrome (n=51)*

Out of 51 UTI cases, 27 caused by E.coli (52.9%), followded by Pseudomonas 5(9.8%) & Morganella 5(9.8%).

**Discussion**

A total of 115 nephrotic syndrome children were included in this study. Infection was present in 63(54.78%) cases. Infection in nephrotic syndrome was common (63.49%) in children age between 2-6 years. Most common infection in nephrotic syndrome was UTI. Out of 115 patients 51(44.34%) had UTI, followed by Pneumonia 5(4.34%), Septicemia 4(3.47%), Peritonitis 1(0.87%), Cellulitis 1(0.87%) and Tuberculosis 1(0.87%). Statistically significant risk factors associated with infection were generalized edema, steroid dependent, steroid resistance, persistent proteinuria and high spot urine protein creatinine ratio. Out 51 UTI cases, 27 caused by E.coli (52.9%), followded by Pseudomonas 5(9.8%) & Morganella 5(9.8%). This finding is consistent with Shenguttuvan et al[4] report where they found 62.7 % infection in Children below 6 years of age. The mean age of 4.5 years was also observed by Chowdhury et al[8] in Bangladesh, whereas Gulati et al[5] found the mean age to be 6.2 years. In this study increased susceptibility to UTI in lower age group nephrotic children may be due to significant hypoalbuminemia, this factor may have a pathophysiological role in predisposing lower age group children to infection. Moreover, nephrotic syndrome in childhood is common between two to six years of ages, and they were found more immunodeficient during active disease and more prone to bacterial infection.[7]

Majority of our study population were from rural areas (73.19%). Our study subjects were mostly from poor and average social class (52.17%). It had a definite reason because the patients from different parts of the country were referred to Dhaka Shishu (Children) Hospital and treatment cost was minimum. Most of the mothers were illiterate or with primary education. So they had very poor knowledge regarding hygiene, sanitation and ifection control. In this study we could not find measles or varicella infection but tuberculosis cases were detected. It reflects the effect of successful immunization programme against those diseases.

The prevalence of UTI in this study population was 51(44.35) which was consistent with previous studies 40.26% by Gulati et al[5], 46% Shenguttuvan et al[4], 65.20% by Karim et al[9], 58.83% by Chowdhury et al[8], 42.22% by Sultana et al[10]. But other previous studies by Gorensec et al[11]; Srivastav et al[12]; Tsa et al[13] suggested much lower incidence of UTI in nephrotic syndrome children which may be due to inclusion of only hospitalized children with complications. In this series the prevalence of UTI is 44.35% which is much higher than the prevalence of 1 to 3% reported in the general population by Stull et al[14]. Maximum UTI were asymtomatic. Steroid non response or relapse was their presenting feature and UTI was diagnosed during screenig of urine for infection as part of the study protocol. Asymtomatic UTI in nephrotic syndrome has also been found in different previous reports.[5,8]

Pus cell count >20/HPF is found in 32(62.75%) cases. Different study reported various findings regarding pyuria and UTI in general population and in cases with suspected UTI.[8,14] In general population pyuria is a recognized finding for diagnosis of UTI. But in nephrotic children pyuria has no diagnostic value; it may present as a feature of chronic disease process or may be due to steroid.

In this study among 51 culture positive cases of UTI, E. coli was the commonest organism 27(52.9%). Similar results were observed by different authors. Shenguttuvan et al[4] observed 36.6%, Gulati et al[5] observed 39%, Chowdhury et al[8] observed 80%, Sultana et al[10] observed 78.94% and 90% observed by Khan et al[15] in UTI cases with nephrotic syndrome. Non E. coli, Gram negative organism accounted for Pseudomonas 5(9.8%), Proteus 3(5.9%) and Klebsiella 2(3.9%). Morganella was 5(9.8%), Candida 6(11.8), Staphylococcus 2(3.9%) and Streptococcus 1(2%). Prasad et al[16] found similar results - 14% Pseudomonas, 8% Klebsiella in 30

nephrotic syndrome children with UTI. Emilia et al[17] also found E coli is the commonest organism followed by Klebsiella. Barua et al[18] found UTI in 30.8% nephrotic children and causative organisms were E coli 50%, Klebsiella 25%, Coliforms 18.7% and Proteus 6.3%.

## Conclusion

Prevalence of infection in nephrotic syndrome is very high and E coli is the commonest organism found in this study. Early intervention with relapse is important as generalized edema, persistent proteinuria, hypoalbuminemia, steroid dependence, steroid resistance are important risk factors for infection.

## References


1. Ahmed M. Abdominal complications in childhood nephrotic syndrome of Bangladeshi children- a hospital based study. FCPS Dissertation, 2004. Bangladesh College of Phsicians and Surgeons.
2. Moorani KN, Khan KM, Ramzan A. Infections in children with nephrotic syndrome. *J Coll Physicians Surg Pak* 2003;**13**:337-39.
3. Anderson S, Garcia DL, Brenner BM. Renal and systemic manifestations of glomerular disease. In: Brenner BM, Recter FC Jr, editors. The Kidney. 4th ed. Saunders Company, Philadelphia.P.1831-70.
4. Shenguttuvan P, Ravanan K, Prabhu N, Tamilarasi V. Infections encountered in childhood nephrotice in a pediatric renal unit. *Indan J Nephrol* 2004;14:85-88.
5. Gulati S, Sharma AP, Sharma RK, Gupta A. Changing trends of histopathology in childhood nephrotic syndrome. *Am J Kidney Dis* 1999;**34**:646-50.
6. Srivastava RN, Moudgil A, Khurana O. Serious infections and mortality in nephrotic syndrome. *Indian Pediatr* 1987;**24**:1077-80.
7. Behrman RE, Kliegman RM, Jenson HB. Nelson Texbook of Paediatric, 17th ed. Saunders Company, Philadelphia. 2004.P.1753-1757.
8. Chowdhury AC. Abdominal complications in childhood nephrotic syndrome of Bangladeshi children - a hospital based study. FCPS Dissertation, Bangladesh College of physicians and Surgeons, 1996.
9. Karim, A. 1999, 'Risk factors for relapse in childhood nephrotic syndrome-a hospital based prospective study', FCPS Dissertation, Bangladesh College of Physicians and Surgeons,1999.
10. Sultana S, Selimuzzaman M, Begum A, Hanif M. Urinary tract infection in nephrotic syndrome. *Bang Renal J* 2004;**23**:52-55.
11. Gorensek MJ, Label MH, Nelson JD. Peritonitis in children with nephrotic syndrome. *Pediatrics* 1988;**81**:849-56.
12. Srivastava RN, Moudgil A, Khurana O. Serious infections and mortality in nephrotic syndrome. *Indian Pediatr* 1987;**24**:1077-80.
13. Tas YK, Chen CH, Tsia WS, Sheu JN. Complication of nephrotic syndrome in children. *J Formos Med Assoc* 1991;**90**:555-59.
14. Stull, TL, LiPuma, JJ. Epidemiology and natural history of urinary tract infection in children. *Medical Clinics of North America* 1991;**75**:287-97.
15. Khan AR. Urinary tract infection in childhood nephrotic syndrome. FCPS Dissertation, Bangladesh College of Physicians and Surgeons; 2000.
16. Prasad S. Serum immunogloulin G (IgG) level and its predictive value in frequently relapsing nephrotic syndrome. MD Thesis, Bangladesh Institute of Child Health, Dhaka Shishu Hospital. University of Dhaka; 2005.
17. Emilia M, Dantas S, Vera H, Maria DF and Yassuhiko O. Influence of nephritic state on the infectious profile in childhood idiopathic nephoitic syndrome. *Rev Hosp Clin Fac Med S Paulo* 2004;**59**;273-78.
18. Barua T, Sultana R, Babul FK, Iqbal S, Sharma JD, Dutta PK. Urinary Tract Infection in Nephrotic Syndrome: A Hospital Based Cross-Sectional Study. *Chattagram Maa-O-Shishu Hospital Medical College Journal* 2016;**15:**41-44.

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ORIGINAL ARTICLE

# Consanguinity and Risk of Congenital Heart Defects in Bangladesh

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**Abstract**

***Background:*** *Consanguineous marriage have been associated with an increased risk to various forms of inherited disease. Potential role of consanguinity in certain common birth defects is less clear especially with congenital heart defects (CHDs).*

***Objective:*** *This study was conducted to evaluate the potential role of consanguinity as a risk factor for congenital heart defects (CHDs) in Bangladesh.*

***Methodology:*** *It was a case control study, conducted from July 2018 to July 2019 at Dhaka Shishu (Children) Hospital. Parents of the children with CHD visited the out-patient department was considered as case. Control was taken from parents of the children who didn't have congenital heart disease. Informed written consent was taken from parents. Data were collected by using a structured questionnaire containing all the variables of interest and analyzed by using SPSS version 21. Chi square test ($S\alpha^2$), Odds ratio (OR) and 95% confidence intervals (CIs) were calculated to estimate the associations between parental consanguinity and all CHDs. Risk factors on bivariate analysis were introduced into a logistic regression model as independent factors and dependent variable was CHDs to find out the association between CHDs and consanguinity.*

***Results****: Among study population consanguinity was present in 33(6.11%) cases. In the case group 23 children (8.85%) were born to consanguineous parents and in control group 10 children (3.57%) were born to consanguineous parents. CHDs were found significantly higher in children born to consanguineous parents ($p<0.05$). On logistic regression analysis consanguinity ($p=0.02$) was independently associated with CHDs. Children who born to consanguineous parents had 2.5 times risk of developing CHDs compared to those who were not born to consanguineous parents.*

***Conclusions:*** *Parental consanguinity is significantly associated with CHDs.*

***Keywords:*** *Consanguinity, Congenital Heart Defects.*

## Introduction

CHDs represent approximately one-third of all congenital anomalies and are the most common group of congenital malformations, affecting almost 1% of live births throughout the world.[1,2] Although advancement in pediatric cardiology and pediatric cardiac surgery have improved long term outcome and promised better quality of life, the etiology of most congenital heart defects are still unknown. Several chromosomal anomalies, certain maternal illnesses and prenatal exposures to specific therapeutic drugs are recognized risk factor. It is difficult to establish the role of a single factor because the cause of a defect is believed to be multifactorial in many cases.[3] Etiology of congenital heart defects are complex and possibly lies within the interaction

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of environmental exposures and inherited factors.[4] Although CHDs can occur in the setting of multiple birth defects as part of a syndrome, most are found as isolated defects with no syndromic association.

CHD encompasses a range of structural abnormalities of the heart, and in many cases, the factors that predispose an individual to disease are not well understood. CHD associated with well-known genetic syndromes often has a known genetic basis or a defined Mendelian inheritance pattern. In contrast, many forms of non-syndromic CHD are thought to usually result from the combined effects of a number of factors, presumably both genetic and epigenetic.[5] Despite this complexity, consanguinity could increase the likelihood of disease, particularly if the disease has a recessive or multifactorial inheritance pattern. Despite the many investigations that have been conducted into the relationship between consanguinity and congenital heart disease, the precise nature and significance of the association remains unclear. However, many of the more common CHDs appear to be genetically heterogeneous, whether diagnosed as isolated anomalies or accompanied by other heart defects.[6]

Consanguineous unions afford the possibility that susceptibility genes identical by descent may be inherited through the relatedness of child-bearing couples, potentially leading to disease depending on the prevalence of consanguineous unions and the genetic contribution to disease. For common birth defects such as CHD, which are thought to have a genetic component, consanguinity may contribute to the risk of disease.[7] From a medical genetics perspective, all marriages between couples related as second cousins or closer are regarded as consanguineous (derived from the Latin *con sanguineus*; i.e. sharing the same blood), and using this definition, it has been estimated that at least 10.4% of the world population are consanguineous.[7] Fung et al[8] found parental consanguinity as a risk factor of CHDs.

Lack of enough information about modifiable risk factors for malformations in fetal heart development has impeded the prevention of CHDs. While the origin of non-syndromic CHD that accounts for most of congenital cardiac abnormalities is still under the veil waiting to be further uncovered. An exploration of the contribution of risk factors that are potentially modifiable is particularly important in the context of the growing health burden of CHD.[9] This study therefore performed to evaluate consanguinity as risk factors of CHD among Bangladeshi population.

## Materials and Methods

This study was conducted from July 2018 to July 2019 at Dhaka Shishu (Children) Hospital. The study population was the parents of children visited to the outpatient department of Dhaka Shishu (Children) Hospital. Parents of the children with congenital heart disease visited the out-patient department of paediatric cardiology of Dhaka Shishu (Children) Hospital was considered as case. Control was taken from parents of the children who din't have congenital heart disease. Children with associated syndromes or major other systemic disease such as Down's syndrome, having congenital anomalies and parents who refused to get involved in the study or to comply with its requirement were excluded. Data were collected by using a structured questionnaire. To minimize recall bias of exposure by mothers, all cases and controls were recruited when they were <1 year old. Data were processed and analyzed by using computer aided statistical software SPSS (Statistical Package for Social Sciences) Version 21. Chi square test ($\chi^2$), Odds ratio (OR) and 95% confidence intervals (CIs) were calculated to estimate the associations between parental consanguinity and all CHDs. Risk factors on bivariate analysis were introduced into a logistic regression model as independent factors and dependent variable was CHDs to find out the association between CHDs and consanguinity.

## Results

Parents of 260 children having CHD was enrolled as case and parents of 280 children having no heart disease was taken as control. Consanguinity was present in 33(6.11%) cases. In the case group, 23 children (8.85%) were born to consanguineous parents. In the control group, only 10 children (3.57%) were born to consanguineous parents (Fig.-1).

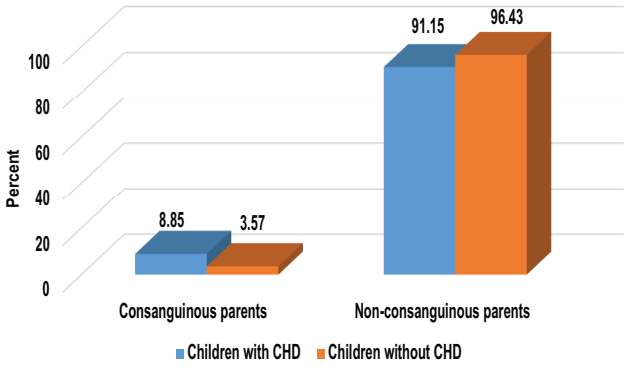


**Fig.-1** *Distribution of gender*

Among children who had CHDs born to consanguineous parents, male were 56.52% and female were 43.48% in case group and in control group male were 60% and female were 40%. In case group 39.13% were from urban area and 60.87% were from rural area and in control group 30% were from urban area and 70% were from rural area. Most of the mother were in 21-30 years age group both in case (60.87%) and control (70%) group. Only 4.35% mother were more than 35 years of age in case and 20% in control. Most of the father of the respondents were in 30-35 years age group both in case (60.86%) and control (70%) [Table I].

Among children who had CHDs born to consanguineous parents, acyanotic congenital heart disease was present in 17(73.91%) cases of them ventricular septal defect in 34.79%, atrial septal defect in 17.39%, patent ductus arteriosus in 17.39% and pulmonary stenosis in 4.35% cases. Cyanotic congenital heart disease was present in 6(26.09%) cases of them transposition of great arteries in 8.69%, complex congenital heart disease in 8.69%, tetralogy of Fallot in 4.35% and pulmonary atresia in 4.35% cases (Table II).

**Table I**

*Distribution of gender of children, residence and parental age at conception of consanguineous parents (n=33)*

| Gender, residence and parental age at conception | | Case (n=23) Number (%) | Control (n=10) Number (%) |
|---|---|---|---|
| Gender of children | Male | 13(56.52) | 6(60) |
| | Female | 10(43.48) | 4(40) |
| Residence | Urban | 9(39.13) | 7(70) |
| | Rural | 14(60.87) | 3(30) |
| Maternal age in year | <20 | 1(4.35) | 1(10) |
| | 21-30 | 16(69.56) | 7(70) |
| | 30-35 | 5(21.74) | 0(0) |
| | >35 | 1(4.35) | 2(20) |
| Paternal age in year | <20 | 0(0) | 0(0) |
| | 21-30 | 7(30.35) | 2(20) |
| | 30-35 | 14(60.86) | 7(70) |
| | >35 | 2(8.69) | 1(10) |

**Table II**

*Type of CHD among children born to consanguineous parents (n=23)*

| Type of CHD | | Number | Percent |
|---|---|---|---|
| Acyanotic CHD | Ventricular septal defect | 8 | 34.79 |
| | Atrial septal defect | 4 | 17.39 |
| | Patent ductus arteriosus | 4 | 17.39 |
| | Pulmonary stenosis | 1 | 4.35 |
| Cyanotic CHD | Transposition of great arteries | 2 | 8.69 |
| | Complex congenital heart disease | 2 | 8.69 |
| | Tetralogy of Fallot | 1 | 4.35 |
| | Pulmonary atresia | 1 | 4.35 |

In the case group, 23 children (8.85%) were born to consanguineous parents. In the control group, only 10 children (3.57%) were born to consanguineous parents. CHD was significantly higher among children born to consanguineous parents ($p<0.05$) [Table III].

**Table III**
*Association of consanguinity and CHD*

| Consanguinity | Case N=260 | Control N=280 | p value |
|---|---|---|---|
| Present | 23 | 10 | 0.01 |
| Absent | 237 | 270 | |

Chi square test ($\chi^2$) was done to find out level of significance

Risk factors on bivariate analysis were introduced into a logistic regression model as independent factors and dependent variable was CHDs. On logistic regression analysis consanguinity ($p=0.02$) was independently associated with CHDs. Children who born to consanguineous parents had 2.5 times risk of developing CHDs compared to those who were not born to consanguineous parents (Table IV).

**Table IV**
*Risk factors for developing CHDs using multivariate logistic regression*

| Risk factors | B | SE | p value | OR | 95% CI for OR |
|---|---|---|---|---|---|
| Sex of children | -0.311 | 0.180 | 0.08 | 0.733 | 0.515-1042 |
| Consanguinity | 0.903 | 0.395 | 0.02 | 2.467 | 1.138-5.347 |
| Residence | -0.427 | 0.244 | 0.08 | 0.652 | 0.404-1.053 |
| Maternal age | 0.413 | 1.383 | 0.76 | 1.512 | 0.100-22.758 |
| Paternal age | 1.302 | 1.126 | 0.24 | 3.676 | 0.405-33.389 |

**Discussion**

Among study population consanguinity was present in 33(6.11%) cases. In the case group 23 children (8.85%) were born to consanguineous parents and in control group 10 children (3.57%) were born to consanguineous parents. CHDs were found significantly higher in children born to consanguineous parents ($p<0.05$). An elevated OR was observed among children with CHDs who born to consanguineous parents compared to those who were not born to consanguineous parents. Among consanguineous parents most of the mothers were in 21-30 years age group both in case (90.7%) and control (85%). Only 4.35% mothers age were more than 35 years in case and 20% in control. Most of the father of the respondents were in 30-35 years age group both in case (60.86%) and control (70%). Among children who had CHDs born to consanguineous parents, acyanotic congenital heart disease was present in 17(73.91%) cases of them ventricular septal defect in 34.79%, atrial septal defect in 17.39%, patent ductus arteriosus in 17.39% and pulmonary stenosis in 4.35% cases. Cyanotic congenital heart disease was present in 6(26.09%) cases of them transposition of great arteries in 8.69%, complex congenital heart disease in 8.69%, tetralogy of Fallot in 4.35% and pulmonary atresia in 4.35% cases

Danish cohort study by Oyen et al[10] estimated recurrence risk ratios and found that among first-degree relatives, the recurrence risk ratio for the same defect was 8.15, whereas it was 2.68 for different heart defects. They have reported a 3.1% prevalence of CHD in first degree relatives. Fung et al[8] in China found parental consanguinity in 3.5% of cases with CHD and was significantly associated with CHDs.

Becker et al[11] examined 1013 patients with CHDs and data indicate that the proportion of first-cousin matings among CHD patients is significantly higher than that of first-cousin intermarriages reported in the general population in the Saudi Arabia ($p<0.001$). The study by El Mouzan et al[12] found that CHDs was present in 9.1 per 1000 consanguineous families versus 4.3 per 1000 non-consanguineous families ($p<0.003$).

Nabulsi et al[13] investigated the consanguinity profile of the 759 CHDs patients and observed that 20.2% of CHD patients were born to first cousins, whereas first cousin marriage in the control group was maximally 13.2%. The difference in cases and controls may suggest an association between CHDs and consanguinity ($p<0.0001$).

In India, Dev et al[14] in their hospital based cross sectional study analyzed 518 cases of CHDs. The parents of 2.92% of the control group were consanguineous versus 6.56% of the CHD families ($p<0.005$). Ramegowda et al[15] also found association between CHDs and consanguinity in India.

After controlling for confounders, Yunis et al[16] reported first cousin consanguinity remained significantly associated with an increased risk of CHD: infants born to first cousin marriages had a 1.8 times higher risk of having a CHD diagnosed at birth compared to those born to unrelated parents ($p<0.001$).

A relatively higher incidence of CHDs was observed in consanguineous marriages by various workers. Quite high incidence (>20%) was observed by Bassili et al[17], Becker et al[11], Nabulsi et al[13] and Ramegowda et al[15]. High incidence (10-20%) was observed by Yunis et al[16]. Almost similar incidence (<10%) to our study was observed by El Mouzan et al[12]. Majority of studies are in support of a significant association between consanguineous parentage and presence of CHDs in their children.

Yunis et al[16] found first cousin marriage was a significant risk factor for ventricular septal defect (VSD), atrial septal defect (ASD), hypoplastic left heart (HLH), and single ventricle (SV). No association was found with transposition of the great arteries, coarctation, pulmonary atresia (PA), atrioventricular septal defect (AVSD), and tetralogy of Fallot (TOF). Settin et al[18] found the most common types of CHD in all population are ventricular septal defect, atrial septal defect, and tetralogy of Fallot. Fazeriandy et al[19] showed that CHDs found in children from consanguineous parents were atrial septal defect (25%), persistent ductus arteriosus (24%), ventricular septal defect (30%), hypoplastic right ventricle (2%), and transposition of the great arteries (6%). This findings are similar to the present study. A study in United Arab Emirates found atrial septal defect (49%) as the most common type of CHD.[20] A South Indian study found that the most common CHDs were atrial septal defect and persistent ductus arteriosus.[15] In contrast, a Pakistani study reported that ventricular septal defect (most common), persistant ductus arteriosus, atrial septal defect, pulmonary stenosis, tetralogy of Fallot, transposition of great arteries, and hypoplastic right ventricle were the common CHDs among consanguineous parents.[21] Hoffman et al[22] in their study in Iraq found that the most common CHD was non-cyanotic type, which was atrial septal defect (66.6%). Other cases were ventricular septal defect, persistent ductus arteriosus and transposition of the great arteries. A similarity in our study was that acyanotic CHDs were more commonly found, with transposition of the great arteries as the most common cyanotic CHD.

This study have some limitations. First, to what extent could confounding play a role in differences between case and control groups? This study used controls from the same hospital to minimize potential confounders. Second, this study determined consanguinity considering at least first and second cousin unions. The history of consanguinity also relied largely on the report by the parent of a child with congenital heart disease. There may be possibility of reporting bias in eliciting the history of consanguinity. In this study association between subtypes of CHDs with consanguinity was also not performed.

Consanguinity should be considered in empiric risk estimates in genetic counselling.[23] Health care providers need to care for families involved in consanguineous unions and discuss and manage potential health concerns in an appropriate manner.

## Conclusions

Parental consanguinity is significantly associated with CHDs.

## References


1. Boneva RS, Botto LD, Moore CA, Yang Q, Correa A, et al. Mortality associated with congenital heart defects in the United States: trends and racial disparities, 1979-1997. *Circulation* 2001;**103**: 2376-81.
2. Hoffman JI, Kaplan S. The incidence of congenital heart disease. *J Am Coll Cardiol* 2000;**39**:1890-1900.
3. Brent RL. Environmental causes of human congenital malformations: the pediatrician's role in dealing with these complex clinical problems caused by a multiplicity of environmental and genetic factors. *Pediatrics* 2004;**113**:957-68.
4. van der Bom T, Zomer AC, Zwinderman AH, Meijboom FJ, Bouma BJ, Mulder BJ. The changing epidemiology of congenital heart disease. *Nat Rev Cardiol* 2011;**8**:50-60.
5. Nora JJ, Nora AH. The evolution of specific genetic and environmental counseling in congenital heart diseases. *Circulation* 1978;**57**:205-13.
6. Benson DW, Sharkey A, Fatkin D, Lang P, Basson CT, McDonough B, et al. Reduced penetrance, variable expressivity, and genetic heterogeneity of familial atrial septal defects. *Circulation* 1998; **97**:2043.

7. Bittles AH. Congenital heart disease and consanguineous marriage in South India. Ann Hum Biol. 2007;34:682-83.; Modell B, Darr A. Science and society: genetic counselling and customary consanguineous marriage. *Nat Rev Genet* 2002;**3**:225-29.
8. Fung A, Manlhiot C, Naik S, Rosenberg H, Smythe J, Lougheed J, et al. Impact of Prenatal Risk Factors on Congenital Heart Disease in the Current Era. *J Am Heart Assoc* 2013;**2**(3): e000064.
9. Jenkins KJ, Correa A, Feinstein JA, Botto L, Britt AE, Daniels SR, et al. Noninherited risk factors and congenital cardiovascular defects: current knowledge. *Circulation* 2007;**115**:2995-3014.
10. Øyen N, Poulsen G, Boyd HA, Wohlfahrt J, Jensen PKA, Melbye M. Recurrence of congenital heart defects in families. *Circulation* 2009;**120**:295-301.
11. Becker SM, Al Halees Z, Molina C, Paterson RM. Consanguinity and congenital heart disease in Saudi Arabia. *Am J Med Genet* 2001;**99**:8-13.
12. El Mouzan MI, Al Salloum AA, Al Herbish AS, Qurachi MM, Al Omar AA. Consanguinity and major genetic disorders in Saudi children: a community-based cross-sectional study. *Ann Saudi Med* 2008;**28**:169-73.
13. Nabulsi MM, Tamim H, Sabbaqh M, Obeid MY, Yunis KA, Bitar FF. Parental consanguinity and congenital heart malformations in a developing country. *Am J Med Genet A* 2003;**116**:342-47.
14. Dev D, Sharma R, Sharma M, Agrawal K, Garg M. Evaluation of consanguinity as a risk factor for congenital heart diseases. *Int J Contemp Pediatr* 2016;**3**:868-71.
15. Ramegowda S, Ramachandra NB. Parental consanguinity increases congenital heart diseases in South India. *Ann Hum Biol* 2006;**33**:519-28.
16. Yunis K, Mumtaz G, Bitar F, Chamseddine F, Kassar M, Rashkidi J, et al. Consanguineous marriage and congenital heart defects: a case-control study in the neonatal period. *Am J Med Genet A* 2006;**140**:1524-30.
17. Bassili A, Mokhtar SA, Dabous NI, Zaher SR, Mokhtar MM, Zaki A. Risk factors for congenital heart diseases in Alexandria, Egypt. *Eur J Epidemiol* 2000;**16**:805-14.
18. Settin A, Almarsafawy H, Alhussieny A, Dowaidar M. Dysmorphic features, consanguinity and cytogenic pattern of congenital heart diseases: a pilot study from Mansoura locality, Egypt. *Int J Health Sci* 2008;**2**:101-11.
19. Fazeriandy A, Ali M, Saing JH, Tobing TCL, Ardiansyah R. Consanguinity and congenital heart disease in offspring. *Paediatr Indones* 2018;**58**:75-79.
20. Jaber L, Merlob P, Bu X, Rotter JI, Shohat M. Marked parenteral consanguinity as a cause for increased major malformations in an Israeli Arab community. *Am J Med Genet* 1992;**44**:1-6.
21. Haq FU, Jalil F, Hashmi S, Jumani MI, Imdad A, Jabeen M, et al. Risk factors predisposing to congenital heart defects. *Ann Pediatr Cardiol* 2011;**4**:117-21.
22. Hoffman JI, Kaplan S. The incidence of congenital heart disease. *J Am Coll Cardiol* 2002;**39**:1890-900.
23. Shieh JT, Bittles AH, Hudgins L. Consanguinity and the risk of congenital heart disease. *Am J Med Genet A* 2012;**158**:1236-41.

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ORIGINAL ARTICLE

# Prevalence and Antibiotic Sensitivity Pattern of Pseudomonas Aeruginosa Isolates from Urine Samples in A Tertiary Care Hospital

**Sohely Sharmin[1], Azizun Nahar[2], Farhana Alamgir[3], Imran Fahim[4]**

**Abstract**

***Background:*** *Urinary tract infection (UTI) is one of the leading causes of infection worldwide. P. aeruginosa is a versatile opportunistic pathogen and it is the third most common organism causing nosocomial urinary tract infections. With the widespread use of antibiotics, multidrug resistance pseudomonas continues to go up rapidly. This multidrug resistance pseudomonas increases the risk of mortality and morbidity.*

***Objective:*** *To determine the prevalence of P. aeruginosa and to understand the current statistics of its antimicrobial resistance pattern.*

***Methods:*** *This retrospective study was conducted from January 2019 to December 2020 in the Department of Microbiology, Bangladesh Medical College Hospital, Dhaka. Clean catch mid-stream urine samples were collected in sterile containers. The samples were cultured on CLED agar media with a standard calibrated loop and incubated at $37^0$C overnight. P. aeruginosa grows well at 25°C to 37°C, and its ability to grow at 42°C helped to distinguish it from other Pseudomonas species. Antibiotic sensitivity test was done according to Clinical and Laboratory Standard Institute (CLSI) guideline.*

***Results:*** *A total of 10427 urine sample were received in the department of Microbiology of BMCH during these two years. Isolation rate of P. aeroginosa was 4% in 2019 and it increased to 6% in 2020. Piperacillin/Tazobactam showed sensitivity which was 63.33% in 2019 and 82% in 2020, followed by imipenem, meropenem, amikacin, ciprofloxacin, ceftazidime and aztreonam; which were 50% to 60% on an average. Sensitivity of the organism to Gentamycin (13.33% in 2019 & 30.3% in 2020), Netilmicin (20% in 2019 & 30.3% in 2020) and Ceftriaxone (13.33% in 2019 & 12.3% in 2020) was found very low.*

***Conclusion:*** *P. aeruginosa isolates in urine culture is increasing in hospital admitted patient and becoming resistant to multiple antibiotics which is frightening.*

***Keywords:*** *P. aeruginosa, urine, sensitivity.*

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## Introduction

Urinary tract infection (UTI) is one of the leading causes of infection worldwide.[1] Escherichia coli is predominantly associated with UTI followed by *Klebsiella, Proteus, Enterobacter, Citrobacter, Enterococci* etc.[2,3] However non fermenting Gram-negative bacilli such as *Pseudomonas* is now an emerging pathogen which is an observation of our laboratory and from others.[4] *Pseudomonas* is a ubiquitous, Gram-negative bacillus that can survive in myriad of environment such aquatic and terrestrial.[5] It is versatile opportunistic pathogen associated with nosocomial infection.The capability of surviving in variety of environmental conditions make it is ubiquitous pathogen, allowing it to persist on numerous living and nonliving surface due to minimum nutritional requirements. According to the report of nosocomial infection surveillance system of center for disease control and prevention *P. aeruginosa* is the third most common organism causing nosocomial urinary tract infections.[6] Recently this bacterium has acquired resistance to various antibiotics. With the widespread use of antibiotics such as quinolones both in the hospital and community settings, multidrug resistance pseudomonas continues to go up rapidly. This multidrug resistance pseudomonas increases risk of mortality and morbidity.[7-9] Therefore, the aim of the present study was to determine the prevalence of *P. aeruginosa* in a tertiary care hospital and to understand the current statistics of the antimicrobial resistance pattern of this Gram-negative opportunistic pathogen.

## Materials and Methods

The study was conducted in the department of Microbiology, Bangladesh Medical College Hospital (BMCH), Dhaka. This retrospective observational study was conducted over a period of two years from January 2019to December 2020. Samples were received from both inpatient and outpatient department of this hospital. Age and gender of the patients were noted. Clean catch mid-stream urine samples were collected in sterile containers. The samples were cultured on CLED agar (Cystine Lactose Electrolyte Deficient) media with a standard calibrated loop and incubated at $37^0$C overnight. All the culture and sensitivity reports of urine with positive Pseudomonas aeruginosa showing $\geq 10^5$ colony forming units /ml were considered as significant bacteriuria. The *P. aeruginosa* isolates were identified by conventional biochemical test. *P. aeruginosa* grows well at 25°C to 37°C, and its ability to grow at 42°C helps to distinguish it from many other Pseudomonas species. Antibiotic sensitivity test was done by Kirby-Bauer disc diffusion method on Meuller Hinton agar media and interpretation were done according to Clinical and Laboratory Standard Institute (CLSI) guideline. Antibiotics against which susceptibility tested were Ceftriaxone (30µg), Amikacin(30µg), Ciprofloxacin (5µg), ceftazidime(30µg), Cefuroxime (30µg), Imipenem (10µg), Meropenem (10µg), Piperacillin/Tazobactam (110µg), Aztreonam (30µg), Netilmicin (30µg), Gentamycin (10µg) and Colistin (10µg).

## Results

A total of 10,427 urine sample were received in the department of Microbiology of BMCH. During these two years out of 10,427, 1337(13%) sample showed growth after culture. Among the positive urine cultures *P. aeroginosa* were identified in 63 (4.7%) cases. Isolation rate of *P. aeroginosa* was 4%in 2019 and it increased to 6% in 2020 (Table I). Out of 63 positive *P. aeroginosa* culture, 51 (81%) was from male. Majority of the samples (84%) were from indoor patient (Table II).

**Table I**
*Percentage of Pseudomonas in urine culture*

| Year | Total sample | Total growth (%) | Pseudomonas species (%) |
|---|---|---|---|
| 2019 | 6330 | 786 (12.42) | 30 (3.82) |
| 2020 | 4097 | 551 (13.45) | 33 (5.99) |

**Table II**
*Distribution of sample according to the age, sex & site of collection (N=65)*

| | | 2019 | 2020 | Total (%) |
|---|---|---|---|---|
| Age | Child | 2 | 7 | 9 (14.29) |
| | Adult | 28 | 26 | 54 (85.71) |
| Sex | Male | 26 | 25 | 51 (80.95) |
| | Female | 4 | 8 | 12 (19.05) |
| Site | Indoor | 29 | 24 | 53 (84.13) |
| | Outdoor | 1 | 9 | 10 (15.87) |

**Table III**
*Antibiotic sensitivity pattern of Pseudomonas species*

| Drugs | Year | |
|---|---|---|
| | 2019 N=30 | 2020 N=33 |
| Ceftriaxone (CRO) | 4 (13.33%) | 4 (12.12%) |
| Amikacin (AK) | 17 (56.66%) | 19 (57.57%) |
| Ciprofloxacin (CIP) | 17 (56.66%) | 13 (39.39%) |
| Ceftazidime (CAZ) | 17 (56.66%) | 14 (42.42%) |
| Imipenem (IPM) | 20 (66.66%) | 18 (54.54%) |
| Cefuroxime (CXM) | 0 | 1 (3.03%) |
| Piperacillin/ Tazobactum (TZP) | 19 (63.33%) | 27 (81.81%) |
| Meropenem (MEM) | 15 (50%) | 21 (63.63%) |
| Aztreonam (ATM) | 16 (53.33%) | 14 (42.42%) |
| Netilmicin (NET) | 6 (20%) | 10 (30.30%) |
| Gentamicin (GN) | 4 (13.33%) | 10 (30.30%) |
| Colistin (CT) | 4 (13.33%) | 11 (33.33%) |

Piperacillin/Tazobactam showed higher sensitivity which was 63.33% in 2019 and 82% in 2020, followed by Imipenem, Meropenem, Amikacin, Ciprofloxacin, Ceftazidime and Aztreonam, which were 50% to 60% on an average. Sensitivity of Gentamycin (13.33% in 2019 & 30.3% in 2020), Netilmicin (20% in 2019 & 30.3% in 2020) and Ceftriaxone (13.33% in 2019 & 12.3% in 2020) against *P.aeruginosa* was found very low (Fig.-1).

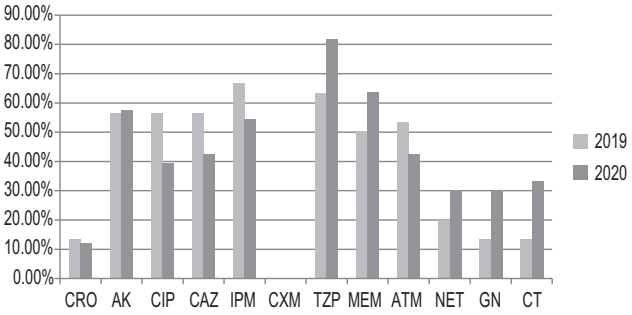


**Fig.-1** *Antibiotic sensitivity pattern of Pseudomonas species*

**Discussion**

Pseudomonas aeruginosa has become one of the leading causes of hospital acquired as well as community acquired infections due to significant changes in the microbial genetics. Also, the indiscriminate use of antibiotics has resulted rapid spread of acquired multidrug resistance (MDR) that has become global problem.

In our study the rate of isolation of Pseudomonas aeruginosa was 4.7% in urine samples. The isolation rate in the present study is compared to some recent studies from India and other countries. Regha et al[10] from Kerala, India found 3.5% in 2018, Singh et al[3] from Uttar Pradesh, India found 6.75% in 2017 and Shah et al[5] found 5.4% from Karachi in 2015. Even though there is a slight variation in the prevalence, *P. aeruginosa* continue to be an important uropathogen in majority of the studies.

When factors such as age, sex in patient and in and outpatient departments were considered, we found that the occurrence of *P. aeruginosa* was higher in male (70%) in adult age. We have also found 85% isolation from indoor patient. Shobha et al[11] from Karnataka, India showed 65% male patients in their urine sample had Pseudomonas growth and among them 84% patients were from indoor department. This male preponderance in Pseudomonas infection in urine also goes in concordance with different studies.[12,13]

The highest sensitivity of *P. aeruginosa* isolates was against piperacillin/tazobactam (63% in 2019 and 82% in 2020), imipenem (66.7% in 2019 & 54.5% in 2020), meropenem (50% in 2019 & 63.6% in 2020). Next to this amikacin (56.66% in2019 and 57.57% in 2020). Sensitivity of ciprofloxacin, ceftazidime, aztreonam has been decreased from 2019 to2020 which is 56.7%

to 39.45%, 56.7% to 42.4%, and 53.3% to 42.4% respectively. In our study imipenem sensitivity decreased from 2019 to 2020 which was 66.7% to 54.5%. Shobha et al[11,14] found 95.45% Imipenem sensitivity against *P. aeruginosa* in 2015 which reduced to 54.2% in 2017. Regha et al[10] from Kerala, India in 2018 found 72% sensitivity of imipenem which was high in comparison to us. Resistance to carbapenem may be due to the result of complex interaction of several mechanisms including production of carbapenemase, over production of efflux system and loss of outermembrane porins.[15]

Present study showed very low sensitivity of gentamycin (13.33% in 2019 & 30.3% in 2020), netilmicin (20% in 2019 & 30.3% in 2020) and ceftriaxone (13.33% in 2019 & 12.3% in 2020) against *P. aeruginosa*. Shobha et al[11] found 37.1% sensitivity of gentamycin in 2011 later in 2017 same group found sensitivity 48.6%.[16] Regha et al[10] found 47% gentamycin sensitivity against *P. aeruginosa* in urine. Pseudomonas resistance to aminoglycosides is probably due to acquisition of resistance genes. Acquisition of aminoglycoside and âlactamresistance gene has been reported in *P. aeruginosa*.[17-19]

Sensitivity of ciprofloxacin has been decreased from 56.7% in 2019 to39.45% in 2020. Principal mode of fluoroquinolone resistance in P. aeruginosa is due to target modifications in DNA gyrase and topoisomerase IV or mutation of regulatory genes of efflux pumps that reduce intracellular concentration of the antibiotic.[20]

Overall, this low sensitivity of urinary *P. aeruginosa* against commonly used antimicrobials is very alarming. The antibiotic resistance in *P. aeruginosa* is multifactorial in that it can occur through innate, acquired or adaptive mechanisms. The diversity of antibiotics mechanisms contributes to the development of multidrug resistance strains and makes conventional antibiotics ineffective for the treatment of *P. aeruginosa* infections.[15]

## Conclusion

*P. aeruginosa* isolates in urine culture is increasing in hospital admitted patient. This organism is becoming resistant to aminoglycoside, fluoro-quinolone, carbapenem and β lactam group of antibiotics which is frightening.

## References


1. Shylaja TS, Mohankumar. A. Antimicrobial Resistance among Uropathogenic Bacteria in Rural Kerala, India. *Int J Curr Microbiol App Sci* 2017; **6**:2287-96.
2. Tanvir R, Hafeez R, Hasnain S. Prevalence of multiple drug resistant Escherichia coli in patients of urinary tract infection registering at a diagnostic laboratory in Lahore, Pakistan. *Pak J Zool* 2012;**44**:707-12.
3. Singh VP, Mehta A. Bacteriological profile of urinary tract infections at a tertiary care hospital in Western Uttar Pradesh, India. *Int J Res Med Sci* 2017;**5**: 2126-29.
4. KL S, Rao GG, Kukkamalla AM. Prevalence of non-fermenters in urinary tract infections in a tertiary care hospital. *Webmed Central Microbiology* 2011;2(1):WMC001464.doi: 10.9754/ journal. wmc.2011.001464
5. Shah DA, Wasim S, Abdullah FE. Antibiotic resistance pattern of Pseudomonas aeruginosa isolated from urine samples of Urinary Tract Infections patients in Karachi, Pakistan. *Pak J Med Sci* 2015;**31**:341-45.
6. Trivedi MK, Branton A, Trivedi D, Nayak G, Shettigar H, Gangwar M, et al. Antibiogram of Multidrug-Resistant Isolates of Pseudomonas aeruginosa after Biofield Treatment. *J Infect Dis Ther* 2015;**3**:244.
7. Collee JK, Miles RS. Tests for identification of bacteria. In: Collee JG, Duguid JP, Faser AK, Mermoin BP, editors. Mackie & MacCartney practical Medical Mictobiology. 13th ed.;1989.P141-60.
8. Wadud A, Rahman M, Wasey A. Antibiotic resistance in Pseudomonas aeruginosa strains isolated from various clinical specimens. *AFMJ* 2004;**34**:31-35.
9. Friedland I, Gallanghor G, King T, Woods GL. Antimicrobial susceptibility pattern in Pseudomonas aeruginosa: data from a multicenter Intensive Care Unit Surveillance Study (ISS) in the US. *J Chemother* 2004;16:437-41.
10. Regha IR. Prevalence and antibiotic susceptibility patterns of pseudomonas aeruginosa in urinary tractSinfections in a Tertiary care hospital, Central Kerala: A retrospective study over 4 rears. *Tropical Journal of Pathology & Microbiology* 2018;**4**:52-58.
11. Shobha KL, Ramachandra L, Rao AS, Anand KM, Gowsrsh R. PseudomonasSpecies Causing Urinary Tract Infection And Its Antibiogram At A tertiary Care Hospital. *Asian J Pharm Clin Res* 2017;**10**: 50-51.

12. Saperston KN, Shapiro DJ, Hersh AL, Copp HL. A comparison of inpatient versus outpatient resistance patterns of pediatric urinary tract infection. *J Urol* 2014;**191**:5 Suppl:1608-13

13. Schaeffer AJ, Nicolle LE. Clinical Practice. Urinary tract infections in older men. *N Engl J Med* 2016;**374**:562-71.

14. Shobha KL, Souza JS, Alva M, Anand KM, Rao G, Ramachandra L. Study of uropathogens and its antibiogram at a tertiary care hospital at coastal Karnataka. *Ijppr Human* 2015;**4**:100-09.

15. Zheng P, Renee R, Bernard RG, Tong-Jun L, Zhenyu C. Antibiotic resistance in Pseudomonas aeruginosa: mechanisms and alternative therapeutic strategies. *Biotechnology Advances* 2019;**37**:177-92.

16. Shobha KL, Rao GG, Kukkamalla AM. Prevalence of Non-Fermenters in Urinary Tract Infections in a Tertiary Care Hospital. Available from: http://www.webmedcentral.com.

17. de Sa Cavalcanti FL, Mirones CR, Paucar ER, Montes LA, Leal-Balbino TC, de Morais MMC, et al. Mutational and acquired carbapenem resistance mechanisms in multidrug resistant Pseudomonas aeruginosa clinical isolates from Recife, Brazil. *Mem Inst Oswaldo Cruz* 2015;**110**:1003-1009.

18. Hong DJ, Bae IK, Jang IH, Jeong SH, Kang HK, Lee K. Epidemiology and characteristics of Metallo-beta-Lactamase-producing Pseudomonas aeruginosa. *Infect Chemother* 2015;**47**:81-97.

19. Bonomo RA. SzboD. Mechanism of Multidrug Resistance in Acinetobacter species and Pseudomonas aeruginosa. *Clin Infect Dis* 2006;**43:** (suppl2):S49- S56.

20. Jalal S, Wretlind B. Mechanisms of quinolone resistance in clinical strains of Pseudomonas aeruginosa. *Microb Drug Resist* 1998;**4**:257-61.

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ORIGINAL ARTICLE

# Influence of Febrile Seizure in Children's Neurodevelopment

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**Abstract**

***Background****: Febrile seizure is one of the most common diseases in early childhood. The impact of early-life Febrile Seizure on the developing brain is an important issue to detect.*

***Objectives:*** *To observe the neurodevelopment of children suffering from different types of febrile seizures.*

***Methods****: This was a prospective observational study; the study was conducted in Dhaka Shishu (Children) Hospital, Dhaka from July 2012 to August 2013. Total 71 children were included in the study who fulfilled the selection criteria. History was taken thoroughly. Rapid neurodevelopmental assessment (RNDA) was performed for initial assessment and subsequent follow up and was advised accordingly.*

***Results****: Total 71 cases were included where mean age was 17.76±8.03 months, median was 16 months; in both the group male child had slight high preponderance. Majority of seizures were <10 minutes duration in both group which was not statistically significant. Important postictal event was found, 12 cases (26.7%) in simple seizure and 16 cases (61.5%) in complex seizures which was found statistically significant, but there was no risk for further seizure. On follow up, RNDA detected risk of impairment in vision, cognition, speech and behavior. In complex group statistically significant association was found with impairment of cognition only at initial and follow up at 3 month.*

***Conclusion****: Neurodevelopment impairment is not influenced by types of febrile seizure but significant cognitive impairment was found in complex seizure.*

***Keywords****: Febrile seizure, neurodevelopment, Rapid neurodevelopmental assessment (RNDA).*

## Introduction

Febrile seizure (FS) is the most common seizure disorder in childhood.[1,2] Incidence of febrile seizure is approximately 2% to 5%.[3-5] Febrile seizures are classified as either simple or complex. Although epidemiological studies have made substantial contributions to our understanding of the frequency, natural history and seizure recurrence, there are critical issues that remain unanswered. The impact of early-life FS on the developing brain has not been

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fully resolved.[6] Numerous authors consider the prognosis of febrile convulsions to be favorable, and assume that parents who are frequently extremely worried require reassurance about the outcome.[7] It was previously emphasized that febrile convulsions are benign events.[8,9] Different studies were also carried out as follow up studies into the intellectual performance of children with febrile convulsions. All of those studies have considerable methodological deficits that is lack of controls, performance of only one neuropsychological test, application of non-standardized test procedures, and too-small patient groups, so that no real conclusions could be drawn regarding mental performance of children following febrile convulsions.[10-13]

Although many studies have been done on this issue but total neurodevelopmental assessment and its association with FS is not seen. In this study an effort has been tried to detect the influence of FS on children's neurodevelopment by using RNDA. The standardized tools used in western settings are too specialized and require levels of skills and resources rarely found in low and middle-income settings. The RNDA is reliable and valid for identifying specific neurodevelopmental impairments including autism spectrum disorders, and when linked to appropriate interventions.[14] So this study was done to see the neurodevelopmental outcome of children suffering from different types of febrile seizures

**Materials and Methods**

This study was conducted at Dhaka Shishu (Children) Hospital, Sher-e-Bangla Nagar, Dhaka. Study was conducted from July 2012 to August 2013. The children suffering from different types of febrile seizure from 5 months - 5 years, fulfilling the inclusion criteria were selected as sample. Hospital admitted children with febrile seizure (Age 5 months to 5 years) were included in the study. The child with cerebral palsy and other developmental delay, known case of neurological disease (trauma, tumor, and neurodegenerative), meningitis or seizures due to CNS infection (encephalitis, abscess) were excluded. A pre-tested questionnaire was administered, Rapid Neuro-developmental assessment kits were used as research instruments. Reassurance was given to parents as there was no harmful effect for babies or economic loss. Clearance was taken from the ethical committee. Children with suspected febrile seizures were admitted in the inpatient department of Dhaka Shishu (Children) Hospital. After admission into the hospital, cases were consecutively screened and subsequently enrolled considering the inclusion and exclusion criteria. The parents or legal guardians of the children eligible to enter the study were fully informed about the aims and objectives of the study and there after consent of the parent was taken. Detailed clinical history and thorough physical examination was performed. Relevant information were taken to differentiate the types of febrile seizure, seizure semiology (Age of onset of febrile seizure, nature of seizure generalized or focal, duration of seizure, frequency of seizure, immediate postictal events- drowsiness, unconsciousness, weakness of any part of the body, abnormal behavior). Rapid neurodevelopmental assessment was done at discharge and after 3 months.

**Result**

Total 71 cases of febrile seizures were included in this study to determine the predictors of neurodevelopmental outcome of febrile seizures 63.4% were in simple and 36.6% were in complex seizures group (Fig.-1).

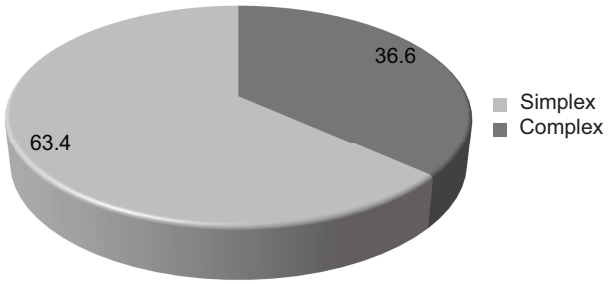


**Fig.-1** *Distribution of types of febrile seizure*

Patients' characteristics on admission showed male child was 70.4% and female was 29.6%. When age distribution was observed it was seen that less than 1 year was 35.2%, more than 1 year was 64.8%. Consanguinity was present in 8% cases. Most of the children came from poor socioeconomic background. Positive family history was found in 25.35% cases (Table I).

**Table I**
*Patient's characteristics at admission (n=71)*

| | | Frequency | Percentage |
|---|---|---|---|
| Sex | Male | 50 | 70.4 |
| | Female | 21 | 29.6 |
| Age | <12 months | 26 | 35.2 |
| | >12months | 45 | 64.8 |
| Consanguinity | Present | 6 | 8.5 |
| | Absent | 65 | 91.5 |
| Socioeconomic status | Average | 22 | 31 |
| | Below average | 49 | 69 |
| Family history | Positive | 18 | 25.35 |
| | Negative | 53 | 74.65 |

In different febrile seizures, seizure semiology was different. Positive family history of febrile seizure was more in simple febrile seizure group (61.1%) and in complex seizure group it was 38.9%. Duration of seizure more than 10 minutes was seen in simple febrile seizure group which was found in 66.7% cases. Degree of fever was not associated with types of seizure. 31.6% of complex seizure group and 68.4% of simple seizure group had high grade fever. Postictal event was more in complex febrile seizure group (59.3%) and p value was <0.05 (Table II).

Neurodevelopmental assessment was observed by RNDA. No significant association was found in febrile seizure when we observed gross motor, fine motor, vision, hearing and language. In cognition it was seen that in initial assessment 42.3% children in complex group had cognitive impairment which was statistically significant. When behavior was observed it was seen that 65.4% had impairment in complex group and 86.5 % had impairment in simple group which was not significant (Table III and IV).

**Table II**
*Association between seizure semiology with simple versus complex*

| | | Complex | Simple | p value | OR |
|---|---|---|---|---|---|
| Family history | Positive | 7(38.9%) | 11(61.1%) | 1 | 0.878(0.292-2.642) |
| | Negative | 19(35.8%) | 34(64.2%) | | |
| Duration of Seizure | <10min | 23(37.1%) | 39(62.9%) | 1 | 1.17(0.269-5.174) |
| | >10 min | 3(33.3%) | 6(66.7%) | | |
| Degree of Fever | High | 18(31.6%) | 39(68.4%) | 0.12 | 0.346(0.105-1.146) |
| | Low | 8(57.1%) | 6(42.9%) | | |
| Immediate post Ictal event * | Yes | 16(59.3%) | 11(40.77%) | **0.003 | 0.202(0.071-0.573) |
| | No | 10(22.73%) | 34(77.3%) | | |

**Table III**
*Initial neurodevelopmental assessment*

| | | Yes | No | p value | OR with 95% CI |
|---|---|---|---|---|---|
| Gross motor | Complex | 3(11.5%) | 23(88.5%) | 0.136 | 5.739(0.565-58.32) |
| | Simple | 1(2.2%) | 44(97.8%) | | |
| Fine motor | Complex | 6(23.1%) | 20(76.9%) | 0.194 | 0.652(0.829-1.802) |
| | Simple | 5(11.1%) | 40(88.9%) | | |
| Vision | Complex | 2(7.7%) | 24(92.3%) | 0.5 | 3.67(0.316-42.55) |
| | Simple | 1(2.2%) | 44(97.8%) | | |
| Hearing | Complex | 2(7.7%) | 24(92.3%) | 1 | 0.854(0.145-5.017) |
| | Simple | 4(8.9%) | 41(91.1%) | | |
| Cognition | Complex | 11(42.3%) | 15(57.7%) | .05 | 2.993(1.009-8.528) |
| | Simple | 9(20%) | 36(80%) | | |
| Expressive language | Complex | 9(34.6%) | 17(65.40%) | 0.278 | 1.853(0.635-5.407) |
| | Simple | 10(22.2%) | 35(77.7%) | | |
| Behavior | Complex | 17(65.4%) | 9(34.6%) | 0.06 | 0.291(.089-0.945) |
| | Simple | 39(86.7%) | 6(13.3%) | | |

**Table IV**
*Follow up neurodevelopmental assessment (after 3 Months)*

| | | Yes | No | p value | OR with 95% CI |
|---|---|---|---|---|---|
| Gross motor | Complex | 1(3.8%) | 25(96.2%) | 1 | 1.76(0.105- 29.378) |
| | Simple | 1(2.2%) | 44(97.8%) | | |
| Fine motor | Complex | 4(15.4%) | 22(84.6%) | 0.182 | 3.909(0.664-23.038) |
| | Simple | 2(4.4%) | 43(95.6%) | | |
| Vision | Complex | 3(11.5) | 23(88.5%) | 0.348 | 2.804(0.437-18.005) |
| | Simple | 2(4.6%) | 43(95.6%) | | |
| Hearing | Complex | 1(3.8%) | 25(96.2%) | 1 | 0.86(0.074-9.971) |
| | Simple | 2(4.4%) | 43(95.6%) | | |
| Cognition | Complex | 8(30.8%) | 18(69.2%) | 0.05 | 3.556(1.021-12.387) |
| | Simple | 5(11.1%) | 36(88.9%) | | |
| Expressive language | Complex | 5(19.2%) | 21(88.8%) | 1 | 1.01(0.319-3.802) |
| | Simple | 8(17.8%) | 37(82.2%) | | |

**Discussion**

Febrile seizure is a benign and common childhood illness. Lots of studies were done on febrile seizure including socio-demographic characteristics, clinical profiles, but the neurodevelopmental assessment were assessed in few studies. In this study among the total samples of febrile seizures 45 cases (63.4%) had simple febrile seizures & 26 cases (36.6%) had complex febrile seizures. The result of our observation was similar to that of Ghasen et al[15] in which simple febrile seizure was 99(61.9%) & complex febrile seizure was 61 cases (38.1%). Another study showed 55% of febrile convulsions were simple and 45 % complex, which almost corresponds to our study.[16] Falah et al[17] found one third of the patient and Al-Zwaini et al[18] found 27% complex febrile seizure in their study.[18]

Among the admitted patients with febrile seizures common age in >12 months. In another study the majority of children were under 2 years of age, they found febrile seizure was in the age range of 6 months to 3 years, with peak incidence at the of age, of 18 months.[21] Our findings were similar to other study, febrile seizures are slightly more common in males.[22] It was found that prevalence of febrile convulsion was slightly predominant in males than females and this was similar with the results of other studies done.[23,24] In our study positive family history was found in 11 (24.4%) cases in simple seizures and 7(26.9%) in complex seizure. In another study had positive family history of febrile convulsion, with the percentage varied from 25% to 40%.[24] Seizure semiology is the description of a seizure. Seizures are usually generalized tonic-clonic, hypotonic, or clonic, short-lasting, and had mild postictal manifestations.[2] Seizure duration, showed majority seizures were <10 min, among them 86.7% was simple and 88.5% was in complex group which was not statistically significant but having risk of further seizures. In a study the majority of patients (78%) had seizure duration less than or equal to 15 minutes.[15]

In 39 (86.7%) cases of simple seizure developed during high fever and 18 (69.2%) cases of complex seizure developed during high grade temperature, which was not statistically significant. The mean rectal temperature during convulsion was 38.3°C ranging from 38-40°C.[15]

Important postictal event was found 12(26.7%) in simple seizure and 16(61.5%) in complex seizures which was found statistically significant (p value<.05), but no risk for further seizure. Seizures may produce mild post-ictal manifestations.[26] It is an important finding which needs further evaluation. Another study showed that the key factors for recurrence are early age at first seizure, family history of febrile

seizures, temperature and duration of febrile illness (the shorter the febrile period, the higher the odds of recurrence).[15]

Neurodevelopmental assessment by RNDA showed important findings in cognition, 42.3% developed impairment in complex and 20% in simple group. If we consider in behavior 65.4% impairment occurred in complex group and 86.7% occurred in simple group. In expressive language, 34.6% impairment occurred in complex group and 22.20% occurred in simple group. There was no association of complex and febrile seizures with cognition, behavior and speech. But there was risk of developing impairment of cognition and speech in complex seizures. Neurodevelopmental impairment in motor and tone ($p<.05$) was observed in a study by Pedespan et al.[22]

At 3 months follow up impairments and disabilities of different domain showed maximum moderate impairment in cognition and behavior and maximum mild impairment in expressive language. No association have been seen in impairment of gross motor and fine motor, vision, hearing and speech with complex and simple febrile seizures. No association of complex and febrile seizures with behavior and speech were found.

Pedespan et al[22] found following febrile convulsion cognitive and motor performance of the subject with febrile convulsion achieved fewer good results which were statistically significant in arithmetic abilities.[22]

Ying-chao et al[28] found that there is subtle neurocognitive dysfunction in school-age children having previous febrile convulsion, although the global outcome is favorable.[28]

Some follow up studies into the intellectual performance of children with febrile convulsions showed similar findings with our study.[28-31] Behavioral abnormalities were exhibited by 22% of the patients and 6% of the healthy children. The neuropsychological test results did not demonstrate significant differences between the children with febrile convulsions and the healthy controls. Non-verbal intelligence was found to be significantly lower as compared with children with simple febrile seizures and with controls.[32]

## Conclusion

Febrile seizure is a common disease in early childhood which was due to its benign natural history does not create significant attention to follow up the children further. Repeated assessment the children who developed impairment in different domain had overcome the problem in early recognition & stimulation. Neurodevelopmental impairment is not influenced by types of febrile seizure but risk has been detected in different developmental domain in the study population.

## Recommendation

A larger scale population and long-term follow-up study is needed to delineate the pattern of neurodevelopmental impairment their associated risk factors among FS children. Significant association has been found between complex seizure and postictal illness which needs further research.

## References


1. Shinar S, Swaiman KF, Ashwal S, Ferriero DM. Febrile seizures. PediatricNeurol: Principles and Practice. 4th ed. St Louis, MO: Mosby; 2006:1079-1090.
2. Leung AK, Robson WL. Febrile seizures. *J Pediatr Health Care* 2007;**21:**250-55.
3. Hauser WA. The prevalence and incidence of convulsive disorders in children. *Epilepsia* 1994;**35**(suppl 2):S1-S6.
4. Sillanpaa M, Camfield P, Camfield C, Haataja L, Aromaa M, Helenius H, et al. Incidence of Febrile Seizures in Finland: Prospective Population-based Study. *Pediatr Neurol* 2008;**38:**391-94.
5. Vestergaard M, Pedersen CB, Sidious P, Olsen J, Christensen J. The long-term risk of epilepsy after febrile seizures in susceptible subgroups. *Am J Epidemiol* 2007;**165**:911-18.
6. Ying-Chao Chang, Chao-Ching Huang, Song-Chei Huang. Review Article Long-term Neuroplasticity Effects of Febrile Seizures in the Developing Brain. *Chang Gung Med J* 2008;**31:**2.
7. Rantala H, Uhari M. Risk factor for recurrence of febrile convulsion. *Acta Neurologica Scandinavia* 1994;**90:**207-10.
8. Aicardi J. Epilepsy in children. New York: Raven press. P. 21-32.
9. Camfield P, Camfield C, Gordon K, Dooley J. What Types of Epilepsy is Preceded by Febrile Seizure? A Population-based Study of Children. *Developmental Med and Child Neurol* 1994;**l36**:887-92.
10. Schiottz-christensen E, Bruhn P. Intelligence, Behavior and Scholastic Achievement Subsequent to Febrile Convulsion: An Analysis of Discordant Twin

Pairs. *Developmental Medicine and Child Neurology* 1973;**15:**565-75.

11. Eilenberg JH, Nelson KB. Febrile Seizure and Later Intellectual Performances. *Archieves of Neurology* 1978;**35:**17-21.
12. Bourgeosis BF, Prensky Al Palkes HS, Talent BK, Busch SG. Intelligence in epilepsy: A prospective study in children. *Annals of Neurology* 1983;**14:**438-44.
13. Khan NZ, Muslima H, Shilpi AB, Begum D, Parveen M, Akter N, et al. Validation of a rapid neurodevelopmental assessment for 2-5 years old children in Bangladesh. *Pediatrics* 2013;**131**:e486-94.
14. Flores S, Puerta H. Importance of screening test for neurodevelopmental evaluation in children. *Bol Med Hosp Infant Mex* 2013;**70:**175-77.
15. Ghasem MA, Ali Kh Afshin Fay J Compr. Clinical, Epidemiological and Laboratory Characteristics of Patients with Febrile Convulsion. *J of Comp Ped* 2013;**4**:134-37.
16. Donaldson D, Trotman H, Barton M, Melbourne-Chambers R. Routine laboratory investigations in infants and children presenting with fever and seizures at the University Hospital of the West Indies. *West Indian Med J* 2008;**57**:369-72.
17. Falah R, Gorleston M. Role of laboratory diagnostic tests in first febrile seizure. *J Pediatr Neurol* 2008;**6**:129-32.
18. Al-Zwaini EJ. Epidemiological and clinical features of hospitalized patients with febrile seizures in Ramadi, West of Iraq. *J Pediatr Neurol* 2007;**5:**311-15.
19. Berg AT, Shinnar S, Hauser WA, Alemany M, Shapiro ED, Salomon ME, et al. A prospective study of recurrent febrile seizures. *N Engl J Med* 1992;**327**:1122-27.
20. Fetveit A. Assessment of febrile seizures in children. *Eur J Pediatr* 2008;**167**:17-27.
21. Tailor DC, Ounsted C. Biological mechanisms influencing the outcome of seizures in response to fever. *Epilepsia* 1971;**12**:33-45.
22. Pedespan L. Updates on Febrile seizures. *Arch Pediatric* 2007;**14**:394-98.
23. Carmant L. Febrile Convulsion in Children. *Eur J Pediatr* 2002:81-89.
24. Waruiru C, Appleton R. Febrile Seizures: An Update. *Arch Dis Child* 2004;**8**:751-56.
25. Lennox MA. Febrile convulsion in childhood: their relation to adult epilepsy. *J Pediatric* 1949;**35**:427-35.
26. Hartfield DS, Tan J, Yager JY, Rosychuk RJ, Spady D, Haines C, et al. The Association Between Iron Deficiency and Febrile Seizures in Childhood. *Clin Pediatr (Phila)* 2009;48:420-26.
27. Berg AT, Shinnar S. Complex Febrile Seizures. *Epilepsia* 1996;**37**:126-33.
28. Ying-Chao Chang, Nai-Wen Guo, Wang ST, Tsai JJ. Neurocognitive Attention and Behavior Outcome of School-age Children with a History of Febrile Convulsions: A Population Study. *Epilepsia* 2000*;***41**:412-20.
29. Ellenberg JH, Nelson KB. Febrile seizure and later intellectual performance. *Archieves of Neurology* 1978;**35**:17-21.
30. Bourgeosis BF, Prensky Al Palkis HS, Talent BK, Busch SG. Intelligence in epilepsy:A prospective study in children. *Annals of neurology* 1983;**14**:438-44.
31. Verity CM, Butler NH, Golding J. Febrile Convulsions in A National Cohort Followed Up from Birth. Prevalence and recurrence in the first five years of life. *B Med Journal* 1985;**290**:1307-10.
32. Golfen W, Pehle K, Konig S. Is the long-term outcome of children following febrile convulsions favorable? *Developmental medicine and child neurology* 1998; **40**:667-71.

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ORIGINAL ARTICLE

# Cut off Value of Red Cell Distribution Width (RDW) in Screening and Diagnosis of Iron Deficiency Anemia and β Thalassemia Trait

**Md. Abu Tayab[1], Md. Ariful Hoq[2], Masuma Begum[3]**

**Abstract**

***Background:*** *The most concerning consequences of iron deficiency in children are the alterations of cognitive, motor, and behavioral performance. Persistent neurocognitive changes despite iron repletion have increased the importance of prevention and early detection of iron deficiency.*

***Objectives****: To evaluate the cut off value of red cell distribution width (RWD) in the screening and diagnosis of iron deficiency anemia (IDA) and â thalassemia trait (BTT).*

***Methods:*** *It is a cross sectional study performed at Dhaka Shishu (Children) Hospital from July 2006 to July 2008. Total 52 patients, age ranged from 1-12 years were included in the study. Among them 27 cases were IDA and 25 cases were BTT. Complete blood count (CBC), serum ferritin and hemoglobin (HB) electrophoresis were measured. The sensitivity, specificity, positive and negative predictive value of differential and cutoff value for RDW discrimination index in differentiation between IDA and BTT were performed.*

***Results****: Age ranged from 1-12 years. In IDA group male were found 16(59%), female were 11(41%) and in BTT group male were 15(60%), female were 10(40%). The Hb% value in IDA group was significantly (p<0.0001) lower than value for BTT. An elevation of RBC distribution width (>14.6) in IDA had a sensitivity of 81%, specificity of 84%, positive predictive value (PPV) of 85% and negative predictive value (NPV) of 81%; value of RBC distribution width (<14.6) in BTT had a sensitivity of 84%, specificity of 81%, positive predictive value (PPV) of 81% and negative predictive value (NPV) of 85%. An elevation of RBC distribution width (>16) had a sensitivity of 67%, specificity of 92%, and positive predictive value (PPV) of 90% in distinguishing iron deficiency anemia from thalassemia trait. Moreover, eleven (11) of 27 patients with iron deficiency had RBC distribution width values greater than 18 compared to one (1) of the patients with thalassemia trait. An elevation of RBC distribution width ≥18 specificity of 96% and positive predictive value (PPV) of 92%.*

***Conclusion:*** *The rersult of the study, in patients with microcytic hypochromic anemia, RDW value e≥14.6% and Hb level< 10gm/dl, iron deficiency is the most likely diagnosis. RDW value (>16) is a reliable diagnostic tool in differentiation between IDA and BTT. Red cell distribution width (RDW) above 16% is the best index of IDA.*

***Keywords:*** *Anemia, iron deficiency anemia (IDA), β thalassemia trait (βTT), RBC distribution width (RDW).*

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**Introduction**

Iron deficiency anemia is the most prevalent nutritional problem in the world today.[1] It was estimated that the number of anemic people worldwide were two billion and that approximately 50% of them were due to iron deficiency. Because anemia is the most common indicator used to screen for iron deficiency, the terms anemia, iron deficiency, iron deficiency anemia are sometimes used interchangeably.[2]

In Bangladesh prevalence of anemia among children aged 6-59 months (preschool children) is 47%. The highest proportion (76%) of anemic children belonged to the 6-11-months of age group.[3]

During the past decade, the possible association between iron deficiency, with or without anemia, and impaired cognitive and psychomotor development has been the subject of much concern. This concern has lead to establishing extensive intervention programme to prevent iron deficiency in many countries.[4] The brain's sensitivity to iron deficiency is mitigated by the severity and timing of the deprivation and the adverse effects of iron deficiency may or may not be reversible.[4-6]

Iron deficiency (ID) is by far the most common cause of anemia in general and of microcytic hypochromic anemia in particular. The most common scenario is the need to distinguish iron deficiency anemia (IDA) from β thalassemia trait (βTT).[7] The thalassemia probably constitutes the world's largest gene disorder and it is one of the commonest inherited diseases in Bangladesh.[8] A conservative World Health report has estimated that 3 percent are carriers of β thalassemia and 4 percent are carriers of Hb-E disease in Bangladesh.[9] Patients of â thalassemia trait (heterozygous state of thalassemia) are near normal except that they are anemic. The patients of β thalassemia trait does not need iron therapy unless there is iron deficiency. Genetic counseling is the effective way to prevent the population from thalassemia; the population at risk needs to be identified. Fortunately iron deficiency anemia (IDA) is treatable. Health care providers have long subscribed to a program of screening for and treating iron deficiency to avoid the consequences of this disorder.[10 -12]

Several approaches are used to assess the iron status of an individual or of a population. Serum ferritin concentration is the most powerful test for ID.[13] A serum ferritin concentration of <12 µg/dl is diagnostic of ID.[14] Additional investigations may also be needed for detection of iron deficiency anemia, such as estimation of serum transferrin receptor, total iron binding capacity (TIBC), serum iron level transferrin saturation & free erythrocyte protoporphyrin (EPP).

It would be impractical, however, to use initially the whole battery of above investigations and simpler approaches for population and individual studies have been suggested.[15] Again, to rule out â thalassemia trait, hemoglobin electrophoresis is needed. All these tests are expensive and time consuming and constitute a significant burden on public health economy in countries with high incidence of microcytic hypochromic anemias. Developing countries have high prevalence of iron deficiency anemia, but facilities to diagnose and treat them are limited.[16]

Iron deficiency anemia (IDA) and thalassemia trait (TT) are the two most common forms of microcytic hypochromic anemia. Therefore there is a need for a simple, low cost rapid and reliable, common routine investigation, which can be used for screening and can easily differentiate between â thalassemia trait and iron deficiency anemia. In order to distinguish between the two, discrimination indices calculated from red blood cell (RBC) indices are used.[17,18] These indices are derived from several simple red blood cell (RBC) indices, like RBC count, mean corpuscular volume (MCV), and Red cell distribution width (RDW), which are provided by electronic cell counters.

Thalassemia minor and iron deficiency anemia are both microcytic and hypochromic anemia, overlap in MCV and MCH. The RDW aids in differentiating anemia that have similar indices. Measures of anisocytosis derived from erythrocyte volume distribution have been advocated for distinguishing iron deficiency from thalassemia minor.[19-21] Red-cell distribution width (RDW) allows discrimination of iron deficiency anemia and thalassemia trait.[21] Kook et al[22] postulated that difference in size and range variation might be diagnostically useful.

The purpose of the study is to see the sensitivity, specificity, positive predictive value and negative predictive value of the test of significance and is to evaluate validity of RDW in the screening and diagnosis of iron deficiency anemia and to differentiate between iron deficiency anemias (IDA)

from β thalassemia trait (βTT). This study might serve as model of management strategy for treating iron deficiency to avoid the consequences of this disorder.

## Materials and Methods

This hospital based cross sectional study was conducted during the period of July 2006 to July 2008. Total 52 patients of 1-12 years age with full verbal explanation to their parents/attendants were included in this study. IDA patients were in group-1 and BTT patients were in group-2, cases were selected from Out Patient Department (OPD) and Thalassemia Center (anemic sibs of thalassemia patients) respectively. Iron deficiency anemia (IDA) cases with Hb value <8.7 gm/dl were excluded because these cases were confused with β thalassemia trait (βTT) in practice. The subjects who had been on any hematinic in last 2 months or received blood transfusion in the past 3 months, acute febrile illness > 5 days, patients who were chronically ill and severely malnourished,, patients with active diseases and those who needed hospital admission were excluded from the study. For each patient, a detail history which included age, gender, family history, consanguinity, socioeconomic status, medical history, diet, use of medications, anemia related symptoms (Pallor, Fatigue, Exercise intolerance, Tachycardia, Palpitation, Irritability & Anorexia) was taken.

In subjects of the group-1, Serum ferritin <12ng/ml was diagnosed to have IDA[14] and of group-2, Hemoglobin (Hb)A2 ≥3.5 % was diagnosed to have β thalassemia trait. The normal value for RDW is 13.4 ±1.2% (mean ± 2SD) and the upper limit of normal is 14.6%.[18,19] A subject was considered to have an elevated red cell distribution width if the value exceeded >14.6 %.[19]

Complete blood count (CBC) included values of hemoglobin (Hb), RBC count, mean red cell volume (MCV), mean red cell hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) and red cell distribution width (RDW). Hematological analyses were measured in all the selected cases with Mythic 18 continuous flow automated analyzer.

Serum ferritin were being assessed using Dimension Rx L Max Biochemistry fully auto analyzer (dade Behring, USA products).Hb electrophoresis was performed on cellulose agar gel at alkaline pH by Helena 5 automated machine. Data and results were presented in the form of tables and figures. Analysis was done by employing statistical package for social science (SPSS Version 12.0) software package. Student's 't' test in continuous variable & chi-square test in categorical variable were calculated. In addition descriptive statistics such as frequency tabulation, mean, median, standard deviation (SD) and test of significance were calculated. The sensitivity, specificity, positive predictive values and negative predictive values of RDW and RBC count were calculated. Statistically significant results were those with values of p≤0.05.

## Results

Age ranged from 1-12 years. In IDA group male were found 16(59%), female were 11(41%) and in BTT group male were 15(60%), female were 10(40%) (Fig.-1).

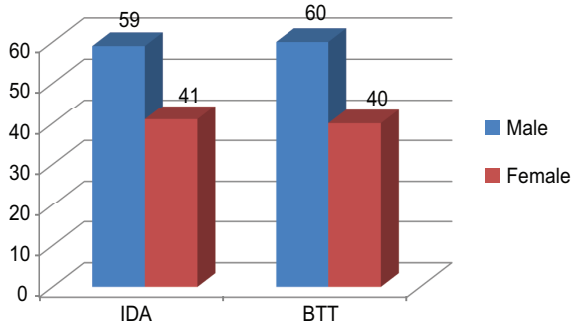


**Fig.-1** *Gender distribution in both groups*

In this study, haematological parameters (Hb%, RBC count, MCV, MCH, MCHC and RDW) of IDA group and BTT group was reviewed and it was found that Hb%, RBC count and RDW was significantly different between the two groups. The mean Hb% value in IDA group was 9.28 (±0.68); the mean Hb% value for BTT was 10.26±0.34. The Hb% value in IDA group was significantly (p<0.0001) lower than the Hb% for BTT. The mean value of MCV was 69.56±4.44 fl in IDA group, in BTT group the mean value of MCV was 67.65±3.79 fl; mean value of MCH in IDA group was 19.40±2.49 pg and in BTT group was 19.28±1.90 pg and the mean value of MCHC in IDA group 27.93±1.15 gm/dl in BTT group was 28.18±1.05 gm/dl. All the above patients of two groups had microcytic hypochromia, three indices MCV, MCH and MCHC overlap in two groups, and there was no significant difference in MCV, MCH and MCHC of two groups.

The mean RDW value for IDA was 16.75 (±2.37), the mean RDW value for BTT was 13.43(±1.50). The RDW value for IDA was significantly (p<0. 0001) greater than value for BTT. Contrary, The RBC count for BTT was significantly (p<0. 0001) greater than value for IDA. The mean RBC count for IDA was 4.41 (± 0.41), the mean RBC count for BTT were 5.20 (±0.35 /$mm^3$). From this result, the study revealed that to differentiate between iron deficiency anemia (IDA) & beta thalassemia trait (BTT) hemoglobin (Hb) level, red cell distribution width (RDW) value and red blood cell (RBC) count might play pivot role in common practice (Table I).

The numbers of patients in each group with an elevated RBC distribution width. Twenty two (22) of 27 patients with iron deficiency had RBC distribution width values greater than 14.6, compared to four (4) of 25 patients with thalassemia trait, and twenty one (21) of 25 patients with thalassemia trait had RBC distribution width values lower than 14.6, compared to five (5) of 27 patients with iron deficiency. The total number of correctly identified patients by using indices RDW is 43(83%). So this index helps us in distinguishing iron deficiency anemia from thalassemia trait. In this study it was found that, eleven (11) of 27 patients with iron deficiency had RBC distribution width values greater than 18 compared to one (1) of the patients with thalassemia trait (Table II).

**Table I**

*Difference of Haematological parameters; Hb%, RBC count, MCV, MCH, MCHC and RDW of IDA group (n=27) and BTT group (n=25)*

| Haematological parameters | IDA (n=27) Mean (±SD) | BTT (n=25) Mean (±SD) | P value |
|---|---|---|---|
| Hb%(gm/dl) | 9.28(±0.68) | 10.26 (±0.34) | <0.001 |
| RBC X $10^{12}$ /L | 04.41(±0.41) | 05.20(±0.35) | <0.001 |
| MCV(fl) | 69.56(±04.44) | 67.65 (±3.79) | 0.10 |
| MCH (pg) | 19.40(±02.49) | 19.28(±01.90) | 0.97 |
| MCHC(gm/dl) | 27.93(±01.05) | 28.18 (±01.15) | 0.40 |
| RDW | 16.75(±2.37) | 13. 43(±1.50) | <0.001 |

**Table II**

*The differential value of RDW for differentiation between IDA and BTT and correctly identified number of the patients by using these indices in each group*

| Differential value | IDA (n=27) | BTT (n=25) | Total number of Correctly diagnosed Patients (n= 52) | Percentage correctly Identified patients (%) |
|---|---|---|---|---|
| RDW (%) | | | | |
| IDA >14.6 | 22* | 4 | 43(22+21) | 83% |
| BTT <14.6 | 5 | 21 * | | |

*True positives. IDA- iron deficiency anemia; βTT- beta thalasemia trait; RBC- red blood cells; RDW- red blood cell distribution width

An elevation of RBC distribution width (>14.6) in IDA had a sensitivity of 81%, specificity of 84%, positive predictive value (PPV) of 85% and negative predictive value (NPV) of 81%; value of RBC distribution width (<14.6) in BTT had a sensitivity of 84%, specificity of 81%, positive predictive value (PPV) of 81% and negative predictive value (NPV) of 85% (Table III).

**Table III**
*Sensitivity, specificity, positive and negative predictive value of discrimination index RDW in differentiation between BTT and IDA*

| Indices | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|
| RDW (%) | | | | |
| IDA >14.6 | 81% | 84% | 85% | 81% |
| BTT<14.6 | 84% | 81% | 81% | 85% |

PPV, positive predictive value; NPV, negative predictive value; positive predictive value: true positive/(true positive + false positive); negative predictive value: (true negative/true negative + false negative)

In this study patients with microcytic anemias, RBC distribution width was elevated in most patients with iron deficiency anemia. Eighteen (18) of 27 patients with iron deficiency had RBC distribution width values greater than 16, compared to two (2) of 25 patients with thalassemia trait. Above table also shows that twenty three (23) of 25 patients with thalassemia trait had RBC distribution width values lower than 16, compared to nine (9) of 27 patients with iron deficiency (Table IV).

**Table IV**
*The differential value of RDW, when cutoff value for RDW >16 in differentiation between IDA and BTT.*

| Differential value | IDA (n=27) | BTT (n=25) |
|---|---|---|
| RDW (%) | | |
| IDA >16 | 18* | 2 |
| BTT <16 | 9 | 23 * |

*True positives. IDA, iron deficiency anemia; βTT, beta thalassemia trait; RBC, red blood cells; RDW, red blood cell distribution width

An elevation of RBC distribution width (>16) had a sensitivity of 67%, specificity of 92%, and positive predictive value (PPV) of 90% indistinguishing iron deficiency anemia from thalassemiatrait. Moreover, eleven (11) of 27 patients with iron deficiency had RBC distribution width values greater than 18 compared to one (1) of the patients with thalassemia trait. An elevation of RBC distribution width e"18 specificity of 96% and positive predictive value (PPV) of 92%. The table had shown validity of RDW that predict presence of IDA and in distinguishing iron deficiency anemia from thalassemia trait (Table V).

**Table V**
*Sensitivity, specificity, positive and negative predictive value of RDW discrimination index in differentiation between BTT and IDA, when cutoff value for RDW >16*

| Indices | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|
| RDW (%) | | | | |
| IDA >16 | 67 % | 92 % | 90 % | 72 % |
| BTT<16 | 92 % | 67 % | 72 % | 90 % |

PPV, positive predictive value; NPV, negative predictive value

**Discussion**

Iron deficiency (ID) is by far the most common cause of anemia in general and of microcytic hypochromic anemia in particular. It is important to make a timely and accurate diagnosis and initiate an early intervention to reduce the negative impact of anemia. Screening for BTT is of increasing importance in genetic counseling. However, differentiating BTT from IDA is warranted because the thalassemia heterozygote should not be given iron in a IV route to normalize MCV.[23]

Decreased levels of serum iron (SI), transferrin saturation (TS) and ferritin with increased levels of total iron binding capacity (TIBC) are the main diagnostic criteria for IDA.[17,18] The presence of characteristic red blood cell microcytosis and elevated levels of HbA2 establish the diagnosis of BTT. Showing body iron status or measuring HbA2 is time-consuming and requires laboratory staff and also not possible at every centers.

Less time-consuming methods are based on the calculation of discrimination indices from red blood cell indices obtained during routine complete blood count. On the basis of this approach, since 1973 some discrimination indices such as Mentzer's index (MI), RBC count, RDW, and RDWI are reported for differentiation between thalassemia trait (TT) and iron deficiency anemia (IDA).[24] Several studies have been done throughout the world to see sensitivity & specificity of most reliable RBC indices.

Though there are many similarities of red cell indices in IDA and BTT but RDW value emerged as an important parameter to differentiate iron deficiency anemia (IDA) from β thalassemia trait (βTT).[20,21,25,26]

There are few publications regarding these topics in pediatrics. An assessment of the value of RDW in the evaluation of pediatric microcytic anemias is the purpose of this study.

The study consists of IDA & BTT subjects; IDA was diagnosed as serum ferritin <12ng/ml and BTT was diagnosed as hemoglobin (Hb) A2 ≥3.5%. In this study, 27 cases of IDA and 25 cases of BTT were the subjects of the study.

Regarding mean weight, height and the mean monthly income of both group showed there was no significant difference of these parameters in the two (2) groups. In present study, the mean age was 5.48(±2.83) years in IDA group & in BTT group it was 5.76(±3.03) years. There was no significant difference between IDA & BTT groups in respect of age (P> 0.05).

Consanguinity was found only in BTT group with a large percentage 16(64%) compare to IDA group (0%).

The present study revealed that the mean hemoglobin level was 9.28(±0.68) gm/dl in IDA group & in BTT it was 10.26 (±0.34). Statistically significant differences were found between iron deficiencies with b-thalassaemia trait (P<0.001).

The mean haemoglobin level in the b- thalassaemia trait was higher than IDA, it was observed by Demir et al[12]. they were found mean Hb% in BTT 12.41(±1.60) & in IDA it was 9.35(±0.81) gm/dl. Madan et al[27] and England et al[28] obtained also similar results, mean Hb concentration was significantly higher in traits as compared to iron deficient subjects (p<0. 0001).

In this study, the mean value of MCV was 69.56±04.44 fl in IDA group and in BTT group it was 67.65±3.79 fl; mean value of MCH in IDA group was 19.40±02.49 pg and in BTT 19.28±01.90 pg and the mean value of MCHC was in IDA 27.93±01.05 gm/dl and in BTT group 28.18±01.15 gm/dl. There was no significant difference of these haematological parameters in IDA and BTT groups. MCV and MCH in beta thalassemia trait (BTT) had lower levels than of iron deficiency anemia. Some study also showed that, MCV and MCH in b- thalassemia trait had higher levels than that of iron deficiency anaemia.[29-30]

The present study showed that the RBC count in b-thalassaemia trait is significantly higher than that of iron deficiency anemia (p<0.0001). The mean RBC counts was 05.20±0.35 x $10^{12}$/L in BTT & the mean RBC count in IDA was 04.41±0.41 x $10^{12}$/L. England et al[19] and Demir et al[24] found that b- thalassaemia trait had significantly higher number of red cells than that of iron deficiency anaemia.

In this study, the mean RDW value for IDA was 16.75±2.37 and the mean RDW value for BTT was 13.43±1.50. The RDW values for IDA are significantly (p<0.0001) greater than value for BTT.

The findings of present study was similar with the findings of Robert et al[31], where the mean RDW was in IDA 19.45± 4.02; and the mean RDW in BTT was 14.91± 1.13. Similar finding also were found by Bessman et al[21] and Demir et al[24] in their studies, the mean Red cell distribution width (RDW) in iron deficiency anaemia (IDA) was significantly higher than the mean RDW in beta thalassemia trait (BTT).

Besides calculating the sensitivity, specificity, positive and negative predictive value of RDW and RBC count in differentiation between BTT and IDA, total number of correctly identified patients also calculated in this study.

In the present study the total number of correctly identified patients by using RDW value is 43(83%) and RBC count is 43(83%) in each group. Similar finding regarding RBC count conforms to the study of Demir et al[24] They found, total number of correctly diagnosed patient by RBC was 90%, but by RDW it was only 59%.

This study revealed that, an elevation of RBC distribution width (RDW) (>14.6) in IDA had sensitivity of 81% and specificity of 84% to differentiate iron deficiency anemia from thalassemia

trait. The positive predictive value (PPV) of RDW >14.6 in cases of IDA were 85%. Robert et al[31] found an elevation of RBC distribution width had a sensitivity of 86%, specificity of 57% to distinguishing iron deficiency anemia from thalassemia trait. Viswanath et al[25] detected role of red cell distribution width in the diagnosis of iron deficiency anemia as RDW had a higher sensitivity than peripheral smear (PS). They also found RDW was suggestive of iron deficiency in 100%, 82.05% and 100 % of patient with mild, moderate and severe anemia respectively.

Regarding RBC count, in this study it was found that an elevation of RBC (>$5x10^{12}$/L) in BTT had a sensitivity of 83% and specificity of 86%. The positive predictive value (PPV) of RBC count >$5x10^{12}$ /L in cases of BTT was 83%. Demir et al[24] was found ninety percent of the children patients were correctly identified with RBC count.

In this study it was found that, the positive predictive value (PPV) of RDW >14.6 in cases of IDA and the positive predictive value (PPV) of RBC count >$5x10^{12}$ /L in cases of BTT were highest as follows: 85% and 83% respectively.

Robert WN found that none of the patients with thalassemia trait had RBC distribution width values greater than 20, elevation of RBC distribution width to greater than 20 was seen exclusively in iron deficiency.[31]

This study showed that when cutoff value for RDW >16 in differentiation between IDA and BTT had Sensitivity 67%, Specificity 92% and positive predictive value (PPV) 90%; and an elevation of RBC distribution width had e"18 specificity of 96% and positive predictive value (PPV) of 92%. Similar study was done by Melo et al[32] they mentioned that, RDW above 16% was the best index of IDA, with sensitivity 69.2% and specificity 80.7% and Laso et al[33] found When 18 was taken as cutoff value for RDW, its positive predictive value was very high in iron deficiency (95%).

In this study, it was found that, the positive predictive value (PPV) of RDW>14.6 are the highest (85%) than other RBC indices. When cutoff value for RDW e"16 % and e"18% to diagnosed iron deficiency anemia (IDA), the positive predictive value (PPV) was 90% and 92% respectively. In such a way, RDW value might be reliable diagnostic tool for differentiation between IDA and BTT.

**Conclusion**

From this study, it may be concluded that Haemoglobin level, RBC distribution width (RDW) and RBC count appears to be perfect and useful device for the management of pediatric microcytic hypochromic anemia. In patients with microcytic hypochromic anemia, RDW value ≥14.6% and Hb level< 10gm/dl, iron deficiency is the most likely diagnosis. RDW value (>16) is a reliable diagnostic tool in differentiation between IDA and BTT. Red cell distribution width (RDW) above 16% is the best index of IDA.

**References**


1. DeMaeyer E, Adiels TM. The prevalence of anaemia in the world. *World Health Statistics Quarterly* 1985;**1638**:302-16.
2. WHO/UNICEF/UNU, Iron deficiency anaemia, Assessment, prevention and control a guide for programme managers, Geneva, World Health Organization, 2001.
3. Amanatullah AZ, Mannan MA, Ali ME. Prevalence of anaemia among children in Bangladesh: Time to act, malnutrition: meeting the Challenges in South Asia, 10th Annual Scientific Conference (ASCON) 2002, June 11-13.ICDDR, B Dhaka, Bangladesh.
4. Aggett PJ, Agostoni C, Axelsson I, Bresson JL, Goulet O. Iron metabolism and requirements in early childhood: Do we know enough? A commentary by the ESPGHAN committee on nutrition. *Journal of Pediatric Gastroenterology and Nutrition* 2002;**34**: 337-45.
5. Beard JL. Iron biology in immune function, Muscle metabolism and neuronal functioning. *Journal Of Nutrition* 2001;**131**:568-79.
6. Lozoff B, Jimenez E, Hagen J, Mollen E, Wolf AW. Poorer behavioral and developmental outcome more than 10 years after treatment for iron deficiency in infancy. *Pediatrics* 2000;**105**:51.
7. Glader B, editors. Anemias of inadequate production. In: Richard EB, Robert MK, Hal BJ, (eds.), Nelson text book oí pediatrics, 17th ed. Philadelphia: Saunders; 2005. P.1606-1617.
8. Haque MS, Alam MA, Khan WA. Thalassemia situation in Dhaka Shishu Hospital. *Dhaka Shishu Hospital Journal* 1999;**15**:30-36.
9. Khan WA. Thalassemia in Bangladesh. *Dhaka Shishu Hospital Journal* 1999;**15**:42-44.
10. Earl RO, Wotecki CE. Iron Deficiency Anemia: Recommended guidelines for the prevention, detection

and management among U.S. children and women of childbearing age. Washington, DC: National Academy Press; 1993.

11. Centers for Disease Control and Prevention. Recommendations to prevent and control iron deficiency. *MMWR Recomm Rep* 1998;**47**(RR-3):1-29.
12. Elwood PC, Waters WE, Greene WJ. Evaluation of iron supplements in prevention of iron-deficiency anaemia. *Lancet* 1970;**2**:175-77.
13. Guyatt GH, Oxman AD, Ali M, Willan A, McIlroy W, Patterson C. Laboratory diagnosis of iron deficiency anemia : An overview. *J Gen Intern Med* 1992;**7**:145-53.
14. Cook JD, Baynes RD, Skikne BS. Iron deficiency and the measurement of iron status. *Nutr Res Rev* 1992;5:189-202.
15. Wharton BA. Iron deficiency in children: Detection and prevention. *British Journal of Haematology* 1999;106:270-80.
16. Bellamy carol. The state of world children, Focus on nutrition: UNICEF, New York: Oxford University Press; 1998.
17. Wharton BA. Iron deficiency in children: detection and prevention. *Br J Haematol* 1999;**106**:270-80.
18. Oski FA. Iron deficiency in infancy and childhood. *N Eng J Med* 1993;**329**:190-93.
19. England JM, word SM, Down MC. Microcytosis, anisocytosis and the red cell indices in iron deficiency. *Br J Haematol* 1976;**34**:589.
20. Bessman JD, einstein DI. Quantitative ansisocytosis as discriminant between iron deficiency and thalassemia minor. *Blood* 1979;**53**;288-93.
21. Bessman JD, Gilmer PR, Gardner FH. Improved classification of anaemias by MCV and RDW. *Am J Clin Pathol* 1983;**80**:22-6.
22. Park KI, Kim KY. Clinical evaluation of Red cell volume distribution width (RDW). *Yonsei Medical Journal* 1987;**28**:282-90.
23. NF. The beta-thalassemias. *N Engl J Med* 1999; **341**: 99-109.
24. Demir A, YaraliN, FisginT, DuruF, KaraA. Most reliable indices differentiation between thalassemia trait and iron deficiency anemia. *Pediatr Int* 2002;**44**:612-16.
25. Viswanath D, Hegde R, Murthy V, Nagashree S, Shah R. Red cell distribution widthinthe diagnosis of iron deficiency anemia. *Indian Journal of Pediatrics* 2001; **68**:1117-19.
26. Aslan D, Gumruk F, Gurgey A, Altay C. Importance of RDW value in differential diagnosis of hypochromic anemia. *American J of Hematology* 2002;**69**:31-33.
27. 29. Madan N, Sikka M, Sharma S, Rusia U, Kela K. Red cell indices and discriminant functions in the detection of beta thalassemia trait in a population with high prevalence of iron deficiency anemia. *Indian J Pathol Microbio* 1999;**42**:55-61.
28. England JM, Fraser PM. Differentiationof iron deficiency from thalassemia trait by routine blood count. *The Lancet* 1973;**3**:449-52.
29. Nahar NN. Incidence of hereditary haemoglobin disorders and iron deficiency in hypochromic blood picture. FCPS dissertation Dhaka: Bangladesh College of Physicians and surgeons.
30. Hinchliffe RF, Lilleyman JS. Frequency of coincident iron deficiency and thalassaemia trait in British Asian children. *Journal of Clinical Pathology* 1995;**48**: 594-95.
31. Robert WN. Red Blood Cell Distribution Width in Pediatric Microcytic. *Anemias Pediatric* 1987;**80**; s251-54.
32. Melo MR, Purini MC,Cancado RD, Kooro F. The use of RBC indices in the differential diagnosis of microcytic anemias: is it approach to be adopted? *Rec Assoc Med Bras* 2003;49:135-36.
33. Laso FJ, Mateos F, Ramos R Herero F. Amplitude of the distribution of erythrocyte size in the differential diagnosis of microcytic anemia. *Med Clin (Barc)* 1990;**94**:1-4.

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ORIGINAL ARTICLE

# Nutritional Study of Picky Eaters: A Case Control Study

**Rana Kumar Biswas[1], Srabonti Ghosh[2], ARM Luthful Kabir[3]**

**Abstract**

***Background:*** *Picky eating is a relatively common problem during childhood. Picky eating may cause parents considerable concern leading to physician visits and may cause conflict between parents regarding handling of their child's eating behavior.*

***Objectives:*** *The present study was conducted to compare the nutritional status and daily calorie consumption among children with and without picky-eating-behavior.*

***Methods:*** *The present study was conducted out in the Department of Paediatrics, Sir Salimullah Medical College and Mitford Hospital, Dhaka and private chambers of paediatrician, general physician from July 2013 to December 2013. The case was defined as a child who had anorexia or took one or two favorite foods as explained by the parents in an otherwise healthy child with picky eating disorder, while a control was defined as a child without having picky eating disorder.*

***Results:*** *Thirty percent of the parents of cases complained that their children were not growing well as opposed to only 4% of the control group ($p<0.05$). Complaint of abdominal pain was considerably higher in the former group than that in the latter group ($p<0.05$). The history of forceful feeding was present in 20% of the cases compared to none in the control ($p>0.05$). The mean 24 hours intake of calorie was lower in the cases than that in the control, but the difference did not reach the level of significance ($p>0.05$). In terms of nutritional status very few children (8%) with picky eating behavior were wasted (low weight-for-height) ($p>0.05$). However, 26% of the picky-eaters were underweight in terms of BMI compared to 7% of the controls, but the difference was not statistically significant ($p>0.05$).*

***Conclusion:*** *The study concluded that the children with picky-eating-behavior are almost similar to their control counterparts in terms of nutritional status (wasting, stunting and BMI) and calorie consumption.*

***Keywords:*** *Picky eater, wasting, stunting, BMI.*

## Introduction

Picky eaters may be defined as "a child who does not eat anything or take one or two favorite foods as explained by the parents in an otherswise healthy child". Picky eating is a relatively common problem during childhood ranging from 8% to 50% of children in different samples and is characterized by a toddler or a child eating a limited amount of food, restricting intake particularly vegetable, being unwilling to try new food, and having strong food preferences often leading parents to provide their child a meal different from the rest of the family.[1] Picky eating may cause parents' considerable concern leading to physician visits and may cause conflict between parents regarding the handling of their child's eating behavior. Although the long-term health effects of

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picky eating are unclear there is evidence in early childhood that picky eaters weigh-less than non-picky eaters. Dubois found that picky eaters ate fewer calories and were twice as likely to be underweight than non-picky eaters.[2,3] A previous study of 135 children aged 5 years from the Stanford Infant Growth Study found that picky eaters consumed fewer calories than non-picky children and showed a less vigorous sucking style as an infant, suggesting that picky eating has trait-like characteristics.[4] Finally, a German study of 426 children 8 to 12 years of age found that picky eaters were more likely to exhibit behavioral problem behaviors than non-picky eaters.[5] Hence, there is evidence in childhood that picky eaters are likely to consume fewer calories and to weigh less, and in later childhood they demonstrate behavioral problems and in adolescence they have symptoms of anorexia nervosa. Hence, the studies to date suggest that a subset of those with picky eating tends to persist over time with similar symptoms, particularly during early and later childhood.[6-8] These types of studies are very few in our country. The present study examined a cohort of children assessed from 2 to 15 years of age to determine the nutritional status of the picky eaters in relation to their daily consumption of calorie.

**Materials and Methods**

Study population was divided into case and control groups. A case was defined as a child who had anorexia or take one or two favourite foods as explained by the parents in an otherwise healthy child with picky-eating-disorder, while a control was defined as a child without having picky eating disorder. A total of 100 children, 2-15 years age (50 cases and 50 controls) were consecutively included in the study. The study was carried out in the Department of Paediatrics, Sir Salimullah Medical College and Mitford Hospital, Dhaka and private chamber of paediatricians and general physicians over a period of 6 months from July 2013 to December 2013. Children having any chronic illness like congenital heart disease, persistent pneumonia, chronic diarrhoea, epilepsy, cerebral palsy, undergoing major surgery and 2nd or 3rd degree malnutrition were excluded from this study. Calorie consumption was calculated based on the food 24 hours consumption which might be inherently associated with re-call bias. The demographic and anthropometric characteristics included in the study were age, sex, weight, height and BMI. Nutritional status was assessed using weight for age, height for age, weight for height Z score for younger children (5 or <5 years) and BMI for older children (>5 years old). Weight, height and age were used to calculate weight for age (measures undernutrition) and height for age (measures stunting)*z*-scores, based on the National Center for Health Statistics 2000 reference data. A cut-off value of –2 *z*-score was used to define undernutrition (moderate to severe form of malnutrition). Weight was measured by using bathroom scale, height by stadiomter and OFC by measuring tape. Using computer software SPSS (Statistical Package for Social Sciences), data were processed and analyzed.

**Results**

The present study was intended to compare the nutritional status and daily calorie consumption between children with and without picky-eating-ehavior. The study included 50 cases (picky-eaters) and 50 controls (non-picky eaters).

All the children in the case group had history of poor feeding as opposed to none in the control group (p<0.001). There was no significant difference between cases and controls in terms of growth of the children (p=0.517).Complaint of abdominal pain was considerably higher in the former group than that in the latter group compared to none in the control group (p=0.278). The frequency of vomiting, loose motion, fever and cough were almost similar between the two groups (p=0.590 and p=0.801 respectively) (Table I).

**Table I**
*Comparison of chief complaints between cases and controls*

| Chief compliments | Group | | p value |
|---|---|---|---|
| | Cases (n = 50) | Controls (n = 50) | |
| Not growing well | 15(30.0) | 12(24.0) | 0.517 |
| Abdominal pain | 16(32.0) | 7(14.0) | 0.070 |
| Forceful feeding | 10(20.0) | 0(0.0) | 0.278 |
| Vomiting /loose motion | 8(16.0) | 9(18.0) | 0.590 |
| Fever/cough | 6(12.0) | 7(14.0) | 0.801 |

The case and control groups were almost alike in terms of their birth history (p=0.832). Exclusive breast-feeding up to 6 months was 40% in case group and 44% higher in either group with no significant intergroup difference (p=0.651). Developmental history was age appropriate in majority of the children of both case and control groups (p=0.338). Family history of picky eating demonstrated their significant presence in cases (18%) than that in control (4%) (p=0.021) (Table II).

**Table II**
*Comparison of history between case and control groups*

| History | Group | | p value |
|---|---|---|---|
| | Case (n=50) | Control (n=50) | |
| Birth history | | | |
| LUCS | 27(54.0) | 26(52.0) | 0.832 |
| NVD | 23(46.0) | 24(48.0) | |
| Feeding history | | | |
| Exclusive breast feeding (up to 6 m) | 20(40.0) | 22(44.0) | 0.741 |
| Early complimentary feeding | 30(60.0) | 28(56.0) | 0.651 |
| Developmental history | | | |
| Age appropriate | 45(90.0) | 47(94.0) | 0.338 |
| Not age appropriate | 5(10.0) | 3(6.0) | |
| Immunization history | | | |
| Completely immunized | 48(96.0) | 50(100.0) | 0.451 |
| Not completely immunized | 2(4.0) | 0(0.0) | |
| Family history of picky eating | 9(18.0) | 2(4.0) | 0.021 |

Majority of the case group (94%) and all of the control groups looked normal at appearance (p=0.245). All the vital signs like temperature, pulse and respiratory rate (RR) were almost identically distributed between the case and the control groups (p=0.951,p=0.191 and p=0.513 respectively) (Table III).

**Table III**
*Physical examination finding between case and control groups*

| Physical examination | Group | | p value |
|---|---|---|---|
| | Case (n=50) | Control (n=50) | |
| Appearance | | | |
| Normal looking | 47(94.0) | 50(100.0) | 0.245 |
| Ill looking | 3(6.0) | 0(0.0) | |
| Vital signs | | | |
| Temperature | 98.3 ± 3.6 | 98.5 ± 4.0 | 0.951 |
| Pulse | 82 ± 7 | 89 ± 6 | 0.193 |
| RR | 23 ± 2 | 22 ± 3 | 0.513 |

The mean 24 hours intake of calorie (estimated on the basis of food consumed during the last 24 hours) was somewhat lower in the case group than that of the control group (p=0.087) (Table IV).

**Table IV**
*Comparison of calorie consumption between case and control groups*

| Calorie consumption | Group | | p value |
|---|---|---|---|
| | Case (n=50) | Control (n=50) | |
| Calorie in 24 hours | 1206.4 ± 201.5 | 1326.9 ± 194.0 | 0.087 |

Data were analyzed using Unpaired t-Test and were presented as mean SD

Over one-quarter (26.3%) of the case group children under weight (BMI below 5$^{th}$ centile) as opposed to only 7.1% of the control group, but the difference between the groups was not significant (p=0.369) (Table V).

**Table V**
*Comparison of BMI between case and control groups*

| BMI (kg/m$^2$) | Group | | p value |
|---|---|---|---|
| | (Case n=19 | Control (n=14) | |
| Underweight (<5$^{th}$ central) | 5(26.3) | 1(7.1) | 0.369 |
| Normal BMI (5$^{th}$ - 85$^{th}$ central) | 13(68.4) | 12(85.8) | |
| Overweight or Obese ≥85$^{th}$ central) | (1(5.3) | 1(4.0) | |

About 8% of children in the case group were wasted (in terms of weight for height Z score) compared to none in the control group (p=0.181). None of the children in either group was stunted (height for age Z score) (Table-VI).

**Table VI**
*Comparison of nutritional status between cases and controls*

| Nutritional status | Group | | p value |
|---|---|---|---|
| | Cases (n=50) | Controls (n=50) | |
| Weight-for-height Z Score | | | |
| Wasted | 4(8.0) | 0(0.0) | 0.181 |
| Normal | 46(92.0) | 50(100.0) | |
| Height-for-age Z Score | | | |
| Normal | 50(100.0) | 50(100.0) | - |

**Discussion**

The present study was intended to determine the nutritional status of the picky-eaters and whether their nutritional status differs from the children with normal eating behavior. In this study we observed nutritional status (in terms of wasting, stunting and BMI) and daily calorie consumption. The study demonstrated that very few children (8%) with picky-eating behavior were wasted (low weight-for-height) and none of them was stunted (low height-for-age). Though, 26% of the picky-eaters were underweight in terms of BMI (BMI < 5$^{th}$ centile) compared to 6% of the control group, but the difference between the groups were not statistically significant (p = 0.369).

Children can become picky eater for a number of reasons. Some children are naturally more sensitive to taste, smell, texture. Other children develop picky eating habits by modeling their parents fussy eating habits. Picky eating habits are more likely to develop when parents punish, bribe, or reward the children's eating behavior.[9]

In a large survey of 7,057 children aged 2-7 years old in Hong Kong, 43% were reported by their parents as being picky eaters.[3] A longitudinal study revealed that 40% of children's picky- eating behavior lasted longer than 2 years.[10] A cross-sectional survey found that the proportion of picky eaters increased from 19% at 4 months old to 50% by age 2 years.[2] Another cross- sectional survey of Chinese preschoolers reported that prevalence of picky eating was higher in 24–35-month-olds (36%) compared to 6-11-month-olds (12%).[11] These findings suggest that picky eating is a chronic problem.

Jacobi et al[8] examined the prevalence of picky eating and the relationship between picky eating and correlates of picky eating, other child eating and behavioral problems and maternal eating problems in a cohort of 426 children aged 8-12 years. The study found that picky and nonpicky eaters differed significantly on all of the child eating behaviors. Overall, picky children were reported to avoid foods in general more often than nonpicky eaters. Picky children did not differ from nonpicky children with regard to their own and maternal eating disturbances. However, picky children displayed more problem behaviors comprising both internalizing and externalizing behaviors.[7,8]

Children with picky-eating habits have previously been identified as being at a potential risk for having nutritional deficits and the association of picky-eating behavior with growth status in children has also been evaluated.[6,10,12] A longitudinal study of 120 children aged 2-11 years, detected no significant effects on growth.[6] A cross-sectional survey in 1,498 children at 2.5, 3.5, and 4.5 years old, analyzed the relationship between eating behaviors, such as picky eating and dietary adequacy, and body weight; this study found that the amounts of energy, total fats, and protein consumedwere significantly less for picky eaters than for non-picky eaters (energy, p = 0.0302, total fats, p = 0.0114; and proteins, p <0.0001).[5] This study found that picky eat-ers were prone to consume fewer than two servings of meat and alternatives per day (odds ratio: 0.319; 95% CI 0.181-0.560). Further research found that picky eaters were twice as likely to be underweight at 4.5 years old as non-picky eaters (odds ratio: 2.415; 95% CI 1.383-4.216).[5]

The University College London's Institute of Child Health (UK) relates that: Typically a child or adolescent with selective eating remains within the normal range for both weight & height and show no abnormality on physical examination.

However, like any other scientific study, the present study is not without limitations. The sample size was very small and calorie consumption was calculated based on food 24 hours consumption which might be inherently associated with re-call bias.

## Conclusion

From the findings of the study it can be concluded that the children with picky eating behavior are almost comparable to their control counterparts in terms of nutritional status (wasting, stunting and BMI) and calorie consumption.

## References


1. Carruth BR, Skinner J, Houck K, Moran J, Coletta F, Ott D. The phenomenon of picky eater: A behavioral marker in eating patterns of toddlers. *Journal of the American College of Nutrition* 1998;**17**:180-86.
2. Carruth BR, Ziegler PJ, Gordon A, Barr SI. Prevalence of picky eaters among infants and toddlers and their caregivers' decisions about offering a new food. *J Am Diet Assoc* 2004;104(Suppl 1):s57-64.
3. Centre for Health Education and Health Promotion, Faculty of Medicine, Chinese University of Hong Kong. *Joint Hands to Create a Healthy Eating Culture in School Children*. (2006). Available from: http://www.cuhk.edu.hk/ cpr/pressrelease/060708e2.htm
4. Dubois L, Farmer AP, Girard M, Peterson K, Tatone-Tokuda F.Problem eating behaviors related to social factors and body weight in preschool children: A longitudinal study. *International Journal of Behavioral Nutrition and Physical Activity* 2007;**4**: 9.
5. Dubois L, Farmer AP, Girard M, Peterson K. Preschool children's eating behaviors are related to dietary adequacy and body weight. *Eur J Clin Nutr* 2007;**61**:846-55.
6. Dubois L, Farmer AP, Girard M, Peterson K, Tatone-Tokuda F. Problem eating behaviors related to social factors and body weight in preschool children: a longitudinal study. *Int J Behav Nutr Phys Act* 2007;**4**:9.
7. Jacobi C, Agras WS, Bryson S, Hammer LD. Behavioral validation, precursors, and concomitants of picky eating in childhood. *Journal of American Academy of Child & Adolescent Psychiatry* 2003;**42**:76-84.
8. Jacobi C, Schmitz G, Agras WS. Is picky eating an eating disorder? *International Journal of Eating Disorders* 2008;**41**:626-34.
9. Kabir ARML, Baki AA. Paediatricians' daily bread & butter in the private chamber. Paper presented in the first International Paediatric Congress, 2006 August 25-27, Sylhet, Bangladesh.
10. Mascola AJ, Bryson SW, Agras WS. Picky eating during childhood: a longi-tudinal study to age 11 years. *Eat Behav* 2010;**11**:253-57.
11. Xue Y, Zhao A, Cai L, Yang B, Szeto IM, Ma D, et al. Growth and development in Chinese pre-schoolers with picky eating behaviour: A cross-sectional study. *PLoS One* 2015;10(4):e0123664.
12. McPherson RS, Hoelscher DM, Alexander M, Scanlon KS, Serdula MK. Dietary assessment methods among school-aged children: validity and reli-ability. *Prev Med* 2000;31:S11-33.

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REVIEW ARTICLE

# Paediatric Diabetes Insipidus: A Review

**Rabi Biswas**

**Abstract**

*Diabetes insipidus is a disease characterized by partial or total inability to concentrate urine due to a vasopressin secretion deficiency (central diabetes insipidus), a resistance to its action (nephrogenic diabetes insipidus) or an excessive consumption of water (primary polydipsia). The main signs and symptoms of the disease are polydipsia, polyuria, and nocturia; central diabetes insipidus has an insidious onset, whereas nephrogenic diabetes insipidus has a gradual onset. Because of the advances in clinical, laboratory, imaging techniques and molecular biology, the etiologic diagnosis of diabetes insipidus has improved, from 50% of patients with idiopathic diabetes insipidus to 10%-20% of patients; therefore, it has been achieved more timely treatments, resulting in reduction of the risk of sequelae. Accordingly, it is pivotal to rule out secondary causes of diabetes insipidus, such as drug consumption or metabolic disorders in patients with nephrogenic diabetes insipidus, brain tumors, encephalic trauma, infiltrative diseases, autoimmune disorders or central nervous system infections in case of patients suffering from central diabetes insipidus. Regarding treatment, it is recommended the use of desmopressin, an analogue of vasopressin, for the treatment of central diabetes insipidus, whereas water consumption, decrease of salt consumption and treatment with diuretic and non-steroidal anti inflammatory drugs are recommended for treatment of patients with nephrogenic diabetes insipidus.*

***Keywords:*** *Pediatrics, Diabetes insipidus, central, nephrogenic.*

## Introduction

Diabetes insipidus was first described in the 18th century.[1] Diabetes is a Greek word meaning "siphon". It is derived from the verb diabaine, which means "to stand with legs apart, as in urination, or to go through. Insipidus is a Latin word meaning "without taste". In contrast to diabetes mellitus (DM), which involves the excretion of sweet urine, diabetes insipidus (DI) involves passing urine that is tasteless because of its relatively low sodium content.[2] DI is a rare, but serious disorder, that can be life threatening as it causes fluid imbalance that results in severe dehydration and electrolyte abnormalities.[3]

DI is characterized by polydipsia, polyuria, hypernatremia and dehydration.[2-5] There are different types of DI; the most common type is the neurological form, called central diabetes insipidus (CDI), which involves a deficiency of arginine vasopressin (AVP) or also known as antidiuretic hormone (ADH). CDI has several other names in literature. It is also known as pituitary, hypothalamic, neurohypophyseal or neurogenic DI. The second common type of DI is the nephrogenic diabetes insipidus (NDI), which is due to resistance of the renal tubules to ADH. NDI can be primary (idiopathic) or secondary, caused by drugs or chronic disorders, such as renal failure, sickle cell or polycystic kidney diseases.[6-11]

## Epidemiology

The incidence of DI in general population is 3 in 100,000, with a higher incidence among males (60%).

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X-linked NDI is very rare, with AVPR2 gene mutations among males estimated to be 4 in 1,000,000.[3] The incidence of compulsive water drinker (CWD) is unknown, but it seems to be that there is a female predisposition (80%). Although, the CWD commonly presents in the third decade of life, cases have been described in patients from 8-18 years of age.[3]

**Etiology**

Deficiency of AVP secretion is referred to as central DI, pituitary DI, or neurohypophyseal DI. Destruction of para-ventricular and supra-optic nuclei of the posterior pituitary by a tumor or surgery results in decreased ADH secretion and CDI. Alternatively, CDI may be idiopathic or inherited as either autosomal dominant or autosomal recessive trait in the locus 20p13.[12-14]

About 50% of central DI cases are idiopathic.[13] It usually appears within 24 hours followed by a 2-3-week period of inappropriate antidiuresis. In a German study, only 8.7% of DI cases persisted for more than 3 months.[15]

Close follow up of patients diagnosed with idiopathic DI is necessary to detect slowly growing intracranial lesions. Other causes of central DI include infiltrative disorders (histiocytosis X, sarcoidosis), anorexia nervosa, infections such as viral meningitis toxoplasmosis, inflammatory conditions including lupus erythematosis, wegener's, and vascular lesions such as arteriovenous malformations or aneurysms. Among them, Neurosurgical procedures, tumors, traumatic brain injury, tumors, infiltrative lesions, and malformations are the most frequent causes of DI.

NDI can be secondary, which is more common, or primary. The acquired form can be secondary to drugs like lithium, amphotericin B, methicillin and rifampin or due to renal disorders. The congenital forms, which are less common but very severe and difficult to treat, are the X-linked, autosomal recessive and autosomal dominant forms.[10] Majority of cases of hereditary nephrogenic DI have X-linked inheritance.[16] Hypercalcemia causes defective urinary concentrating ability which is generally reversible with correction of the hypercalcemia and may be associated with reductions both in sodium chloride reabsorption on the thick ascending limb of the loop of Henle, thereby interfering with the countercurrent mechanism. Persistent severe hypokalemia can have similar effects in the collecting tubule and the thick ascending limb of the loop of Henle. A variety of renal diseases can give rise to nephrogenic DI. Apart from lithium multiple medications are associated with nephrogenic DI.[8]

**Pathophysiology**

Arginine vasopressin (ADH) is an antidiuretic hormone that is first synthesized in cell bodies of the nuclei in the hypothalamus and is transported for the hypothalamus through the neural component of the pituitary stalk and stored in the nerve terminals in the posterior pituitary. ADH is usually transported in the blood to the receptor sites on the baso-lateral surface of the collecting duct membrane. Activation of the ADH receptor increases cyclic adenosine monophosphate (cAMP) production through a G protein adenylate cyclase coupling, and stimulates protein kinase A; leading to increased recycling of the protein aquaporin in the plasma membrane, which enhances water entry into the cell from the lumen. Absence of ADH receptor does not allow the process to take place, causing inhibition of water intake and polyuria. Alternatively, defective or absent aquaporin impairs the process in the absence of normal arginine vasopressin receptor (AVPR2 or V2 receptor).[17,18] There are different types of receptor for vasopressin. The V1 receptor present in the endothelial cells leads to a pressor effect by the activation of Ca++ pathway whereas the V2R is the one responsible for water reabsorption by activating cyclic adenosine monophosphate (cAMP) in the kidneys and opening of the aquaporin channels.[19,20]

Although there are many factors responsible for the secretion of vasopressin like nausea, acute hypoglycemia, glucocorticoid deficiency, smoking, the most important stimulus is increased plasma osmolality.[21] The increase in plasma osmolality can be as small as 1%.[22] The baroregulatory system usually does not cause the secretion of vasopressin during the normal circumstances unless there is a large volume loss, in which case there is release of some amount of this hormone.[23] Vasopressin acts as an antidiuretic by reabsorbing water via the principle cells of collecting ducts and the thick ascending loop of Henle, thereby increasing the plasma blood volume and decreasing the plasma osmolality.[24,25] It can also cause contraction of the smooth muscles in the blood vessels and release of von Willebrand factor and is regulated at the para-

ventricular and supra-optic nuclei, which sense the changes in osmolality.[9]

NDI arises from a defect or absent receptor site at the cortical collecting duct segment of the nephron (X- linked, vasopressin V2 receptor deficiency of locus Xq28) or of a defective or absent aquaporin, the probe that transport water at the collecting duct (autosomal recessive, locus 12q13, with several mutations being associated with ND1. The X- linked variety of ND1 accounts for about 90% of such cases.[26-28]

Polyuria and polydipsia with dilute urine, hypernatremia and dehydration are the hallmark of DI in infants and children. There are three common conditions that give rise to polydipsia and polyuria in these patients. The commonest is CDI, related to a deficiency of vasopressin, and less common is NDI, including X-linked recessive, autosomal recessive, and autosomal dominant types due to renal resistance to vasopressin. Finally, these symptoms can also occur in some compulsive water-drinking (CWD) patients who demonstrate physiologic inhibition of vasopressin secretion.[2-4]

**Table I**
*Main etiological causes of polyuria in children*[2-4]

| |
|---|
| Increased solute-load like diabetes mellitus |
| Central (neurogenic) |
| Diabetes Insipidus (vasopressin deficiency) |
| Acquired (more common) |
| Primary tumours or metastasis: germinoma, craniopharyngioma, glioma |
| Infectious/infiltrative lesions e.g. histiocytosis |
| Meningitis (encephalitis) |
| Congenital (less common) |
| AVP-NPH gene defect |
| Familial, autosomal dominant, autosomal recessive |
| Congenital anatomic defects |
| Agenesis of corpus callosum |
| Septo-optic-dysplasia |
| Familial pituitary hypoplasia |
| Nephrogenic diabetes insipidus (vasopressin resistant) |
| Acquired - drugs e.g. lithium, amphotericin B, methicillin and rifampin |
| Congenital - renal failure, X-linked, autosomal recessive and dominant |
| Primary polydipsia |
| Psychogenic - compulsive water drinking |
| Dipsogenic - defect thirst mechanism |

**Clinical manifestations**

The age of presentation is dependent on the etiology, it can present at any age, and the prevalence is equal among males and females although there is one study showing higher prevalence in the males.[27] In an alert and conscious patient, diabetes insipidus presents with intense thirst (polydipsia), craving for ice water together with polyuria. The volume of fluid ingested may range from 2L to even 20L a day.[29] Less severe cases may present with persistent enuresis. Most patients with an intact hypothalamic thirst centre maintain their fluid balance by drinking water. But patient who are unable to access free water as seen in neonates and elderly present with clinical features of hypernatremia and dehydration.[30] Lethargy, altered mental status, hyperreflexia, seizure, or, may be other presenting symptoms especially in the older age group, neonates and infants (Table-II).

**Table II**
*Clinical characteristics of patient presenting with central and nephrogenic diabetes insipidus*

| | Central diabetes insipidus | Nephrogenic diabetes insipidus |
|---|---|---|
| Age at presentation | Child between 5-6 years, rarely adulthood | Antenatal hydramnios, neonatal age, early infancy |
| Incidence | Rare | Common |
| Aetiology | Often acquired | Mostly acquired |
| Mode of inheritance | AD, AR | X-linked, AD, AR |
| Gene | AVPNP11, WFSI | AVPR2, AQD2 |
| Clinical presentation | Marked thirst, Growth failure | Severe thirst, Failure to thrive, Mental retardation |

AD - Autosomal Dominant, AR - Autosomal Recessive

Dehydration may lead to contraction of intravascular volume which in severe cases causes traction of dural veins and sinuses leading to intracranial hemorrhage.

**Diagnosis**

Diagnosis of DI can be difficult, as the non- specific symptoms of excessive crying, poor feeding, failure to thrive and irritability, are common in infants. Therefore, high index of suspicion is necessary. In addition to a complete medical history and physical examination, including the child's daily fluid intake, dietary intake, medication and bowel and bladder (voiding) habits, the diagnostic procedure may include: assessing the urine specific gravity of the first morning sample can be helpful. In doubtful cases, an accurate 24-hour urine collection is important to confirm polyuria in the first place. Diluted urine with a relatively high serum sodium concentration and osmolality effectively establish the diagnosis. The serum sodium level may be high >150 mmol/L (150 mEq/L), with the serum osmolality greater than 300mosmol/kg. A serum osmolality >300 mosmol/kg with urinary osmolality <300 mosmol/kg in a case with pathologic polyuria and polydipsia is diagnostic for DI. Serum potassium, and calcium concentrations are important to exclude the possibility of polyuria secondary to hypokalemia or hypercalcemia; both can interfere with renal concentrating mechanisms.[2-4]

The definitive diagnostic study is water deprivation test (WDT), which can be used both to confirm the diagnosis and distinguish between CDI and NDI on the basis of response to vasopressin analogue. The test should be performed by an experienced individual and under close supervision.[2-4] The normal response to dehydration or desmopressin includes urine osmolality greater than 450 mosml/kg, urine to serum osmolality ratio of 1.5 or higher, and an increase in urine to serum osmolality of 1 or more from baseline. A normal response to dehydration would be observed in CWD and to vasopressin analogue in CDI, but not in NDI, which is due to renal tubular unresponsiveness to vasopressin.

However, patients with CWD may have limited ability to concentrate urine and both of CDI and NDI may be partial, therefore a diagnostic confusion may arise between these conditions may arise as all may be capable of producing a similar rise in urine osmolality during WDT.[31,32] The hypertonic saline test offers an alternative approach to WDT in diagnosing DI and differentiating it from other polyuric states such a challenging situation. It is based on defining the relation between serum osmolality and plasma AVP concentrations. The test is well established in adults, with some limitations of reporting experience of its use in children.[33,34] Mohn et al[35] from UK reported using this test in five children (11 months to 18 years) who had diagnostic problems.

MRI pituitary and hypothalamus is an important tool for the assessment of the cause of CDI, and should always be performed after gadolinium injection, to check for abnormal enhancement within the stalk.[36]

Renal Ultrasonography helps ruling out primary renal disorders like polycystic renal disease and ureteric obstruction. Massive hydronephrosis and mega ureter are seen in children with polyuria-polydipsia of long duration. Gene testing for familial forms of CDI and NDI are now available.[27]

**Management**

The first step in DI management starts with patient's education about the disease and its management. The therapeutic goals are primarily reducing polyuria and decreasing thirst, so that the patient is able to grow adequately and maintain a normal life-style. This can be achieved through several strategies; a free access to water; patients with DI can drink enough fluid to replace their urine losses. When oral intake is inadequate and hypernatremia is present, replace losses with dextrose in water or intravenous hypo-osmolar fluids with respect to patient's serum osmolality.[2-4] Only sterile water cannot be administered intravenously without dextrose, as it can cause hemolysis.[33] To avoid hyperglycemia, volume overload, and overtly rapid correction of hypernatremia, the fluid replacement should be provided slowly aiming to reduce serum sodium by 0.5 mmol/L (0.5 mEq/L) every hour. Careful monitoring in intensive care settings should be provided.[34]

Dietary management aims to optimize free water excretion. Modification in the diet is helpful in decreasing solute load to renal and has been shown to be useful especially in NDI. Diet with low sodium (1 mmol/kg/day), low protein intake of 2 g/kg/day with high calories food providing a high caloric value which is also essential for growth and development.[37]

Vasopressin and its analogues should also be used in treating CDI, and lifelong supplementation

remains the mainstay of management. In older children with CDI aqueous vasopressin, lysine vasopressin may be used to minimize water excretion. Desmopressin (1-deamino-8-*D*-arginine vasopressin, dDAVP) is the current drug of choice for long-term therapy of CDI.[38] This synthetic analogue has more specific antiduretic action, negligible pressor activity and a longer half-life than the native molecule. It can be given parenterally, orally, or intranasally. Oral tablets although 20 folds less potent than the intranasal form, are highly effective and safe in children, with more flexibility of dosing and have largely replaced the intranasal form. The recommended dose off dDAVP is 100-1200 µg/ day in three divided doses orally; 2-40µg once or twice a day intranasally; and, 0.1-1µg parenterally.[36] There is a large variability in action amongst individuals and hence the duration between doses needs to be determined in each patient.[39] It is a safe practice to allow a short period of diuresis between two doses. Dilutional hyponatremia, headache, hypertension and nasal congestion are some of the side effects occasionally seen. Vasopressin tannate in oil is also used in the dose of 2-5U intramuscular every 25-72 hours. Lysine vasopressin is used if shorter duration of action of 2-8 hours is needed.[40]

Certain precautions should be taken for known patients or suspected ones for hypopituitarism undergoing surgery, considering hormonal replacement therapy such as corticosteroid, vasopressin and adequate fluids. As a practical consideration, any patient with post-operative anterior pituitary insufficiency should receive corticosteroid replacement therapy. Decreased bone mineral density has been reported in children with CDI; and significant improvement in bone mineral density was observed after treatment with oral alendronate.[41]

NDI is difficult to treat and cannot be effectively treated with desmopressin. Underlying pathology should be treated first. In idiopathic cases, hydrochlorothiazide in a dose of 2-4 mg/kg/day in divided doses could be used to ameliorate the sodium and water loss in the urine in addition to other general measures.[42,43] Amiloride given additionally or alone; and it has similar effect but is useful in preventing hypocalcaemia. A similar reduction in urine flow may be achieved with the prostaglandin synthetase inhibitor indomethacin, given in doses of 1.5-3.0 mg/kg.[36] A relatively new and promising approach is the combination of a thiazide, indomethacin, and desmopressin, which may reduce urine output by up to 80%. It is essential that all these patients drink adequate fluid volumes to quench their thirst.[43]

**Prognosis**

Central DI occurring after pituitary surgery usually remits within days to weeks but if structural damage has occurred to the stalk, it may even be permanent. The clinical course of chronic central DI is more of inconvenience to daily life than a dire medical condition. Currently available treatments with Desmopressin do a good job to control symptoms but patients must be watched closely for side effects, water intoxication, and hypernatremia. Prognosis of NDI is satisfactory only where the underlying aetiology could be resolved adequately.

**Conclusion**

DI is not that uncommon pediatric disorder. The clinical presentation varies with age of onset and underlying cause. Water deprivation test is useful in establishing the diagnosis, when it is not typical, and help in differentiating between the various causes; however, it should be performed under close supervision by an experienced team familiar with the test. Management of DI is essentially planned to treat the underlying cause. Desmopressin is the drug of choice for CDI, and the oral formulation is more preferred. Thiazide diuretics with other oral drugs showed promising result in NDI management.

**References**

1. Lindholm J. Diabetes insipidus: historical aspects. *Pituitary* 2004;**7:**33-38.
2. Chan JCM, Kemp S, Roth KS, Wilson TA. Pediatric diabetes Insipidus. Medescape 2013.
3. Saborio P, Tipton GA, Chan JCM. Diabetes Insipidus. *Pediatric in Review* 2000;**21**:122-29.
4. Ghiradello S, Garre ML, Rossi A, Maghnie M. The diagnosis of children with central diabetes insipidus. *J Pediatr Endocrinol Metab* 2007;**20**:359-75.
5. Di Largi N, Napoli F, Allergi A, Oliveri I, Bertteli C, Gallizia A, et al. Diabetes Insipidus, diagnosis and management. *Horm Res Pediatr* 2012;**77**:69-84.
6. Maghnie M, Cosi G, Genovese E. Central diabetes insipidus in children and young adults. *N Engl J Med* 2000;**343**:998-1007.

7. Babey M, Kopp P, Roberttisem GL. Familial forms of diabetes insipidus: clinical and molecular characteristics. *Nat Rev Endocrinol* 2011;**7**:701-14.
8. Bockenhauer D, Van't-Hoff W, Dattani M. Secondary nephrogenic diabetes insipidus as a complication of inherited renal diseases. *Nephron Physiol* 2011;**116**:23-29.
9. Catli G, Abaci A, Demir K, Ulusoy E, Altincik A, Buyukgebiz A, et al. Clinical profile and etiologies of children with central diabetes insipidus in a single center experience from Turkey. *J Pediatr Endocrinol Metab* 2012;**25**:499-502.
10. Robertson GL. Diabetes Insipidus. *Endocrinol Metab Clin North Am* 1995;**24**:549-72.
11. Kohn B, Nirman ME, Feldman H, Their SO, Singer I. Hysterical polydipsia (compulsive water drinking) in children. *Am J Dis Child* 1976;**130**:210-12.
12. Al Agha AE, Thomsett MJ, Ratcliffe JE, Cotterill AM, Batch JA. Acquired central diabetes insipidus in children: a 12-year-old Brisbane experience. *J Pediatr Child Health* 2001;**17**:172-75.
13. Chaker F, Chihaoui M, Slimane H. Etiological diagnosis of Central Diabetes Insipidus: about 41 cases. *Pan Afr Med J* 2016;**348**:995-1005.
14. Mohamed S, Osman A, Al Jurayyan N, Al Nemri A, Salih M. Congenital toxoplasmosis presenting as central diabetes insipidus in an infant: A case report. *BMC* 2014;**7**:184-88.
15. Kristof RA, Rother M, Neuloh G, Klingmuller D. Incidence, clinical manifestations, and course of water and electrolyte metabolism disturbances following transsphenoidal pituitary adenoma surgery: A prospective observational study. *Journal of Neurosurgery* 2009;**111**:555-62.
16. Arthus MF, Lonergan M, Crumley MJ. Report of 33 novel AVPR2 mutations and analysis of 117 families with X- linked nephrogeni. *Journal of the American Society of Nephrology* 2000;**11**:1044-54.
17. Mulders SM, Bichet DG, Rijss JP. An aquaporin-2 water channel mutant which causes autosomal dominant nephrogenic diabetes insipidus is retained in the Golgi Complex. *J Clin Invest* 1998;**102**:57-66.
18. Moses AM, Sangani G, Miller JL; Proposed cause of marked vasopressin resistance in a female with X-linked recessive V2 receptor abnormalities. *J Clin Endocrinol Metab* 1995;**80**:1184-88.
19. Morel A, O'Carroll AM, Brownstein MJ, Lolait SJ. Molecular cloning and expression of a rat Vla arginine vaso- pressin receptor. *Nature* 1992;**356**:523-26.
20. Sugimoto T, Saito M, Mochizuki S, Watanabe Y, Hashimoto S, Kawashima H. Molecular cloning and functional expres- sion of a cDNA encoding the human V(1b) vasopressin recep- tor. *Journal of Biological Chemistry* 194;**269**:27088-92.
21. Kronenberg HM, Melmed S, Polonsky KS, Larsen PR. Williams Textbook of Endocrinology, Saunders, 11th edition, 2008.
22. Kasper DL. Harrison's Principles of Internal Medicine, McGraw-Hill, New York, NY, USA, 17th edition, 2008.
23. Cowley AW Jr., Monos E, Guyton AC. Interaction of vasopressin and the baroreceptor reflex system in the regulation of arterial blood pressure in the dog. *Circulation Research* 1974;3**4**:505-14.
24. Grantham JJ, Burg MB. Effect of vasopressin and cyclic AMP on permeability of isolated collecting tubules. *The American Journal of Physiology* 1966;**211**:255-59.
25. Fejes-Toth G, and A. Naray-Fejes-Toth A. Isolated principal and intercalated cells: hormone responsiveness and Na+-K+-ATPase activity. *American Journal of Physiology* 1989;**256**:F742-F750.
26. Faerch M, Christensen JH, Corydon TJ. Partial nephrogenic diabetes insipidus caused by a novel mutation in the AVPR2 gene. *Clin Endocrinol (Oxf)* 2008;**68**:395-403.
27. Wildin RS, Antush MJ, Bennett RL. Heterogenous AVPR2 gene mutations in congenital nephrogenic diabetes insipidus. *Am J Hum Genet* 1994;**55**: 266-77.
28. Moses AM. Clinical and laboratory observations in the adult with diabetes insipidus and related syndromes. In: Czernichow P, Robinson AG, editors. Diabetes Insipidus in Man. Frontiers of Hormone Research. S Karger, Basel, Switzerland; 1985. P156.
29. Robertson GL. Diagnosis of diabetes insipidus. In: Diabetes Insipidus in Man. Frontiers of Hormone Research. Czernichow P, Robinson AG, editors. S Karger, Basel, Switzerland, 1985.P176.
30. Baylis PH. Diabetes insipidus. *Medicine* 1997;**25**: 9-11.
31. Miller M, Dalakos T, Moses AM, Fellerman H, Streeten DHP. Recognition of partial defects in antidiuretic hormone secretion. *Ann Intern Med* 1970;**73**:721-29.
32. Baylis PH, Thompson CJ. Osmoregulation of vasopressin secretion and thirst in health and disease. *Clin Endocrinol (Oxford)* 1988;**29**:549-76.

33. Moses AM, Streeten DHP;Differentiation of polyuric states by measurement of responses to changes in plasma osmolality induced by hypertonic saline infusion. *Am J Med* 1967;**42**:368-77.

34. Baylis PH, Robertson GL;Plasma vasopressin response to hypertonic saline infusion to assess posterior pituitary function. *J R Soc Med* 1980;**73**: 255-60.

35. Mohn A, Acerini CL, Cheetham TD, Lightman SL, Dunger DB. Hypertonic saline test for the investigation of posterior pituitary function. *Arch Dis Child* 1998;**79**:431-34.

36. Czernichow P, Garel C, Leger J. Thickened pituitary stalk on magnetic resonance imaging in children with diabetes insipidus. *Horm Res* 2000;**53** (Supplement 3):61-4.

37. Blalock JT, Gerron G, Quiter E, Rudman D. Role of diet in the management of vasopressin-responsive and resistant diabetes Insipidus. *Am J Clin Nutr* 1977;**30**:1070-76.

38. Cunnah D, Ross G, Besser GM. Management of cranial diabetes insipidus with oral desmopressin (DDAVP). *Clin Endocrinol (Oxf)* 1986;**24**:253-57.

39. Colaco P. Disorder of water and electrolyte homeostasis. In: Desai MP, Menon PS, Bhatia V, editors. Pediatric Endocrine Disorders. 2nd ed. New Delhi: Orient Longman Pvt Ltd;2008.P445-57.

40. Lam KS, Wat MS, Choi KL, Ip TP, Pang RW, Kumana CR. Pharmacokinetics, pharmacodynamics, long-term efficacy, and safety of oral 1-deamino-8-D-arginine vasopressin in adult patients with central diabetes insipidus. *Br J Clin Pharmacol* 1996;**42**: 379-85.

41. Mishra G, Chandrashekhar SR. Management of Diabetes Insipidus in Children. *Indian J Endocrinol Metab* 2011;**15** (Supplement):S180-87.

42. Muglia LJ, Majzoub JA. Disorders of the posterior pituitary. In: Sperling MA, editor. Pediatric Endocrinology. 3rd ed. Philadelphia: Saunders; 2008. P.356-73.

43. Rivkees SA, Dunbar N, Wilson TA. The management of central diabetes insipidus in infancy, desmopressin, low renal solute load formula, thiazide diuretics. *J Pediatr Endocrinol Metab* 2007;**20**: 459-69.

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CASE REPORT

# Alagille Syndrome: A Case Report

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## Introduction

Alagille syndrome is an autosomal recessive disorder which occur because of notch signaling pathway defects, primarily as a result of JAG1 mutation (ALG type 1), but it conjointly occurs seldom because of neurogenic locus notch homolog protein (NOTCH2) mutation (ALG type 2).[1,2] The syndrome and severity of Alagille can vary widely, often in the same family, from person to person. Some people may have mild form, while others may have more severe form. It is characterized by abnormalities in the liver, heart, eyes, face and skeleton. The main clinical manifestation of Alagille syndrome is cholestasis resulting from paucity of intrahepatic bile ducts and it is commonly associated with other clinical signs: heart disease, skeletal abnormalities, ocular abnormalities and facial dysmorphism.[3]

Typical facial alterations include sunken eyes, wide forehead, prominent chin, bulbous nose and small or malformed ears. Laboratory findings are increased blood levels of bile acids and direct bilirubin; increased transaminase, alkaline phosphatase, and gamma-glutamyltransferase activities and hypercholesterolemia. Histological findings are the presence of bile pigments in the cytoplasm of hepatocytes and in the lumen of bile canaliculi, ductules and ducts often associated with secondary cell injury.[4,5]

Several diseases can present cholestasis as a symptom; therefore, differential diagnosis continues to pose a challenge for pediatrician. In this case report, we present a patient in whom diagnosis of Alagille syndrome was done. It is important to be familiar with Alagille syndrome, so that its diagnosis can be suspected when a patient presents specific physical and morphological features, in addition to jaundice.

## Case report

A 7 months old female infant born of non-consanguineous parents presented with a history of jaundice since birth with progressive worsening along with episodes of acholic stool, intense itching and abdominal distension. There was no family history of sib death or family history of similar types of illness. She had mild pallor, icterus along with peculiar facial features in the form of broad forehead, deep seated eyes and prominent chin. Anthropometrically the child was severely under-weight, severely wasted and moderately stunted. Skin survey revealed multiple scratch mark due to excessive itching. On abdominal examination liver was enlarged 5cm from right costal margin, firm in consistency and on cardiovascular examination cardiac murmur splits at pulmonary area.

**Fig.-1:** *Triangular face with broad forehead, and saddle nose, deep set eyes and pointed chin*

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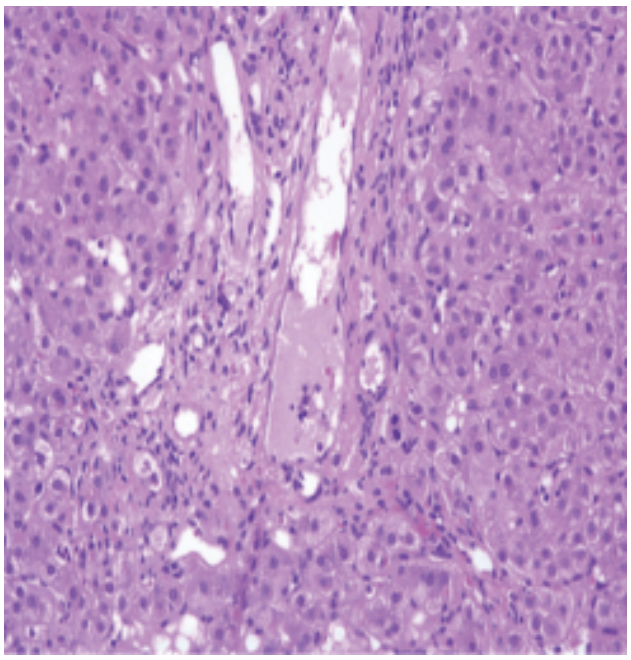

**Fig.-2** *Liver biopsy shows portal tract without any bile duct*

Investigations showed normal blood counts. Serum total bilirubin was 19.9 mg/dl (conjugated bilirubin 11.69 mg/dl), alanine transaminase 173 U/L, alkaline phosphatase 266 U/L, γGT 660 U/L, INR 1.09. A blood test for cytomegalovirus IgM was negative. Ultrasonography of whole abdomen hepatomegaly with raised parenchymal echotexture. X-ray spine showed butterfly vertebra. Echocardiography showed pulmonary stenosis. Hepatic histopathological examination revealed paucity of interlobular bile ducts. The child was diagnosed as a case of Alagille syndrome and started on ursodeoxycholic acid, cholestyramine and fat soluble vitamins. Jaundice and pruritus was improved partially with these treatments.

**Discussion**

Allagille syndrome is a multisystem autosomal dominant disorder, additionally referred to as arteriohepatic dysplasia, Alagille-Watson syndrome, Watson-Miller syndrome or syndromic common bile duct paucity which is characterized by variable clinical manifestations,[6] even among the similar family and usually include hepatic cholestasis, characterized by bile duct paucity in conjunction with liver (liver biopsy), cardiac abnormalities primarily involving the pulmonary arteries, skeletal (butterfly-like vertebrae and arch defects), ophthalmological finding (posterior embryotoxon) and facial findings. Additional features are intracranial bleeding and dysplastic kidneys.[7]

A diagnosis of Alagille syndrome is created mostly based upon identification of characteristic symptoms, a detailed patient history, a thorough clinical analysis and associated with a variety of tests including abdominal ultrasound, liver biopsy, echocardiography, vertebral radiography, slit lamp examination of the eyes, renal ultrasound with dropler, brain MRI and molecular genetic testing to rule out the symptoms.[8] In a study of 92 cases of Alagille syndrome, Emerick et al[9] described interlobular bile ductular paucity in 85%, cholestatic jaundice in 96%, cardiac abnormalities in 97%, characteristic triangular facies in 96% cases. Vertebral defects (butterfly vertebra) found in 51% and posterior embryotoxon in the eyes in 78% cases. Though we could not do mutation analysis due to lack of facilities in our country but our case had four of five features of Alagille syndrome and these were characteristic triangular facies, pulmonary artery stenosis, butterfly vertebra and bile ductular paucity. Pruritus was the major symptom and some of the cases respond to bile acid binding agents like cholestyramine. Our patient also showed response to cholestyramine.

The presence of heart murmur is the most common manifestation of Alagille syndrome. The majority of these murmur is caused by pulmonary stenosis. Intracardiac lesions such as Tetralogy of fallot and extra cardiac vascular lesions such as coarctation of aorta, patent ductus arteriosus may be present.[10] Our patient had pulmonary stenosis.

The most common radiological finding is butterfly shaped thoracic vertebrae, secondary to clefting abnormalities of the vertebral bodies. The reported frequency of butterfly vertebra ranges from 33% to 93%.[11] In the present case, vertebral radiography showed butterfly vertebrae.

Treatment for patients with Allagille syndrome aimed towards optimizing nutrition and managing complications associated with cholestasis and pruritus. Specific treatment is additionally indicated for individuals with the medications ursodeoxycholic acid, antihistamine, rifampin and cholestyramine.[1] In our case we treated our patient with ursodeoxycholic acid, cholestyramine powder and fat soluble vitamins.

## Conclusion

Cholestatic jaundice in infancy is one of the biggest diagnostic challenges faced by paediatricians. Paediatrician who first see the patient must be familiar with the several diseases involved to facilitate an early diagnosis. Alagille must be a part of the differential diagnosis in patients who in addition to jaundice present with physical and morphological characteristics of this syndrome.

## References


1. Padmakar S, Alishar S, Tabasum MA. A case report on Alagille syndrome and its clinical features. *Int J Res.Pharm Sci* 2021;**12**:18-21.
2. Chitayat D, Kamat, B, Saleh M. Alagille syndrome: Clinical perspectives. *The Application of Clinical Genetics* 2016;**9**:75-82.
3. Alagille D, Estrada A, Hadchouel M, Gautier M, Odievre M, Dommergues JP. Syndromic paucity of interlobular bile ducts (Alagille syndrome or arteriohepatic dysplasia): Review of 80 cases. *J Pediatr* 1987;**110:**195-200.
4. Krantz ID, Colliton RP, Genin A et al. Spectrum and frequency of jagged 1 (JAG1) mutations in Alagille syndrome patients and their families. *Am J Hum Genet* 1998;**62**:61-69.
5. Turnpenny PD, Ellard S. Allagille syndrome: Pathogenesis, diagnosis and management. *Eur J Hum Genet* 2012;**3**:251-57.
6. Huang T, Yang G, Dang X. Implementing targeted region capture sequencing for the clinical detection of Alagille syndrome: An efficient and cost-effective method. *Molecular Medicine Reports* 2017;**16**:76-81.
7. Saleh M, Kamath BM, Chitayat D. Alagille Syndrome: Clinical perspectives. *The Application of clinical Genetics* 2016:**9**:75-82.
8. Ayoub MD, Kamath BM. Alagille Syndrome: Diagnostic challenges and advances in management. *Diagnostics* 2020;**10**:907-07.
9. Emerick KM, Rand EB, Goldmuntz E, Krantz ID, Spinner NB, Piccoli DA. Features of Alagille syndrome in 92 patients: Frequency and relation to prognosis. *Hepatology* 1999;**9:**822-29.
10. Shim H, Park C, Kim S, Park Y.N. Alagille Syndrome-A case report. *The Korean Journal of Pathology 2004;***38:**56-59.
11. Kamath BM, Loomes KM, Piccoli DA. Medical management of Allagille Syndrome. *Journal of Pediatric Gastroenterology & Nutrition* 2010;**50**: 80-86.

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CASE REPORT

# Allergic Proctocolitis (AP) with Protein Losing Enteropathy (PLE): A Case Report

**Sharmin Akter[1], Aysha Sabiha[2], Nahide-E-Subha[3], Maimuna Sayeed[4], Bishnu Pada Dey[5], ASM Bazlul Karim[6]**

## Introduction

Allergic Proctocolitis (AP) is an immune mediated gastrointestinal disorder characterized by inflammation of the distal colon and this inflammation occurred in response to one or more food proteins. The disorder usually presents within a few months after birth but occasionally may present as early as first week of life.[1] The prevalence rate is 18 to 64 percent among infants with rectal bleeding.[2,3] 50 percent of AP babies are breastfed. But it is less common in infants fed with cow's milk-based or soy protein-based formulas.[4-6]

Infant with AP babies are generally healthy, presents with visible specks or streaks of blood mixed with mucus in the stool.[7] Some infant experience increased gas, episodic emesis, pain with defecation, and abdominal pain.[8] Cow's milk (CM), soy, egg and corn in the maternal diet are most common causative foods in breast-fed infants with AP, although other foods such as meat, fish, apple, carrot, wheat, and sesame have been mentioned.[9] There is transient colitis in AP which may cause hypoalbuminaemia due to protein losing enteropathy.[10,11]

## Case report

Here, we are reporting a 7 month old female baby, second issue of non-consanguineous parents got admitted in the department of pediatric gastroenterology and nutrition, BSMMU with the history of gradual swelling of whole body for 1 month, loose stool for 9 days. She had h/o occasional mucus-streaked stool since 5 month of age. Then she developed swelling of abdomen which gradually spread on whole body. There was also history of loose stool for last 9 days, passed 10 to 15 stools per day, not mixed with blood or mucous. Regarding feeding history baby was on exclusive breast feeding since birth & there was no history of drinking of cow's milk. There was no history of fever, vomiting, per rectal bleeding, atopic dermatitis, family history of atopy, scanty micturation, jaundice, feeding mismanagement. There was history of one unit of blood transfusion at six month of age. On examination the child was ill looking, no skin or hair change, vitals were within normal limit. The child was mildly pale, edeomatous, moderately wasted, bed side urine for albumin was nil. Per abdominal examination showed ascites. Other systemic examination revealed nothing abnormality.

The laboratory data showed Hb% 10 gm/dl, ESR 15 mm in 1st hr, Total count 19,000/cmm, neutrophil 32%, lymphocyte 63%, Eosinophil 7%. Electrolytes within normal limit, serum albumin 17 gm/l, liver

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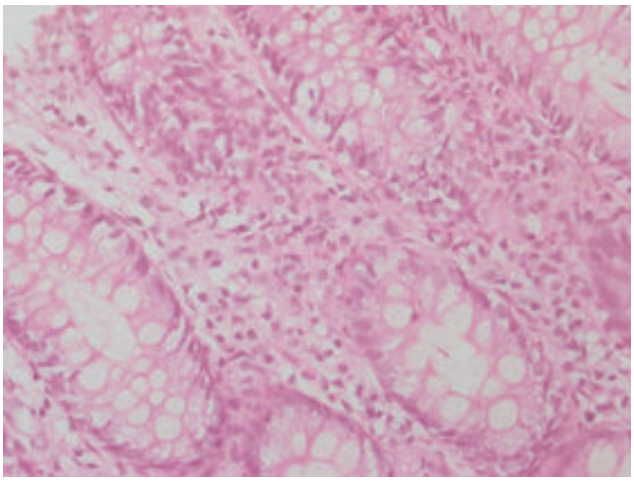

**Fig.-1a:** *H&Ex200: Allergic colitis with mucosal edema and many eosinophils in the lamina propria.*

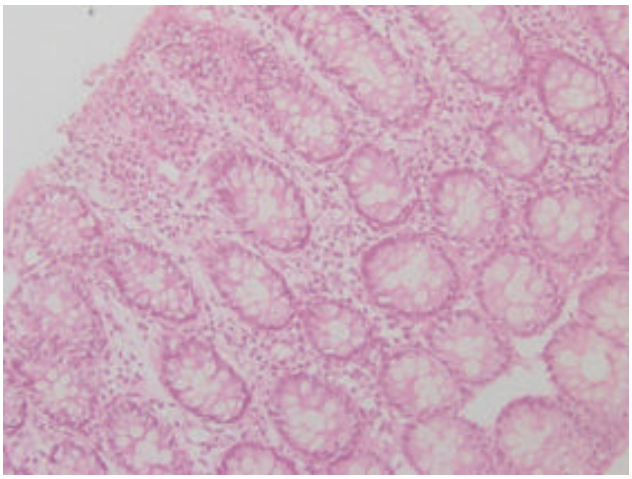

**Fig.-1b:** *H&Ex100:Allergic colitis with mucosal edema and many eosinophils in the lamina propria.*

function test normal, urine microscopic examination showed no proteinurea and no growth in urine culture. Stool microscopic examination showed RBC 1- 5, pus cell >50, macrophage 1-5 and OBT positive. Upper endoscopy and colonoscopy studies revealed grossly normal appearing mucosa lining the upper and lower gastrointestinal tract. Subsequent histologic examination revealed chronic nonspecific colitis.

Initially we sequentially eliminated cow's milk and dairy product, then egg from maternal diet. But patient's condition did not improved. Then we eliminated soy from maternal diet and started to feed the baby khichuri with mustard oil and the frequency of stool passing gradually became normal. Finally we diagnosed the case as allergic proctocolitis with protein losing enteropathy.

Sections of the colonic mucosa shows mucosal edema, increased number of eosinophils (>60 per 10 HPF) in the lamina propria, in the crypt abscesses and around muscularis mucosa. Focal area shows mild active colitis (Fig.-1).

**Discussion**

AP is a non-IgE-mediated food protein hypersensitivity reaction. In 1982 Lake et al[11] described AP in six exclusively breastfed infants with rectal bleeding during the first month of life.

Exact mechanisms of AP are not known, but it is assumed that the disease may be the result from maternal ingestion of a protein allergen (mostly CM) that is passed through breast milk in a form that can be immunologically recognized.[8]

Infant usually present within first six month of life with intermittent blood streaked stool and normal to moderately loose stool.[12] Our patient had history of occasional mucus-streaked stool since 5 month of age and at 7 month of age presented with loose stool but no visible blood in stool. AP is more common in breastfed babies than in infant fed with cow's milk-based or soy protein-based formulas.[4] Our patient was on breast fed since birth.

On examination the AP infant appears generally well. Anaemia may be noted in some cases without necessity of blood transfusion. Mild edema also noted.[13] The reported case was pale and edeomatous, she had history of one unit blood transfusion at six month of age. We excluded hepatic and renal causes of edema by doing liver function test and renal function test. We also excluded malnutrition by taking feeding history and considered the edema due to protein losing enteropathy.

Microscopic examination of the stool and a complete blood count (CBC) with differential may be helpful when diagnosis is unclear. The laboratory findings consistent with anemia, peripheral blood eosinophilia, hypoalbuminemia and hypoproteinemia.[13] Our patient had anaemia, eosinophil count was 7%, hypoalbuminaemia and feature of colitis in stool but no growth in culture. Stool OBT was positive.

Colonoscopic evaluation with biopsy is indicated for some selected patients present with unusual or atypical symptoms, such as constipation, diarrhea with mucus-streaked stools but without grossly

visible bleeding, or severe rectal bleeding or anemia despite a trial of cow's milk elimination diet.[6] Our patient had diarrhea without visible bleeding and generalized edema due to hypoalbuminaemia. By colonoscopy we also excluded early onset inflammatory bowel disease.

Colonoscopic findings include a mild colitis with patchy erythema and edematous mucosa with loss of vascularity confined to the distal colon.[2,4] Biopsies typically reveal high numbers of eosinophils (including eosinophilic abscesses) in the lamina propria and muscularis mucosa.[12,14]

An USA-based prospective cohort study of infants with rectal bleeding, demonstrated that 14 of 22 (64 percent) are AP, based on biopsy findings from flexible sigmoidoscopy.[6] Five (23 percent) had normal biopsies, and three (14 percent) had nonspecific colitis. Upper endoscopy & colonoscopy studies of our patient revealed grossly normal appearing mucosa lining the upper and lower gastrointestinal tract. Subsequent histologic examination revealed chronic nonspecific colitis

Allergic proctocolitis (AP) is almost always a clinical diagnosis. Diagnosis usually made by typical history of rectal bleeding, exclusion of infections and other causes of rectal bleeding, and response to an elimination diet. After elimination of offending food clinical resolution of symptom within 72-96 hours.[11]

Treatment is dietary restriction in mother when baby is on breast feeding or in infant of formula feeding.CM and all dairy product should be eliminated first. In the breastfed infants, when symptom not controlled by the elimination of cow's milk and soy, additional eliminations may be done including wheat and egg. Milk hydrolysate may be considered when the child is not breastfed or when the mother decides to stop breastfeeding, but the persistence of bleeding means the need for an amino-acid formula. Food introduction should be done at home gradually over 2 weeks.[15]

Diagnosis of the reported case was made through clinical history, exclusion of infection and other causes of edema and response to an elimination diet. After counseling we sequentially eliminated cow's milk and dairy product, egg, soy from the maternal diet. The frequency of stool passing gradually became normal and edema subsided. There may be recurrence of bleeding when oral food challenge takes place within the first 6 months.[15] We did not do any food challenge test of our patient.

The prognosis is excellent. Around 50 percent of patients with AP achieve food tolerance by 1 year of age[16] and most of the patient by 3 years.[3] After two months follow up she had no subsequent episodes of edema, diarrhea and occult blood test was negative. We advised our patient to continue dietary restriction up to 1 year age, then to reintroduce food gradually over 2 week.

## Conclusion

Allergic proctocolitis (AP) is a common condition in infancy, but its association with PLE is rare. This case highlights the importance that when a infant present with generalized edema and diarrhoea, AP with PLE may be one of the differential diagnosis. AP infants are generally healthy appearing and happy. Because of this, many infants have symptoms for weeks or months before they are formally diagnosed. This delay in diagnosis may be the cause of development of edema and anaemia. So a high degree of suspicion and awareness of this rare condition is important for early diagnosis, management and prevention of unusual complication.

## References


1. Boné J, Claver A, Guallar I, Plaza AM. Allergic proctocolitis, food-induced enterocolitis: Immune mechanisms, diagnosis and treatment. *Allergol Immunopathol (Madr)* 2009;**37**:36-42.
2. Arvola T, Ruuska T, Keränen J, Hyöty H, Salminen S, Isolauri E. Rectal bleeding in infancy: Clinical, allergological, and microbiological examination. *Pediatrics* 2006;**117**:e760-68.
3. Xanthakos SA, Schwimmer JB, Melin-Aldana H, Rothenberg ME, Witte DP, Cohen MB. Prevalence and outcome of allergic colitis in healthy infants with rectal bleeding: A prospective cohort study. *J Pediatr Gastroenterol Nutr* 2005;**41**:16-22.
4. Lake AM. Food-induced eosinophilic proctocolitis. *J Pediatr Gastroenterol Nutr* 2000;**30** Suppl:S58.
5. Lake AM, Whitington PF, Hamilton SR. Dietary protein-induced colitis in breast-fed infants. *J Pediatr* 1982;**101**:906-10
6. Pittschieler K. Cow's milk protein-induced colitis in the breast-fed infant. *J Pediatr Gastroenterol Nutr* 1990;**10**:548
7. Caubet JC, Szajewska H, Shamir R, Nowak-Wêgrzyn A. Non-IgE-mediated gastrointestinal food allergies in children. *Pediatr Allergy Immunol* 2017;**28**:6-17.

8. Nowak-Wêgrzyn A. Food protein-induced enterocolitis syndrome andallergic proctocolitis. *Allergy Asthma Proc* 2015;**36**:172-84.

9. Erdem SB, Nacaroglu HT, Karaman S, Erdur CB, Karkýner CU, Can D. Tolerance development in food protein-induced allergic proctocolitis: single centre experience. *Allergol Immunopathol (Madr)* 2017; **45**:212-219

10. Feuille E, Nowak-Wêgrzyn A. Food Protein-Induced Enterocolitis Syndrome, Allergic Proctocolitis, and Enteropathy. *Curr Allergy Asthma Rep* 2015;**15**:50.

11. Lake AM, Whitington PF, Hamilton SR. Dietary protein-induced colitis in breast-fed infants. *J Pediatr* 1982;**101:**906-10.

12. Winter HS, Antonioli DA, Fukagawa N. Allergy-related proctocolitis in infants: diagnostic usefulness of rectal biopsy. *Mod Pathol* 1990;**3**:5-10.

13. Connors L, O'Keefe A, Rosenfield L, Kim H. Non-IgE-mediated food hypersensitivity. *Allergy Asthma Clin Immunol* 2018;14(Suppl 2):**56**:84-91.

14. Goldman H, Proujansky R. Allergic proctitis and gastroenteritis in children. Clinical and mucosal biopsy features in 53 cases. *Am J Surg Pathol* 1986;**10**:75-86.

15. Dupont C.Food Protein-Induced Enterocolitis Syndrome and Proctocolitis. *Ann Nutr Metab* 2018;**73**(suppl 4):8-16.

16. Kaya A, Toyran M, Civelek E, Misirlioglu E, Kirsaclioglu C, Kocabas CN. Characteristics and prognosis of allergic proctocolitis in infants. *J Pediatr Gastroenterol Nutr* 2015;**61**:69-73.

# ABSTRACTS FROM CURRENT LITERATURE

## Gastrointestinal Manifestations of SARS-CoV-2 Infection and Virus Load in Fecal Samples From a Hong Kong Cohort: Systematic Review and Meta-analysis

Ka Shing Cheung, Ivan FN Hung, Pierre PY Chan, KC Lung, Eugene Tso, Raymond Liu, YY Ng, Man Y Chu, Tom WH Chung, Anthony Raymond Tam, Cyril CY Yip, Kit-Hang Leung, Agnes Yim-Fong Fung, Ricky R Zhang, Yansheng Lin, Ho Ming Cheng, Anna JX Zhang, Kelvin KW To, Kwok-H Chan, Kwok-Y Yuen, Wai KLeung.

*Gastroenterology. 2020;159:81-95.*

**Background & aims:** Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19), which has been characterized by fever, respiratory, and gastrointestinal symptoms as well as shedding of virus RNA into feces. We performed a systematic review and meta-analysis of published gastrointestinal symptoms and detection of virus in stool and also summarized data from a cohort of patients with COVID-19 in Hong Kong.

**Methods:** We collected data from the cohort of patients with COVID-19 in Hong Kong (N = 59; diagnosis from February 2 through February 29, 2020),and searched PubMed, Embase, Cochrane, and 3 Chinese databases through March 11, 2020, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We analyzed pooled data on the prevalence of overall and individual gastrointestinal symptoms (loss of appetite, nausea, vomiting, diarrhea, and abdominal pain or discomfort) using a random effects model.

**Results:** Among the 59 patients with COVID-19 in Hong Kong, 15 patients (25.4%) had gastrointestinal symptoms, and 9 patients (15.3%) had stool that tested positive for virus RNA. Stool viral RNA was detected in 38.5% and 8.7% among those with and without diarrhea, respectively (P = .02). The median fecal viral load was 5.1 $\log_{10}$ copies per milliliter in patients with diarrhea vs 3.9 $\log_{10}$ copies per milliliter in patients without diarrhea (P = .06). In a meta-analysis of 60 studies comprising 4243 patients, the pooled prevalence of all gastrointestinal symptoms was 17.6% (95% confidence interval [CI], 12.3-24.5); 11.8% of patients with nonsevere COVID-19 had gastrointestinal symptoms (95% CI, 4.1-29.1), and 17.1% of patients with severe COVID-19 had gastrointestinal symptoms (95% CI, 6.9-36.7). In the meta-analysis, the pooled prevalence of stool samples that were positive for virus RNA was 48.1% (95% CI, 38.3-57.9); of these samples, 70.3% of those collected after loss of virus from respiratory specimens tested positive for the virus (95% CI, 49.6-85.1).

**Conclusions:** In an analysis of data from the Hong Kong cohort of patients with COVID-19 and a meta-analysis of findings from publications, we found that 17.6% of patients with COVID-19 had gastrointestinal symptoms. Virus RNA was detected in stool samples from 48.1% patients, even in stool collected after respiratory samples had negative test results. Health care workers should therefore exercise caution in collecting fecal samples or performing endoscopic procedures in patients with COVID-19, even during patient recovery.

## Vitamin K deficiency bleeding in Australian infants 1993-2017: an Australian Paediatric Surveillance Unit study

Yvonne Zurynski, Cameron J Grover, Bin Jalaludin, Elizabeth J Elliott.

*Arch Dis Child 2020;105:433-438.*

**Objective:** To undertake surveillance of vitamin K deficiency bleeding (VKDB) in Australia from 1993 to 2017, during a time of change to national recommendations and available vitamin K formulations.

**Methods:** Paediatricians reported cases of VKDB in infants aged <6 months and provided demographic, clinical and biochemical information via the Australian Paediatric Surveillance Unit.

**Results**: 58 cases were reported, of which 5 (9%) were early, 11 (19%) classic and 42 (72%) late VKDB. 53 (91%) were exclusively breast fed. Seven (12%) received oral prophylaxis, the majority (86%) of whom did not receive all three recommended doses. The overall reported incidence was 0.84 per 100 000 live births (95% CI: 0.64 to 1.08) and the incidence of late VKDB was 0.61 per 100 000 live births (95% CI: 0.44 to 0.82), which are similar to rates reported by other countries where


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intramuscular vitamin K is recommended. VKDB rates were significantly higher (2.46 per 100 000 live births; 95% CI: 1.06 to 4.85) between 1993 and March 1994 when oral prophylaxis was recommended ($p<0.05$). Vitamin K was not given to 33 (57%) cases, primarily due to parental refusal, and the number of parental refusals increased significantly after 2006 ($p<0.05$). There were six deaths, all due to intracranial haemorrhage, and three associated with home delivery and parental refusal of vitamin K.

**Conclusions:** Incidence rates of VKDB in Australia are among the lowest in the world; however, we have identified an increasing trend of parental refusal. Ongoing surveillance and educational campaigns for health professionals and parents are needed to prevent VKDB.

### Hyponatraemia despite isotonic maintenance fluid therapy: a time series intervention study

Milan Chromek, Åsa Jungner, Niclas Rudolfson, David Ley, Detlef Bockenhauer, Lars Hagander

*Arch Dis Child 2021;106:491-495.*

**Objective:** To examine the prevalence of dysnatraemias among children admitted for paediatric surgery before and after a change from hypotonic to isotonic intravenous maintenance fluid therapy.

**Design:** Retrospective consecutive time series intervention study.

**Setting:** Paediatric surgery ward at the Children's Hospital in Lund, during a 7-year period, 2010–2017.

**Patients:** All children with a blood sodium concentration measurement during the study period were included. Hypotonic maintenance fluid (40 mmol/L NaCl and 20 mmol/L KCl) was used during the first 3 years of the study (646 patients), and isotonic solution (140 mmol/L NaCl and 20 mmol/L KCl) was used during the following period (807 patients).

**Main outcome measures:** Primary outcomes were sodium concentration and occurrence of hypona-traemia (<135 mmol/L) or hypernatraemia (>145 mmol/L).

**Results:** Overall, the change from hypotonic to isotonic intravenous maintenance fluid therapy was associated with a decreased prevalence of hyponatraemia from 29% to 22% (adjusted OR 0.65 (0.51-0.82)) without a significantly increased odds for hypernatraemia (from 3.4% to 4.3%, adjusted OR 1.2 (0.71-2.1)). Hyponatraemia <130 mmol/L decreased from 6.2% to 2.6%, and hyponatraemia <125 mmol/L decreased from 2.0% to 0.5%.

**Conclusions:** Routine use of intravenous isotonic maintenance fluids was associated with lower prevalence of hyponatraemia, although hyponatraemia still occurred in over 20% of patients. We propose that the composition and the volume of administered fluid need to be addressed.

### Breaking bad news: what parents would like you to know

Marije A Brouwer, Els L M Maeckelberghe, Agnes van der Heide, Irma M Hein, Eduard A A E Verhagen

*Arch Dis Child 2021;106:276-81.*

**Objective:** Breaking bad news about life-threatening and possibly terminal conditions is a crucial part of paediatric care for children in this situation. Little is known about how the parents of children with life-threatening conditions experience communication of bad news. The objective of this study is to analyse parents' experiences (barriers and facilitators) of communication of bad news.

**Design:** A qualitative study consisting of a constant comparative analysis of in-depth interviews conducted with parents.

**Setting:** The Netherlands.

**Participants:** Sixty-four parents-bereaved and non-bereaved-of 44 children (aged 1-12 years, 61% deceased) with a life-threatening condition.

**Results:** Based on parents' experiences, the following 10 barriers to the communication of bad news were identified: (1) a lack of (timely) communication, (2) physicians' failure to ask parents for input, (3) parents feel unprepared during and after the conversation, (4) a lack of clarity about future treatment, (5) physicians' failure to voice uncertainties, (6) physicians' failure to schedule follow-up conversations, (7) presence of too many or unknown healthcare professionals, (8) parental concerns in breaking bad news to children, (9) managing indications of bad news in non-conversational contexts, and (10) parents' misunderstanding of medical terminology.

**Conclusions:** This study shows healthcare professionals how parents experience barriers in bad news conversations. This mainly concerns practical aspects of communication. The results provide practical pointers on how the communication of bad news can be improved to better suit the needs of parents. From the parents' perspective, the timing of conversations in which they were informed that their child might not survive was far too late. Sometimes, no such conversations ever took place.

# INSTITUTE NEWS

Academic wing of Bangladesh Shishu Hospital & Institute was established in 30 January 1983. It is affiliated with Dhaka University, Bangabandhu Sheikh Mujib Medical University (BSMMU) and Bangladesh College of Physicians and Surgeons (BCPS). It has established Basic Science Department in the year 2006. It has been conducting different courses e.g. FCPS (in General Paediatrics and also subspeciality like FCPS Neonatology, Paediatric Nephrology, Paediatric Haemato-oncology, Paediatric Neurology and Development, Paediatric Pulmonology, Paediatric Cardiology under BCPS), MD Residency Course in General Paediatrics and Neonatology and Nephrology under BSMMU. MD Non residency courses under Dhaka University and BSMMU, MS (Paediatric Surgery) Residency Course under BSMMU, MS (Paediatric surgery) non residency course under Dhaka University, DCH course under BSMMU. BSH&I is also conducting Diploma in Paediatric Nursing course under Bangladesh Nursing Council, BSc in Health Technology course under Dhaka University. It organizes different programme, seminars and symposium on Paediatrics. Apart from these the Institute also runs its regular academic activities. During COVID-19 Pandamic BSH&I is conducting online classes and other academic activities and seminars since April 2020. Now BSH&I has resumed normal class and activities.

**Library facilities**

The library of BSH&I has a rich collection of updated medical texts and reference books and reputed Medical Journals form home and abroad. BSH&I has introduced Broad Band facilities which are open to all students, teachers/ consultants of hospital for 24 hours. Facilities of library are also improved by HINARI. Students can download 2230 Medical Journals & more than 50 Paediatric Journals.

# Postgraduate Courses and Training in Paediatrics in BSH&I

1. BSH&I has course for FCPS in General Paediatrics (2nd part): Student can be registrared twice in a year, in the months of January and July.
2. BSH&I and Dhaka Shishu (Children) Hospital is a recognized center by BCPS for training in FCPS (Paeditric Medicine and Surgery).
3. It is a recognized centre for course and training in different subspeciality of Paediatrics like Neonatology, Paediatric Nephrology, Paediatric Haematology and Oncology, Paediatric Pulmonology, Paediatric Neuroscience and Paeditric Cardiology.
4. There is MD Residency program in General Paediatrics, Neonatology, Paediatric Nephrology and MS Paediatric Surgery. Phase A commences in the month of March every year. There is also MD Paediatrics and Paediatric Surgery Non Residency Courses which commences in the month of January and July.
5. DCH course: Once in a year in the month of July.
6. Other courses conducted by BSH&I are
    - Paediatric Nursing.
    - BSc in Health Technology.
    - Three months certificate course: Every year the institute conducts 3 months certificate course on Paediatrics for general practitioners & other post graduate candidates e.g. MCPS.
    - Training programme on Essential Newborn Care for doctors and nurses, KMC (Kangaroo Mother Care) training, ETAT (Emergency Triage, Assessment and Treatment) training, IMCI (Integrated management of childhood illness), newborn and paediatric standards and use of oxygen therapy for hypoxemia management etc. are conducted by BSH&I.

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E-mail: infodshjournal@gmail.com, info.bich@gmail.com

# Students Qualified from Bangladesh Shishu Hospital & Institute (Former BICH)

**Student qualified from BSH&I till June 2021**

| Course | Number |
|---|---|
| DCH | 375 |
| MD Paediatrics | 106 |
| MS Paediatrics | 100 |
| FCPS Paediatrics | 16 |
| MD Neonatology | 11 |
| MD Pediatrics Nephrology | 05 |
| Total | 613 |

**Foreign student qualified from BSH&I till June 2021**

| Course of origin | Course | Number |
|---|---|---|
| Nepal | DCH | 23 |
| | MS (Paediatric Surgery) | 02 |
| | MD (Paediatrics) | 01 |
| India | MD (Paediatrics) | 01 |
| Iran | DCH | 01 |
| Iraq | DCH | 01 |
| Somalia | DCH | 01 |
| Sudan | DCH | 01 |
| Total | | 31 |

**Present Students (June 2021)**

| Name of Courses | Number of Students |
|---|---|
| MD (General Paediatrics) Phase - A | 24 |
| MD (Neonatology) Phase - A | 5 |
| MD (Paediatric Nephrology) Phase - A | 3 |
| MS (Paediatric Surgery) Phase - A | 14 |
| FCPS (Paediatric) Part - II | 2 |
| MD (Paediatrics) Part - III | 8 |
| FCPS (Paediatric Cardiology) | 1 |
| FCPS (Paediatric Nephrology) | 1 |
| MS (Paediatrics Surgery) Part - III | 2 |
| DCH | 23 |
| MD (General Paediatrics) Phase - B | 19 |
| MD (Neonatology) Phase - B | 5 |
| MD (Nephrology) Phase - B | 3 |
| MS (Paediatric Surgery) Phase - B | 5 |
| Total | 115 |

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Dhaka Shishu (Children) Hospital Journal is the official organ of Bangladesh Shishu Hospital & Institute (BSH&I). It is a peer reviewed, open access journal published twice a year since 1984. This journal is recognized by Bangladesh Medical and Dental Council (BMDC) which is the highest body for the recognition of medical journals in Bangladesh. All parts of the journal are indexed/ tracked/covered by DOI/CrossRef and BanglaJOL. The present Editorial board has decided that the cover design will be in accordance with the subjects of editorial in each issue. The editor welcomes articles to be published to the journal as leading article, original article, review article, case report, current issues of child health, short report and junior's page where trainee doctors are encouraged to publish their topic of interest.

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- Title should not exceed 100 characters (Font size 16, bold).
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- Abstract with a structured format with five sections (about 250 words maximum): Background, Objective, Methods, Results and Conclusion. All these sections will be in Times New Roman, Font size 12, italic and bold. Text will not be bold and after the text there will be Key words (not more than 10). No references are allowed in the abstract.

For review article abstract will be non structured and in case report no need to give abstract.

- Text will also comprises with five sections (Introduction, Materials and Methods, Results, Discussion and Conclusion).
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# BANGLADESH SHISHU HOSPITAL & INSTITUTE

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3. BT, CT, PT, APTT
4. Routine urine exam, including pH, urobilinogen, bilirubin, haemoglobin and morphology of RBC in urine.
5. Routine stool exam, including reducing substances and occult blood test
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4. Gas analyzer - Blood pH, $PCO_2$, $PO_2$, $HCO_3$, $O_2$ saturation, Base excess, Oxyhemoglobin, Carboxy hemoglobin, Methemoglobin, Deoxyhemoglobin, Oxygen binding capacity

### Blood Bank

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3. Color Doppler study by SIEMENS Color Doppler Machine (Sonoline - G40), study of abdominal vessels, portal vein, renal artery, cerebral arteries, vascular malformation of neck- upper/lower limbs
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Director
**Bangladesh Shishu Hospital & Institute**

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