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Diagnosis of Tuberculosis
Srinidhi et al,
Research Scholar

1st Anniversary
Vivek Gharpure,
Editor-in-chief, PST

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About the journal

Aims and Objectives

The *Pediatric Surgery in Tropics* (PST) aims to improve scientific communication among pediatric surgeons of the tropical countries. It is intended to be an author and reader friendly journal. Articles are aimed to enlighten, educate and entertain the readers. We focus more on the content of manuscripts than on their presentation or formatting. We understand the compelling circumstances in which tropical doctors are working. Hence, we sympathetically accept to publish even partial evidences when advanced facilities for complete work-up are not available. Socio-cultural peculiarities, economic inequality, illiteracy of patients, limitedness of resources and lack of advanced training that are typical of tropical countries will be taken into consideration while accepting articles for publication.

What Do We Publish?

We publish all types of scientific manuscripts that are useful to practicing pediatric surgeons. The following topics are generally suitable for PST:

1. Pediatric surgical conditions peculiar to tropical countries or warm humid climate
2. Any pediatric surgical condition treated in tropical centers with advanced facilities
3. Any pediatric surgical condition treated in resource-poor setting
4. Any article that is potentially useful to practicing pediatric surgeons in tropical or resource poor settings
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6. Break-through innovations relevant to the practice of pediatric surgery

We are not limited to the article types mentioned below:

1. Original innovations
2. Clinical trials (randomized & non-randomized)
3. Clinical audits (including report of > 5 cases)
4. Experimental studies (animal & in-vitro)
5. Meta-analysis
6. Systematic reviews
7. Descriptive review articles
8. Case reports highlighting a new aspect (less than 4 cases)
9. Rare disease record (The clinical frequency of pathology should be > 1 in 50000. Case descriptions should include as many details as possible)
10. Clinical images highlighting a learning point
11. Letters to editor
12. Short communications (Point-blank description or message)
13. Historical vignettes
14. Personal viewpoints (longer than 2 pages with in-depth analysis)
15. Surgical hypothesis (Theoretical proposals backed by partial or incomplete evidences)
16. Invited commentaries on papers in PST
17. Policy & Regulations pertinent to Pediatric Surgery
18. Technical, or clinical tips (50-200 words)
19. Clinical dilemma (case reports ending with questions rather than conclusions)
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21. Research ideas
22. Research methodology (Detailed research proposals with fine details of methods)
23. Debates on controversies (To be written by two (or two sets) of authors each supporting one view of the controversy)
24. Obituary of accomplished pediatric surgeons
25. Editorials (both invited and spontaneous)
26. Patient perception giving insight to surgeons
27. Poetry and other entertaining articles reflecting tropical pediatric surgery
28. Journal club (detailed critical appraisal of articles published in another journal)
29. Pantheon (Section notifying the summary of important articles published elsewhere)
30. Surgical Jugaads (Indigenous improvisations)

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Pediatric Surgery in Tropics

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Contents

PST PEDIATRIC SURGERY IN TROPICS

Pediatric Surgery in Tropics
2025 (Jan-Mar); Volume 2, Issue 1: Pages 12-13
DOI: 10.70947/pst.2025.01

Editorial

First anniversary of Pediatric Surgery in Tropics

Vivek Gharpure

Chief Editor, Pediatric Surgery in Tropics

The collective efforts of editors, board members, reviewers, authors and of course readers have given a cause to celebrate the first birthday of this journal. Mighty oaks are born of tiny acorns, and we hope, in the coming years, this journal will become useful to pediatric surgeons across the world.

In the first issue of PST, I wrote about the need for a new journal, emphasizing the difficulties faced by independent surgeons and researchers from low-middle income countries, in publishing their work. After reading manuscripts, and understanding the difficulties faced by our colleagues across the world, we realize the importance and utility of such a journal. When we realize that basic imaging (e.g. plain x-ray) is not available in some hospitals, ventilator and intensive care unit facilities are lacking, nurses have to be trained, expert anesthesia services do not exist; and yet our pediatric surgical friends are doing a good job of saving children. We feel that their voice must be heard.

We published editorials written by stalwarts like professors Sameh Shehata, Naeem Khan, Jamshed Akhtar and Patta Radhakrishna. We also provided opportunity to young surgeons, Ketaki Gharpure and Sultana Dhilras, to write on issues like difficulties faced by women surgeons and innovation.

In the four issues that have been published, we have had contributions from India, Bangladesh, Pakistan, Cambodia, Senegal, Burkina Faso, Egypt, Democratic Republic of Congo, Malaysia, Puerto Rico, Nigeria, Rwanda, Russia and the USA. (Fig. 1) It encourages us to have reached so many countries in such a short period. We are very happy to have attracted manuscripts from these countries. At the same time, we will be more than happy to receive manuscripts and editorial board representations from South American, Central America, and Southeast Asian countries.

Fig 1. *Author-distribution (location marks) map of Pediatric Surgery in Tropics (2024)*

The PST being a diamond open-access journal (i.e. no publication charges for authors and no subscription fees for readers), the readership has grown significantly covering a large portion of the globe. (Fig. 2) We strongly believe that knowledge should be free, and it is the birthright of everyone. We have resolved to retain this model and continue serving pediatric surgeons across the globe.

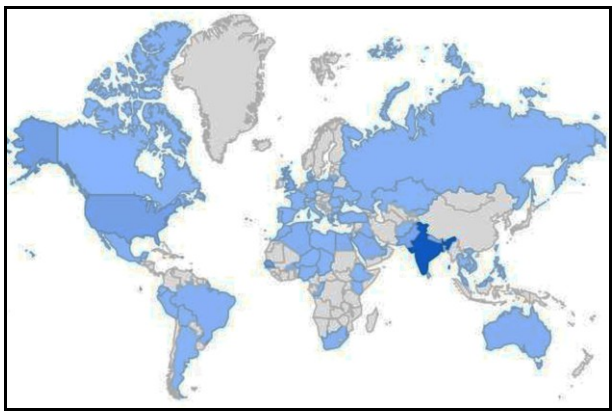

Fig 2. *Reader-distribution map of Pediatric Surgery in Tropics (2024). Intensity of blue colour is proportional to the number of readers.*

Surgeons rarely understand the personal hardship faced by patients. Therefore, we published first person account of Mr. Steve Wyles, a 63-year-old survivor of tracheo-esophageal fistula (TEF) who lives in England, and runs a non-government organization for TEF patients and their parents. By the commendable work, he is helping hundreds of parents.

We still have much scope for improvement and I believe in the principle of kaizen. Everything can always be done better; perfection is death.

We have received great support from our design team led by Mr. Akshay Kulkarni. He has created an exclusive cover design, a unique color scheme and an innovative logo that give a brand identity to the journal. Our web management team is helping us in creating an interface and in uploading of articles. On behalf of the editorial team, I thank all of them for their continued support. Without them, the journal would not exist.

In tandem with our commitment towards dissemination of knowledge, an online workshop on the art of Manuscript Reviewing was organized in July 2024. It was well attended and many of the participants have become part of the reviewer panel of the PST. Yet another Continuing Medical Education program on 'Tropical Pediatric Surgery' is being held in collaboration with the Institute of Child Health, Chennai on 25 January 2025. There will be more such programs in future. We also intend to publish books, manuals and guidelines on tropical pediatric surgery.

Young members of team, Drs. Aravind and Krishna Kumar are taking care of their editorial responsibilities quite well. Senior editors, Raveenthiran and Yogesh Sarin are old hands at the work of running a journal.

Considering the highest mortality of infants in the first year of life, we feel happy to have survived that critical period of PST, despite some troubles here and there. We will continue to strive hard to publish issues on a regular basis, sticking to the international publication standards, and provide a platform to our colleagues across the world.

Once again, I thank everyone for this short-term success.

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Welcome to New Members of the Editorial Board

Editors and Board Members of the *Pediatric Surgery in Tropics* are pleased to welcome the new members of the Editorial Board.

Lisieux Eyer de Jesus (Editorial Board Member)

Prof. Lisieux Eyer de Jesus is currently the President of the Antonio Pedro University Hospital, a Pediatric Surgeon at the Federal Hospital of Servants of the State of Rio de Janeiro and the Chief of the Service at the Fluminense Federal University. She is the President of the Society of Pediatric Surgery of Rio de Janeiro and the Pediatric Surgery Session of the Brazilian College of Surgeons. She edits the Journal of the Association of Pediatric Surgery of the State of Rio de Janeiro (CIPERJ). She is also a member of the editorial board of the Journal of the Brazilian College of Surgeons, the International Brazilian Journal of Urology, the Journal of Pediatric Urology and the Urology Committee of the Brazilian Society of Pediatric Surgery. Her area special interest is pediatric urology, sexual abuse, disorders of sex development, and pediatric abdominal surgery. She speaks five languages. She has contributed more than 180 publications, 28 book chapters, 51 conference presentations.

Iftikhar A Jan (Editorial Board Member)

Prof. Iftikhar Jan is currently working as Adjunct Clinical Professor of Surgery at the Khalifa University, United Arab Emirate (UAE). He is also the Chairman of the Division of Pediatric Surgery and Pediatric Urology, the Program director of Pediatric Surgery Residency and the Pediatric Trauma Lead at the Sheikh Shakhbout Medical City (SSMC), Abu Dhabi, UAE. Previously he was a Professor of Pediatric Surgery at National Institute of Child Health, Islamabad, Pakistan. He also had worked at prestigious institutions of United Kingdom and Japan. He has published more than 80 research papers and several book chapters. He is serving as editorial board member and reviewer of several indexed journals. He is bestowed with the UAE Distinguished Surgeon Award and the SEHA Best Employee Awards.

Milind Chitnis (Editorial Board Member)

Dr. Milind Chitnis is Associate Professor and Head of the Department of Pediatric Surgery at the East London Hospital Complex, affiliated to the Walter Sisulu University, South Africa. He has been the Honorary Secretary of the College of Pediatric Surgeons of South Africa (2020-23) and a member of the Council of the College of Pediatric Surgeons of South Africa (2017-26). He is currently the Honorary Secretary of the Pan African Pediatric Surgical Association (PAPSA) and the Global Initiative for Children's Surgery (GICS). He is also a founding Trustee of the not-for-profit organization *Eyabantwana* for the Children.

Aravindh Radhakrishnan (Assistant Editor)

Dr. Aravindh Radhakrishnan is currently a Consultant Pediatric Surgeon at the Naruvi Hospitals, Vellore, Tamil Nadu (A unit of SANCO Foundation and a licensee of the Henry Ford Health System, Detroit, USA). He was qualified from the Jawaharlal Institute of Postgraduate Medical Education & Research and got trained in pediatric surgery from the Maulana Azad Medical College, New Delhi. He has special interest in neonatal surgery and reconstructive pediatric urology. He has keen interest in academics and research.

PST PEDIATRIC SURGERY IN TROPICS

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Historical Vignette

The Centenary of Pediatric Surgery in South Africa (1923-2024)

Milind Chitnis

Department of Pediatric Surgery, Frere and Cecilia Makiwane Hospitals, Affiliated to Walter Sisulu University, East London, South Africa.

Keywords
History of Medicine
Pediatric Surgery services
South Africa

Abbreviations
CPSSA - College of Pediatric Surgeons of South Africa
RCWMCH - Red Cross War Memorial Children's Hospital
SAAPS - South African Association of Pediatric Surgeons

Abstract

This article narrates the history of pediatric surgery South Africa over 100 years. The first department was established in 1923 at Johannesburg. Professor Jannie Louw, who did pioneering work, is considered the Father of South African Pediatric Surgery. Subsequently, 9 universities started training programs in pediatric surgery. The South African Association of Pediatric Surgeons and the College of Pediatric Surgeons of South Africa were founded in 1976 and 2010 respectively. Gender disparity that prevailed in apartheid era is slowly rectified and now there are more women pediatric surgeons in South Africa than before. The year 2024 is the centenary year of South African Pediatric Surgery.

INTRODUCTION

A batsman reaching a century is widely celebrated in cricket. The 'Master Blaster' Sachin Tendulkar, a former Indian cricketer, is idolized for achieving a century of international centuries! A seasoned batter refocuses after scoring a century and starts all over again. After a century of pediatric surgical care (1923-2023) in South Africa, it is time to introspect, learn from the past, correct the past injustices, and continue striving for a better future for all the stakeholders including ailing children, their parents, trainees and specialists in pediatric surgery. This article is an honest attempt to remember and analyze the past, assess the present, and look at the future of pediatric surgery in the most industrialized nation of the African continent.

GEOPOLITICAL BACKGROUND

South Africa is a middle-income country with a population of 63 million, of which 40% are children below the age of 15 years. It is one of the most unequal societies in the world, with a high rate of HIV infection, obesity, violent crime, teenage pregnancies and motor vehicle accidents. Thirty years after the implementation of the democracy, even though the government spends 7.5% of the gross domestic product (GDP) on healthcare, most of the indigenous Black population still suffers from poor literacy, poverty, unemployment, malnutrition, and poor health outcomes.[1] Children, the most vulnerable members of a society, suffer the most. Healthcare services at all public hospitals are free for children under the age of six years. Yet, morbidity and mortality among pediatric sur-

gical patients are still high due to several factors which include lack of awareness, 'absent father effect' of child rearing, poverty, dilapidated health facilities in rural areas, poor road infrastructure, total lack of antenatal care, widespread use of traditional medicines, delayed presentation and a critical shortage of nurses and doctors.

AT THE DAWN

The history of Pediatric Surgery in South Africa can be arbitrarily divided into two eras: pre-democratic era (1923-1994) and democratic era (1994-2024). In South Africa, democratic election was first held in April 1994. Prior to that racial segregation and sub-human treatment of Blacks were enforced by the law. The country was ruled by a minority (15%) of White people who enjoyed all the privileges, including easy access to education real estate, better job opportunities, higher pay, and excellent healthcare. Most of the White children lived in cities and they had a fair chance to become a doctor and subsequently a Pediatric Surgeon. Majority of indigenous Africans were dispossessed of their land and were forced to live outside the city limits in townships or in rural areas. They received substandard education and were prevented from becoming doctors; no need to say about becoming a pediatric surgeon. They were forced to leave the country and excel as pediatric surgeons elsewhere. It was only in 2002 that the first pediatric surgeon of colour could be registered in South Africa.[2]

FIRST DEPARTMENT

In 1923, pediatric surgery was established as a subspecialty of general surgery at Johannesburg. Initially, surgery of children was performed by general surgeons interested in unique pathologies of this age group. Though pediatric surgery quickly became a recognized discipline within General Surgery, it took many years before getting full recognition as an independent specialty in 2008.[3]

Professor Jannie Louw (Fig. 1) is considered the 'Father of Pediatric Surgery' in South Africa. His firstborn child had died of complications of congenital intestinal atresia in the late 1940s. It is said that he pledged to understand the cause of this pathology as well as other related abnormalities and help the children born with congenital malformations.[4] He collaborated with Christian Barnard (who later became world famous for the first successful heart transplant) to conduct experiments in fetal puppies to demonstrate that most of the jejuno-ileal atresia were caused by late intrauterine vascular accidents.[5]

Fig 1. *Professor Jannie Louw, the Father of Pediatric Surgery in South Africa*

FURTHER DEVELOPMENTS

Sidney Cywes, who followed Louw in Cape Town in 1976, was the first surgeon in the country to restrict his practice exclusively to pediatric age group. Michael Dinner (Johannesburg) and Robert (Bob) Mickel (Durban) together with Cywes (Cape Town) were the 3 pioneers in the field of pediatric surgery in the late 1970s and early 1980s. Dinner, a full-time surgeon at the Baragwanath Hospital, was appointed as full-time pediatric surgeon in 1966 and a Professor in 1976. In his induction lecture, he stated, "The greatest satisfaction of the operation must be to afford the infant a 70-year cure, in conjunction with a happy childhood".

Cywes established the Red Cross War Memorial Children's Hospital (RCWMCH) in Cape Town. (Fig 2) He saw in children the future of our country and realized that somehow, he had to take care of them. He was a fierce advocate of surgical children. He developed a dedicated neonatal surgery unit (1976), a surgical intensive care unit (1983), a trauma unit (1984), a liver transplantation program (1987), and a day-care surgery centre (1989). His motto was, "Don't tell me what you want to do; show me what you have done." Mickel was a quiet, gentle giant of South African pediatric surgery who had touched the lives of thousands of children through his clinical practice at Durban.[3]

Fig 2. *Red Cross War Memorial Children's Hospital, Cape Town (founded in 1956).*

The driving forces behind establishing children's hospitals in South Africa were a group of socially conscious women and returning soldiers from the World Wars I and II. Out of the 7 children's hospitals of the country that were founded since 1923, only three - the RCWMCH (founded in 1956), the Tygerberg Children's Hospital, Cape Town (2000), and the Nelson Mandela Children's Hospital at Johannesburg (2017) - are active at present. Other children's hospitals have been closed over the last few decades due to a lack of funding, poor planning, and restructuring of health services at the provincial and national levels. Though Addington Children's Hospital at Durban is also currently functioning, it no longer offers pediatric surgical services. Children are assessed there and if an operation is required, they are referred to Inkosi Albert Luthuli Academic Hospital in the same city.

The RCWMCH was the first freestanding children's hospital in sub-Saharan Africa, and it continues to provide quaternary health services to needy children. The Red Cross Children's Hospital Trust was established in 1994 to support the needs of the RCWMCH. The Tygerberg Children's Hospital, located in the sprawling complex of Tygerberg Academic Hospital, shares all ancillary services, including operating theatres, administration and finances, with its adult counterpart. The Nelson Mandela Children's Hospital opened its doors to patients in 2017 with significant financial support from Nelson Mandela Children's Fund. Mr. Nelson Mandela said, "The Children's Hospital will be a credible demonstration of the commitment of African leaders to place the rights of children at the forefront. Nothing less would be enough."

ESTABLISHMENT OF UNIVERSITY DEPARTMENTS

With the establishment of 9 independent provincial health authorities, 9 medical schools (Fig 3) and an unequal private and public health sector, pediatric surgery in South Africa is in an enviable position of having been adopted a national unitary institution whilst maintaining the independence of each academic unit.

SOUTH AFRICAN ASSOCIATION OF PEDIATRIC SURGEONS (SAAPS)

The first three professors of pediatric surgery - Cywes, Dinner, and Mickel - formed the South African Association of Pediatric Surgeons (SAAPS) in 1976. The SAAPS is a membership-based, not-for-profit organization that has significantly influenced the development and recognition of pediatric surgery in South Africa. It represents professional practice matters in both public and private (self-funded) sectors. It is a vibrant organization facilitating education and scientific advances in clinical,

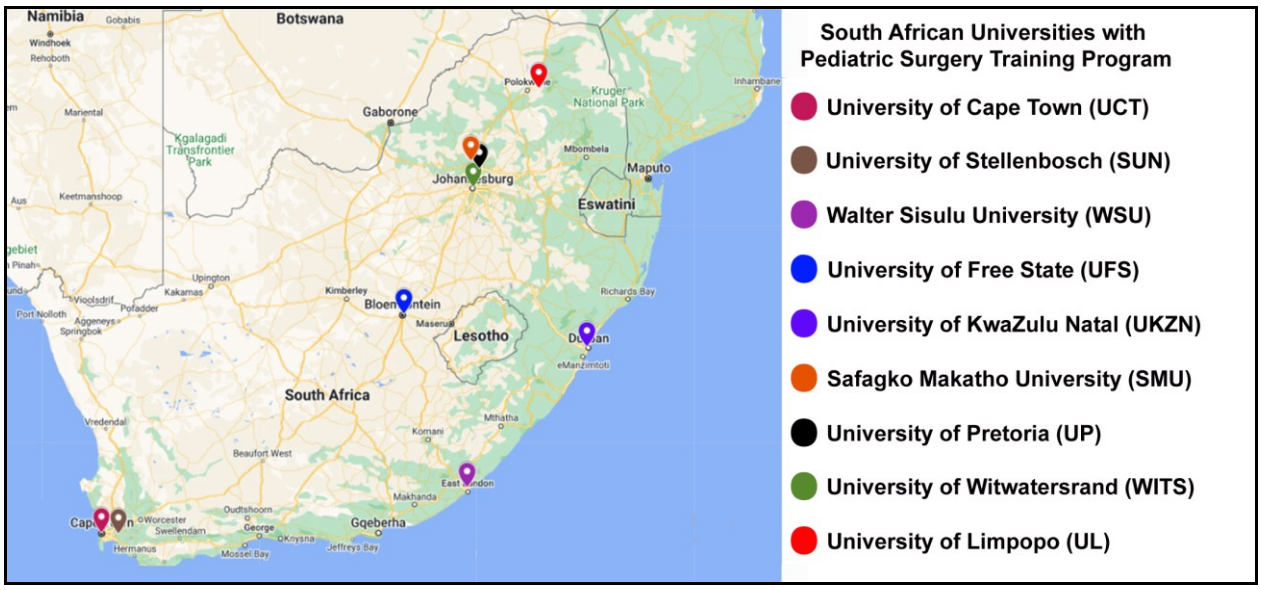

Fig 3. *Map of South Africa showing the 9 medical schools and universities offering pediatric surgical training. SMU was previously known as Medical University of South Africa (MEDUNSA) and WSU as University of Transkei (UNITRA)*

experimental and innovative surgery in related sciences. The SAAPS also holds biennial scientific meetings. In the 48-year history of SAAPS, Prof. Samad Shaik was the first non-White to be elected as its Honorary Secretary in 2017 and Honorary President in 2023. (Fig 4)

THE COLLEGE OF PEDIATRIC SURGEONS (CPSSA)

Establishment of an autonomous Fellowship in Pediatric Surgery is the result of perseverance and determination to overcome indifference, opposition and established privileges. It was a drawn-out, systematic journey from conceiving the idea (1975), endorsement (2000), certification (2002), and eventually to full specialty status (2007) and an independent Fellowship (2008). The College of Pediatric Surgeons of South Africa (CPSSA) was formed in 2010. It is a part of the broader Colleges of Medicine of South Africa. It represents academic interests including training, research and examinations of pediatric surgical trainees.

THE ROAD TO SPECIALIZATION

The training program is flourishing and entry is competitive. Trainees can choose from any of the

Fig 4. *Prof Samad Shaik - The current President of the South Africa Association of Pediatric Surgeons and the College of Pediatric Surgeons.*

9 accredited units. Each unit functions independently; but follows a single national curriculum. The program extends over five years, although the final examination may be taken after four years of training. Since 2010, national exit examination convened by the CPSSA is offered biannually and a fellowship diploma (FCPS-SA) is awarded to the successful candidates. Trainees must then clear an MMed examination at their respective universities

before being registered as pediatric surgeons by the Health Professions Council of South Africa.

The College has dedicated the last few years to transitioning to a modern, defensible examination format. The final examinations now consist of two single best-answer papers that must be passed to enter the structured oral assessment component. This comprises paper-based, standardized clinical scenarios and structured oral examinations covering surgical anatomy, pathology, and operative technique. Both components of the examination are delivered in an online format.

Starting January 2025, Workplace-Based Assessment will be phased into the academic program. A list of Entrustable Professional Activities relevant to our practice has been discussed and developed.

PEDIATRIC SURGERY WORKFORCE

A formal review of the workforce was undertaken in 2020. Trainee posts have increased from 31 in 2020 to 42 in 2023 and the registered Pediatric Surgeons from 44 in 2020 to 56 in 2023. The median age is 45, and more than 65% of the trainees and specialists are female. Since 2010, the skewed racial distribution of trainees and consultant pediatric surgeons has been addressed and the imbalances of the past are rectified. The racial distribution is now reflecting the demographics of the country. While most of the pediatric surgeons are concentrated in the urban areas, plans are afoot to expand services to our rural children. On a global scale, South Africa has about 2.6 pediatric surgeons per million children under the age of 14 years, as compared to 20-40 in the Western world and 0.1 to 0.4 per in our neighboring countries.[6]

WOMEN PEDIATRIC SURGEONS

The extended duration of training, irregular and long working hours and on-call responsibilities presented significant difficulties in the past for women specializing in pediatric surgery, resulting in a male-dominated practice. Until recently, there was an acute scarcity of female role models and mentorship in South African pediatric surgery. This gender disparity changed significantly when the profile of medical students changed from mostly males to a more equal gender distribution. The increased presence of females in the pediatric surgery work-force in the past 18 years has resulted in women leading 3 university departments. This has brought in new challenges that require mechanisms to create supportive structures to ensure sustainable specialist services, personal career development, research and a balanced psychological and family life. Thozama Siyotula, consultant pediatric surgeon at the RCWMCH, has undertaken a project to research on the role of women in South African pediatric surgery and the results are eagerly awaited.

THE SOUTH AFRICAN PEDIATRIC SURGERY TRAINEES ASSOCIATION (SAPSTA)

The trainees (registrars) in pediatric surgery are represented by the South African Pediatric Surgery Trainees Association (SAPSTA). Both SAAPS and CPSSA are actively support in this body. The SAPSTA plays an essential educational role by organizing an annual symposium for examination preparation and represents the needs of trainees.

MODERN ERA (1995-2024)

The establishment of a regional pediatric surgery service in the rural Eastern Cape Province has been one of the remarkable success stories of post apartheid South Africa. The author of this article is privileged to be involved in this project since the very beginning. In February 1995, Colin Lazarus (a local surgeon) and Milind Chitnis (a young pediatric surgeon from India) started the Department of Pediatric Surgery in East London. From a modest beginning, this unit has become a nationally and internationally recognized fourth largest department of the country. As an Honorary Secretary of the Pan-African Pediatric Surgical Association (PAPSA) and the Global Initiative for Children's Surgery (GICS), Milind Chitnis has the rare honor

of representing South African pediatric surgery at African and international forums. To celebrate the 30th anniversary of the Department of Pediatric Surgery Foundation in East London, the upcoming SAAPS conference in 2025 will be held at the Mpekweni Beach Resort, near East London, from Thursday, 1 May to Sunday, 4 May 2025.

THE FUTURE

Pediatric Surgery in South Africa has undergone a significant change in the leadership between 2013 and 2015, with *en masse* retirement of the long-standing heads of the departments. The younger incumbents have since made significant strides in growing the discipline, raising awareness, and enabling national standards in training and examinations. Whilst South Africans have always featured in global organizations as individuals, representation of our entire community is preferred. Establishing intercollegiate relationship is an ideal starting point. With a good complement of pediatric surgeons now available in South Africa, our vision is to establish the profession in the public eye, in the political arena and within our medical community by leveraging our unique position in the care and welfare of children in South Africa.

CONCLUSION

In spite of several challenges, Pediatric Surgery in South Africa is flourishing. Redressing the disparities and injustices of the past - in terms of racial, gender and socio-economic barriers in training - remains our top priority.

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Tropical Surgery Series

Diagnosis of Tuberculosis in Children (Part 1): Demonstration of the Causative Organism

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Keywords
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Fluorescent stains
Gene Xpert™
Laboratory Diagnosis
Lipoarabinomannan
Loop-mediated isothermal amplification (LAMP)
MGIT culture media
Mycobacterium
Polymerase chain reaction
Sample collection
Sample transport
Tuberculosis
Ziehl-Neelsen staining

Abbreviations
(See - Appendix 1)

Abstract

Tuberculosis (TB), despite being a preventable and treatable infection, still remains a major cause of mortality worldwide. Delay in establishing the diagnosis significantly contributes to the mortality. Early diagnosis, especially in children, is faced with several challenges. This article reviews the current knowledge and challenges of TB diagnosis.

The philosophy of TB diagnosis is based on two principles: (1) demonstration of the causative organism in the host, and (2) demonstration of the host-reaction to the invading pathogen. Staining and culture demonstrate intact bacilli, while molecular methods demonstrate cellular fragments of mycobacteria. Staining techniques use a unique property of mycobacterial cell wall that resists decolourization with acid-alcohol. Fluorescent stains (e.g. auramine-rhodamine) are better than the conventional Ziehl-Neelsen stain. When the bacterial load is too low to be detected in stained smears, culturing is used to increase the bacterial density. The WHO recommends Bactec MGIT-960™ medium because of its better yield than the conventional Lowenstein-Jensen medium.

Dead or multiplying bacilli shed their genetic materials (DNA and RNA) as well as cell wall antigens into the host secretions or circulation. Techniques like polymerase chain reaction amplify the miniscule amount of bacterial nucleic acids and facilitate their detection. The specificity and sensitivity of these techniques are often greater than 90%. Hence, the WHO recommends cartridge-based nucleic acid amplification test (CB-NAAT) as the preferred investigation of childhood TB. Lipoarabinomannan, a cell wall glycolipid specific to mycobacteria, is a useful urinary biomarker of TB, especially in HIV patients.

"*More human lives have been lost to tuberculosis than to any other disease.*" - *Stewart Cole* [1]

INTRODUCTION

Tuberculosis (TB), despite being a preventable and treatable infection, continues to be a major cause of mortality worldwide. Its incidence is 127 per 100,000 of the population. In 2022, over 1.25 million children developed TB and 214,000 died of the infection.[2] Notably, 80% of these deaths occurred in children under the age of 5 years, and 96% of them had never received any anti-tubercular treatment (ATT).[2] Obtaining accurate statistics of childhood TB is challenging for several reasons, including under-recognition of the disease, difficulties in confirming the diagnosis, and under-reporting to national TB programs. Early diagnosis is crucial not only for timely treatment but also to halt disease transmission by identifying and isolating the source of infection.[3] This article (the first of a two-part series) reviews the available methods and the challenges of diagnosing TB in children.

DIAGNOSTIC CHALLENGES

Several factors contribute to the diagnostic difficulties of pediatric TB.[4,5] The chief among them is the non-specific nature of clinical and radiological features of TB, which are often confused with that of other microbial infections and tumors. Demonstration of the causative organism in children is challenging as they typically have paucibacillary disease. The mycobacterial load is directly proportional to the age of patients. For example, sputum smears were positive for acid-fast bacilli (AFB) in only 7% of children, as compared to 52% in adults.[6] Smear positivity is 14% in children aged 5-14 yr while it drops to 0.5% in those aged 0-4 yr.[6] The diagnostic yield of mycobacterial cultures and molecular tests is also less than 25-40% in children as compared to 60-85% in adults.[7]

Clinical manifestation of TB is a spectrum, ranging from latent tuberculosis infection (LTBI) to active miliary disease. TB can occur in any organ and it is sometimes classified as pulmonary TB (PTB) and extrapulmonary TB (EPTB). Innumerable permutation of these clinical presentations poses unique diagnostic challenges. For example, LTBI is a dormant infection without any overt symptoms. Hence, a clinical suspicion is rarely raised.[8] Sensitivity of TB screening tests seldom exceeds 85% and screening an entire population is impractical due to huge economic implications.

Co-morbidities such as acquired immune deficiency syndrome (AIDS) not only alter the clinical manifestations of TB, but also interfere with the diagnostic tests, especially those based on immunological reactions.[9] Social stigma of TB, lack of awareness, poverty, non-availability of diagnostic tools and lack of expertise are challenges peculiar to resource-limited countries, where TB is endemic.[10] Last, but not least, is the shared morphological and immunological properties of typical and atypical mycobacteria that make differential diagnosis difficult, if not impossible.

TYPICAL AND ATYPICAL MYCOBACTERIA

Mycobacteria are categorized into three groups: the *Mycobacterium tuberculosis (MTB)* complex, *Mycobacterium leprae* (not relevant to this review article), and non-tubercular mycobacteria (NTM). Typical mycobacteria refer to the species included under the MTB complex that are morphologically similar, but vary in their host specificity, pathogenicity, genetic make-up and biochemical reactions. For example, *Mycobacterium bovis* infects cattle; but can be a zoonosis in human beings. The two subtypes of *Mycobacterium africanum* (East and West African types) have special affinity to black races and are responsible for 50% of TB in sub-Saharan countries. Perplexingly, it is seldom seen outside Africa.[11] *Mycobacterium canettii* specifically affects lymph nodes in children.[12]

Atypical mycobacteria, also known as NTM,[13-17] are mostly non-pathogenic environmental species.

They rarely cause opportunistic infections, particularly in susceptible individuals such as children, patients with human immunodeficiency virus (HIV) infection and those undergoing immunosuppressive treatment.[18-20](Table 1) They may also contaminate laboratory samples and cause diagnostic confusion.[21,22] NTM mimic typical MTB in many aspects including clinical manifestations and staining properties; yet they differ in their genetic make-up, culture characters and drug susceptibility. NTM are classified based on their growth rates (slow vs. rapid growers) and their ability to produce pigments (chromogens vs. non-chromogens).[22] Diagnosis of NTM can be challenging due to their complex morphology and growth characteristics.[18,20]

Table 1. Organs affected by various mycobacteria [#]

Mycobacterial species	Affected organs
Typical mycobacteria	
M. africanum	All organs
M. bovis	All organs (Zoonosis)
M. canettii	LN
M. caprae,	All organs (Zoonosis)
M. pinnipedii	All organs
M. suricatae	All organs (Zoonosis)
M. tuberculosis	All organs
Atypical mycobacteria	
M. abscessus †	Lung, SS, Bone, LN*, DD*
M. arupense	Bone
M. asiaticum	Lung*
M. aubagnense	Lung
M. avium §	Lung, LN, DD, SS, Bone*
M. bacteremicum	Bone
M. boenickei	SS, Bone
M. bolleti	Lung
M. brisbanense	SS, Bone
M. canariasense	Bone
M. celatum	Lung, DD*
M. chelonae †	LN, DD, SS, Bone, Lung*
M. chimaera	Heart
M. conspicuum	DD*
M. cosmeticum	Bone
M. flavescens	DD
M. fortuitum †	Lung, LN, DD, SS, Bone
M. genavense	Colon, Lung*, DD*
M. goodii	Heart valves
M. gordonae	SS
M. haemophilum	DD, SS*,Bone*,Lung*, LN*
M. heraklionense	Bone
M. hiberniae ‡	SS, Bone
M. houstonense	SS, Bone
M. immunogenum †	DD*, SS*, Bone*
M. intracelluare §	Lung, LN, DD, SS, Bone*
M. iranicum	Bone
M. kansasii	Lung, Bone, DD, LN*, SS*
M. kumamotonense	Bone
M. lentiflavum	DD
M. longobardum	Bone
M. mageritense	SS
M. malmoense	Lung, LN, DD, SS, Bone*
M. marinum	SS, Bone, DD*
M. massiliense	Lung
M. monacense	Bone
M. mucogenicum †	DD
M. neoaurum	Heart
M. neworleansense	SS, Bone
M. non-chromogenicum‡	SS, Bone*
M. peregrinum	SS, Bone
M. phocaicum	Lung
M. porcinum	SS, Bone
M. salmoniphilum	Bone
M. scrofulaceum	LN, Lung*, DD*
M. senegalense	SS, Bone
M. shimoidei	Lung*
M. simiae	LN, SS, Bone, DD*, Lung*
M. smegmatis †	SS, LN, Lung*, Bone*
M. szulgai	SS, Bone, Lung*,LN*,DD*
M. terrae ‡	SS, Bone
M. thermo-resistibile	Bone
M. triviale ‡	SS, Bone
M. ulcerans	SS, Bone
M. vaccae	SS
M. wolinskyi	Heart
M. xenopi	Lung, Bone, DD*

 # Source: Griffith[13], Sharma[14], Tran[17], Bittner[15], Brown[16], Pennington[21]
DD-Disseminated disease, LN-Lymph node, M-Mycobacterium, SS-Skin and soft tissue.
** Uncommon organs to be affected*
† Rapid growers (<7 days on subculture), others are slow growers
§ Combinedly known as M. avium intracelluare complex
‡ Combinedly known as M. terrae complex

PRINCIPLES, CLASSIFICATION AND OVERVIEWS

Basically, TB is diagnosed either by demonstrating the causative organism in clinical samples or by demonstrating the host-reaction to the invading pathogen. (Tables 2 & 3) Microscopic examination of stained smears is the simplest way of detecting mycobacteria. It is suitable for luminal and celomic TB from where infected body secretions can easily be sampled. Although it can be done with fine needle aspiration (FNA) specimens of soft tissues, the diagnostic yield will be relatively poor (18-36%) as compared to secretions (48-75%).

The threshold limit of bacterial load in the clinical sample that can be detected by stained smears is 5000-10000 AFB/ml. If the bacterial density is less than this limit (paucibacillary disease), it has to be increased by culture. Alternatively, fluorescent stains or immunochemical stains may be used to increase the diagnostic yield. Demonstration of the causative organism in histology is extremely difficult even when these special stains are used. This is due to extremely low bacterial density in tissue specimens, thick microscopic sections, and indistinguishable staining pattern of the host cytoplasm from that of the mycobacteria. The common pitfall of diagnosing TB by demonstrating MTB is its inability to distinguish environmental NTM contaminants and real pathogens.

Dead or multiplying AFB shed their cellular debris (genetic materials and cell wall components) into the body fluids and blood circulation. Detection of these cellular fragments, now popularly known as liquid biopsy, provides indirect evidence for the presence of MTB in the host.[23] Modern molecular techniques, such as the polymerase chain reaction (PCR), amplify the miniscule amount of genetic material and facilitate easy detection of species-specific DNA or RNA sequences. As the sensitivity of this approach is usually very high (80-95%), the World Health Organization (WHO) recommends rapid, automated cartridge-based nucleic acid amplification test (CB-NAAT) as the preferred

Table 2: Diagnosis of tuberculosis: Tests based on causative organism

Goal of test	Examples
Detection of intact organism	Smear study Hot stains Ziehl-Neelsen stain Wade-Fite Stain GMS stain Cold stains Kinyoun stain Hallberg stain Gabbett stain Tison stain Zhao stain Fluorescent stains Auramine-O Auramine-Acridine orange Auramine-Rhodamine Immunochemical tagged stains pAbBCG Anti-MPT64 antibody Electron microscopy Culture* Solid medium Liquid medium Indicator medium Fine needle aspiration cytology Immunohistochemistry
Detection of bacterial DNA or RNA	Polymerase chain reaction (PCR) LAMP Reverse transcription-PCR Truenat™ CB-NAAT GeneXpert MTB/RIF™ GeneXpert MTB/RIF Ultra™ GeneXpert MTB/XDR™ GeneXpert Omni/Edge™
Detection of bacterial cell wall antigen	Lipoarabinomannan (LAM)

** See Table 4 for more details*
CB-NAAT-Cartridge-based nucleic acid amplification test; GMS-Grocott methenamine silver; LAMP- Loop-mediated isothermal amplification; Truenat-Taqman RTPCR based nucleic acid test

.

Table 3: Diagnosis of tuberculosis: Tests based on host reaction

Goal of test	Examples
Direct proof of tissue changes	Conventional histopathology Immunohistochemistry Fine-needle aspiration cytology Imprint cytology
Indirect proof of tissue changes (Imaging)	Radiography Ultrasonography Computed Tomography Scan Magnetic Resonance Imaging Positron Emission Tomography Isotope scans
Demonstration of in-vivo cell mediated immunity	Mantoux test Tine test† Heaf test†
Demonstration of in-vitro cell mediated immunity	CD4+ T-cell response to Mycobacterium†
Demonstration of in-vivo humoral immunity	Anti TB IgG (against Mce1A) Anti TB IgM
Demonstration of in-vitro humoral immunity	Interferon-gamma release assays (IGRA) QFT Gold (QFT-G)™ ELISA QFT Gold-Plus (QFT-Plus)™ QFT Gold-in-tube (QFT-GIT)™ T-SPOT.TB assay TB-Feron ELISA™ A-60 ELISA MagPlas ELISA
Detection of host-based biomarkers†	Diacetylspermine Hydroxykynurenine Mass-to-charge ratio 241.0903 MPT64 N-acetylhexosamine Neopterin PPE17 (Rv1168c) protein Sialic acid Ureidopropionic acid *(Continued)*
Detection of non-specific inflammatory markers	Erythrocyte sedimentation rate Leukocyte Count C-Reactive Protein Adenosine deaminase Interleukins (IL-6) Lactate dehydrogenase (LDH) VEGF† Tumor necrosis factor (TNF)
Non-biological inference interface	Artificial intelligence (AI)

† Not routinely practiced now

CD - Cluster differentiation; ELISA-Enzyme linked immuno sorbant assay; QFT-QuantiFERON-TB; T.SPOT-TB assay-Tuberculosis-specific enzyme-linked immuno-spot assay; MagPlas-Magnetoplas-monic; VEGF- Vascular endothelial growth factor

diagnostic method in pediatric TB where the AFB load is typically low.[5,24] Nonetheless, the high sensitivity of molecular methods is also a disadvantage that they leading to over diagnosis. They simply detect cell debris rather than live bacilli. Thus, false positivity is resulted from the residual debris that persist even after several months of successful treatment.[25] Further, many of the children with incipient and subclinical TB detected by CB-NAAT, may not proceed to develop clinical infection thanks to the immune system.[26]

Among the diagnostic methods based on the host response to bacterial invasion, histopathology is the most reliable. Unique antigens and chemicals expressed by MTB cause a distinct inflammatory reaction with granuloma formation. Histological demonstration of this characteristic tubercle is diagnostic of TB, particularly in endemic areas. Histology is suitable for TB affecting any organ, especially the extra-luminal lesions. However, it requires a surgical operation to secure the specimen. FNA is a surrogate of histopathology, but it is inferior to tissue biopsy in terms of detecting granuloma (49% vs. 98%), demonstration of AFB (9% vs. 17%) and culture positivity (40% vs. 70%).[27] Very rarely other diseases (e.g. sarcoid-

osis) may mimic TB in histology, especially in the evolving phases of granuloma.[28]

Ability of the host immune system to mount an attack on mycobacteria could be an indirect evidence of microbial invasion. The humoral and cell-mediated immune responses can be measured either in-vitro or in-vivo. (Table 3) However, these antibody-based tests tend to over diagnose clinical infection, as they are also positive in healthy individuals with adequate immunity against TB. Further, in immuno-compromised children these tests will be negative despite active infection. For these reasons, the WHO discourages these tests in routine practice. Intradermal tuberculin test is an exception to this notion and it is widely used as screening tool because of its simplicity and cost-effectiveness. Antibody-based tests are also useful in diagnosing LTBI, assessing the effectiveness of anti-TB vaccination and predicting the risk of developing TB in high-risk individuals such as the contacts.[29]

Apart from the foregoing specific evidences of mycobacteria, several indirect, non-specific investigations may raise a suspicion of TB. The chief among them are radiological shadows caused by tubercular granuloma and its sequelae. They are studied using a variety of modalities such as plain or contrast radiography, ultrasonography, computed tomographic (CT) scan, magnetic resonance imaging (MRI), positron emission tomography (PET) and scintigraphy. Although they can identify lesions of internal organs, the images are neither pathognomonic of TB, nor are detectable in the early stage of the disease. Nevertheless, they are important tools for screening for TB and monitoring the therapeutic progress.

TB, being an infectious disease, causes an increase in the serum levels of certain inflammatory markers (e.g. erythrocyte sedimentation rate, adenosine deaminase). Despite being non-specific, they are often used as corroborative indirect evidences of chronic inflammation. They are also useful in monitoring the response to ATT. As they are cheap and easy to do, they are widely used as surrogates for complex molecular tests.

From the foregoing description, it is obvious that no single test can confidently establish or exclude the diagnosis of TB. Complementation of more than one test and correlation of clinical features are the essential principles of TB diagnosis.

SPECIMEN SAMPLING

Sample Collection and Its Types

Accurate diagnosis of TB depends on appropriate collection, transportation and handling of the specimen.[30] It is essential to avoid contamination of NTM from environmental sources (e.g. tap water), as this will result in false-positives. TB is clinically classified into pulmonary and extrapulmonary infections. Extrapulmonary TB may be luminal (affecting the gastrointestinal and genito-urinary tracts), celomic (involving pleura, peritoneum, pericardium and meninges), soft tissual and bony infections. Specimens appropriate for diagnosing TB depend upon the affected site.

Sample collection is relatively non-invasive in luminal TB as sputum, urine and stool can be obtained easily. But they are at a high risk of contamination with commensal flora and hence require at most care in collection and handling.[31] Samples of extra-luminal lesions are generally not contaminated; but they require varying degrees of invasive sampling, which ranges from needle aspiration to open biopsy by craniotomy or thoracotomy. In case of celomic TB, aspiration of pleural, pericardial, ascitic or cerebro-spinal fluid provides an uncontaminated specimen. Soft tissue and bone TB requires FNA, core-needle biopsy or tissue sampling by endoscopic or open biopsy. The biopsy specimen should be dispatched to the lab in normal saline for mycobacterial detection, and formalin for histology. Cut surface of the biopsied tissue may be pressed against a glass slide for

imprint cytology. Homogenate of biopsied tissue may be used for culture and other microbiological studies.

Microbial Sampling of Pulmonary TB

Sputum sampling

Sputum is the best material to detect the causative organism in aero-digestive TB. Originally examination 3 sputum smears obtained on two days was recommended.[32] In the 'Spot–Morning–Spot' strategy, a spot sample is collected at the first hospital visit, followed by an early morning sample collected at home, and a third spot sample collected during the second visit. However, for operational convenience WHO now recommends only 2 spot samples (Spot-Spot) collected on the same day. Although early morning sputum was held to have higher concentrations of AFB, recent studies confirmed that spot samples are also reliable.[125]

Induced sputum sampling

When young children cannot produce enough sputum by expectoration, several induction techniques are employed to increase the sputum yield. They include pre-sampling inhalation of bronchodilators, nebulization with 3-5% hypertonic saline and nasopharyngeal aspiration.[33-35] Lung Flute™ is a new device that works on the principles of oscillatory positive expiratory pressure (OPEP) facilitating sputum collection in young children.[36] (Fig. 1) The reeds in it generate 18–22 Hz sound waves at 110–115 dB with 2.5 cmH_2O pressure.[37] These vibrations travel through the tracheobronchial tree, loosen mucus and enhance mucociliary clearance of the sputum.

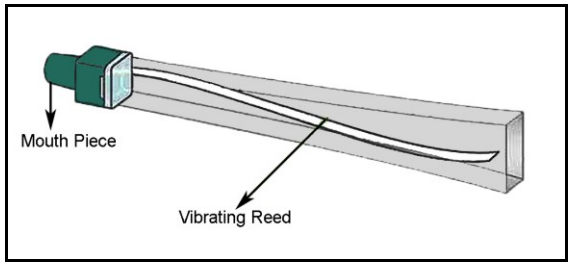

Fig 1. *Lung Flute™ for induced sputum collection*

Gastric Aspirate sampling

Young infants who have not learnt to spit sputum tend to swallow it. Hence, the standard practice in them is to collect two to three fasting gastric aspirates on consecutive mornings.[38,39] About 5-10 ml of gastric content should be aspirated using a nasogastric tube. If the secretions are inadequate for sampling, saline lavage can be used to augment the yield.[40] It is essential to neutralize the acidity of gastric samples by adding sodium bicarbonate before dispatching them to the laboratory.[41,42]

Stool sampling

Drancourt recommended against routine use of gastric aspirate because, stool samples are equally effective in detecting the swallowed AFB.[43] Stool samples, though diagnostic of gastrointestinal and pulmonary TB, are notorious to be contaminated with NTM and colonic commensals. They should be collected from diapers or cling-wrap placed on the toilet seats, and a nylon water-proof material should be used for infants with liquid stools.[44,45]

Endoscopic sampling

Broncho-alveolar lavage done using bronchoscopy is specifically useful in sputum-negative PTB or paucibacillary disease.[46] However, it is invasive, costly, requires endoscopic expertise and is not universally available.[47].

Microbial Sampling of Extrapulmonary TB

Demonstration of mycobacterium in extrapulmonary TB (EPTB) is often difficult due to low mycobacterial load and anatomical inaccessibility.[48] The choice of diagnostic sample depends on the anatomical site of the lesion.[49] Frequently EPTB is diagnosed by molecular diagnostics or by invasive (endoscopic or open) biopsy.

Fine-Needle Aspiration (FNA) Sample

FNA provides satisfactory sample for a wide range of investigations such as smear staining, culture, molecular diagnostics, immunochemistry and cyto logy.[50] Of particular interest, cytology is a surro-

gate of histopathology. Unlike histology, FNA cytology does not show the arrangement pattern of inflammatory cells. Yet, demonstration of typical cells such as AFB, epithelioid cells, Langhans giant cells and caseation necrosis are sufficient to diagnose TB in endemic areas.[51] FNA can be done at bedside and is highly suitable for lymph nodal, intrathoracic, intracranial and abdominal lesions wherein a major surgery for securing specimen can be avoided. FNA can be done blindly or under imaging guidance. It is not ideal for luminal TB and lesions less than 1 cm in diameter. FNA will also miss the diagnosis in HIV-positive children infected with *Mycobacterium avium* as they evoke poor granulomatous reaction.[50]

Imprint Smears

Imprint cytology was first described by Dudgeon and Patrick in 1927. It is suitable for solid organs with TB granuloma. Cut section of the surgically excised specimen is pressed against a glass slide, which is then processed by routine staining.[52] It is cost-effective, quick, universally available and efficient. It accurately diagnosed 93% of tubercular lymphadenitis.[52] It avoids the need for frozen sections, thus preventing cryostat contamination.

Specimen Transport

Specimen with live AFB should be sent to laboratory as soon as possible. If delay is inevitable, they should be refrigerated. For delays exceeding 3 days, an equal volume of 1% cetyl pyridinium chloride in 2% sodium chloride should be added to the clinical sample, which can keep AFB viable for 8 days at the room temperature.[53,54] Recently, special transport media such as Wright medium for FNA samples[55] and PrimeStore™ for molecular studies [56] have been introduced.

Infectious specimens intended to be transported must be packaged in accordance with national biosafety guidelines and relevant international regulations.[57] Mycobacterial cultures should be transported to reference laboratory using solid media in screw-cap tubes. Cultures on Petri dishes or in liquid media should not be shipped. Mycobacterial cultures are generally classified by WHO as Category A (high risk). However, for surface transport, they can be considered as Category B (moderate risk).[58] For transporting Category B samples, the WHO recommends them to be kept in a leak-proof primary container that is surrounded by successive layers of absorbent materials, secondary leak-proof container, cushioning materials and a sturdy outer packing. The outer pack should be clearly labeled with a biohazard symbol and appropriate handling instructions.[58] (Fig. 2)

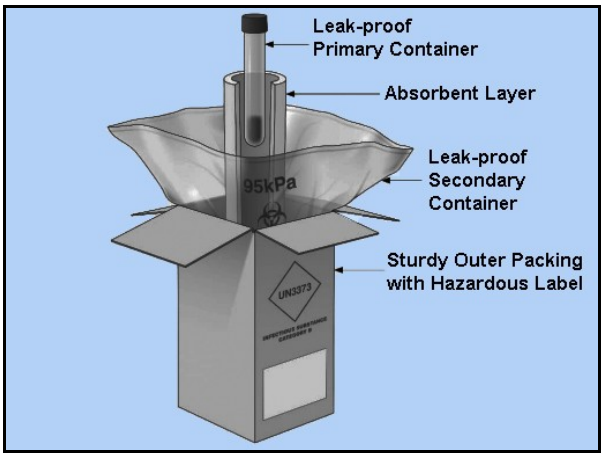

Fig 2. *Triple packaging of Category B bio-hazardous specimens for transport (WHO 2022)*

DEMONSTRATION OF MYCOBACTERIUM - STAINING

Principle of Acid-Fastness

Gram's stain that is routinely used in bacteriology cannot stain mycobacteria due to the waxy coating on their cell wall.[59] Hence, they are called "Gram-ghost bacilli" (neither positive, nor negative). A phenol-based stain or a fluorescent stain is needed to visualize mycobacteria.

In staining the cell wall, two different techniques are used to penetrate the waxy barrier. In the hot-staining process, the specimen mixed with appropriate stain is slightly warmed (not boiled). In the

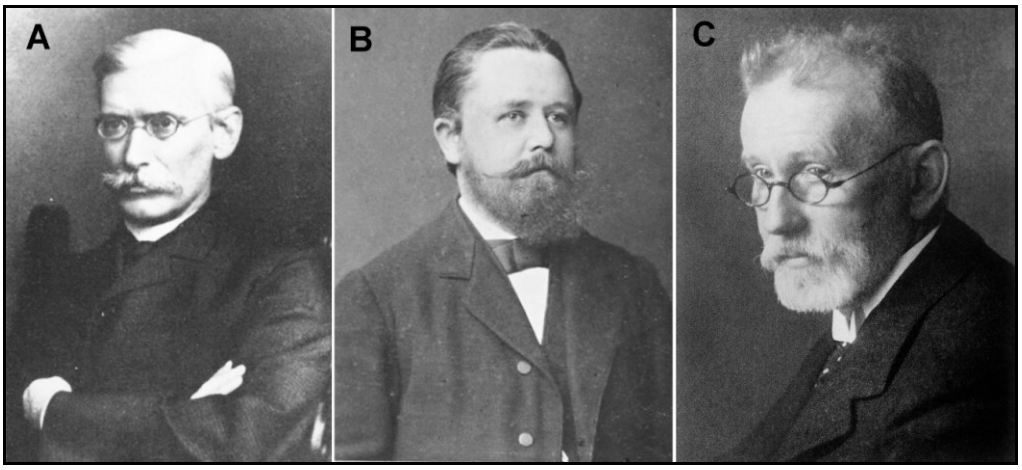

Fig 3. *Men who made Mycobacterium visible by staining techniques: (A) Franz Ziehl - 1882 (B) Friedrich Neelsen - 1883 and (C) Paul Ehrlich - 1882. (Sources: Fig. A is reproduced under Fair Use doctrine from Bishop and Neumann, Tubercle 1970; Fig. B is a public domain image from Sachsen Digital Museum - Object ID 8041; Fig. C is a public domain image from the Prints and Photographs division of the United States Library of Congress, digital ID hec.04709)*

cold-staining method, concentration of the staining chemical is increased in lieu of heating. Once fixed to the cell wall of mycobacteria, these stains cannot be removed by exposing them to acids - hence the name 'acid-fast bacilli'. This unique property is due to the presence of mycolic acid, peptidoglycan and arabinogalactan in the cell wall of mycobacteria.[59,60] Only a few other microbes like *Nocardia* and *Brucella* share this unusual character and hence acid-fastness is considered to be conclusive of mycobacteria.[60] Contaminating bacteria that are not acid-fast, are made visible by a counter stain.

By conventional staining techniques, AFB will be seen as pink or red rods on the contrasting blue background of the counter stain. It is to be noted that acid-fast mycobacteria may also turn acid-labile (negative AFB), if cellular synthesis of mycolic acid is inhibited,[59] as it is in nutrient-deficient cultures, isoniazid treatment and mutant strains. Rapidly multiplying virulent bacilli (e.g. aggressive disease as in HIV patients) as well as non-dividing dormant bacilli (e.g. LTBI) do not produce enough mycolic acid and hence they do not exhibit acid-fastness. This phenomenon is known as the Koch Paradox.[59] Acid-lability of MTB adds yet another challenge to the diagnosis of LTBI. For the same reason, detection of AFB in patients undergoing ATT will also be difficult. Acid-lability could be a proxy indicator of isoniazid susceptibility.

Hot Stains

The most popular hot-staining is the Ziehl-Neelsen protocol.[61] It was originally developed by Paul Ehrlich (1854–1915) and later modified by Franz Ziehl (1857–1926) and Friedrich Karl Adolph Neelsen (1854-1894).[32] (Fig. 3) In Ziehl-Neelsen technique 0.75% carbol fuchsin is used as primary stain that stains bacilli with pink or red colour and the counterstain methylene blue gives a blue background. (Fig. 4) It is easy to perform and has a sensitivity of 70% and specificity of 97%. False positives are due to contamination from laboratory equipments or dietary fibers. False negatives are due to too thick or thin smears, overheating of stains and poor standardization of the technique.

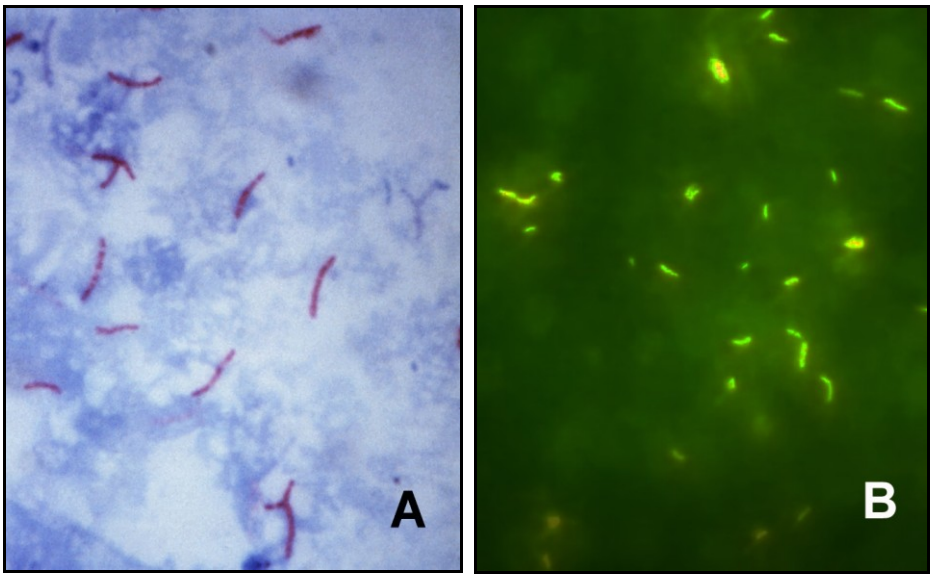

Fig 4. *Staining of mycobacteria (A) Ziehl-Neelsen stain (Magnification 1000X) showing pink coloured mycobacteria; (B) Auramine-Rhodamine stain showing bacilli as brilliantly fluorescent yellow or green rods. (Sources of images: Fig. A is public domain image from US Center for Disease Control and Prevention - Public Health Image Library ID #5789 credited to Dr. George P. Kubica. Fig. B courtesy of Dr. Ajay Kumar Chaurasiya @ https://medicallabnotes.com)*

Although Ehrlich originally used 30% nitric acid, and Neelsen used 25% sulphuric acid as decolorizing agents, a weak 3% hydrochloric acid has been found to reduce false negativity as it removes less stain from the bacterial cell wall, thus making it easily visible.[63] Recently, controlled heating with microwave oven [64] has been suggested to reduce false negativity that is attributable to overheating.

Cold Stains

Generally hot stains more effectively penetrate the waxy layer of mycobacterial cell wall and provide a better colour contrast of the bacilli against the blue background.[65] However, technical errors in heating may result in destruction of the bacterial cells. Hence, Gabbett in 1887 described a technique of cold staining. Kinyoun's staining is similar to Ziehl-Neelsen method, except that the concentration of carbol fuchsin is 3.1% rather than 0.75%.[66] Hallberg method uses carbol-Nachtblau (midnight-blue) solution as the primary stain and carbol fuchsin as the counterstain resulting in blue colour bacilli on red background (inverse of Ziehl-Neelsen appearance). Tison used Nachtblau as the primary stain and orange-G as the counterstain (blue bacilli on orange background). Colour contrasting plays a major role in reducing false negatives. Thus, blue bacilli against orange background are less likely to be missed as compared to pink bacilli against dark blue background.[67] Hok combined Kinyoun's primary stain and Gabbett's decolorizing agent. Zhao used dioxogen to fix the primary stain in lieu of heating.[60,68]

Grocott's methenamine silver (GMS) stain is rarely used to visualize non-viable mycobacteria that are not acid-fast. It is also useful in intracellular bacilli engulfed by the host macrophages, AFB obscured by inflammatory cells and paucibacillary TB.

Fluorescent Stains

Ziehl-Neelsen stain is a poor technique to demonstrate mycobacteria in tissue sections or when the bacterial load is less than 5000-10000 AFB/ml of the specimen.[59] This limitation can be overcome by using a fluorescent stain, such as auramine-O,

instead of carbol fuchsin in the Ziehl Neelsen protocol. The diagnostic threshold of fluorescent stains is as low as 500-1000 AFB/ml of specimen which is 10 times lower than that of the conventional stains.[69] Combining two fluorescent stains that bind different components of the bacterial cell has been shown to improve the diagnostic yield. For example, auramine-O that binds to the mycolic acid of the bacterial cell wall can be combined with either acridine orange that binds to nucleic acids (RNA and DNA) or rhodamine-B that binds to mitochondrial membrane and DNA. SYBR-Gold™ is a novel stain that has a strong affinity to nucleic acids of AFB.[70]

Several studies have attested to the superiority of fluorescent stains over conventional stains.[71-73] Sensitivity and specificity of auramine-rhodamine staining exceed 95% and it diagnoses 10-25% of cases that are missed by the conventional Ziehl-Neelsen technique.[71,72] Several factors contribute to the improved diagnostic yield: (1) Bright yellow or orange fluorescence of viable bacilli and green glow of non-viable mycobacteria against a dark background is easy to recognize even by colour blinded individuals. (Fig. 4) (2) Fluorescent stains bind to not only the mycolic acid in the bacterial cell wall but also to nucleic acid and mitochondrial membranes inside the cell.[59] Thus, they resist decolourization better than conventional stains. (3) Fluorescent preparations are read typically under low magnification, thus enabling examination of a larger field in a shorter time.

Auramine-rhodamine staining is ideal for culture-negative or paucibacillary TB, as it is in children. Its disadvantages are high cost, need for a fluorescence microscope and false-positivity due to excessive background fluorescence from organic debris in the specimen. (Fig 5) In resource-poor settings, light-emitting diode (LED) microscope is shown to be a cheaper alternative to expensive fluorescence microscope.[74,75] Distracting background fluorescence can be reduced by using suitable counter-

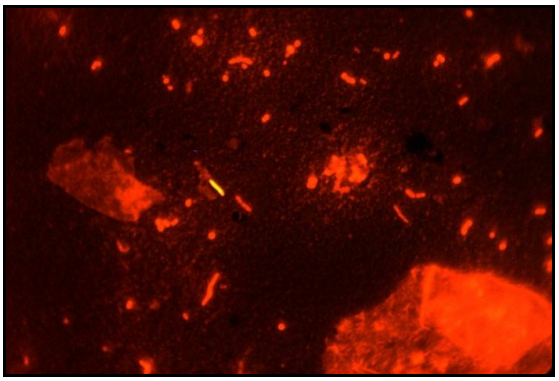

Fig 5. *Mycobacteria stained with auramine-acridine orange (Magnification 900X). Note the distraction caused by excessive background fluorescence of organic debris. (Source: Public domain image from Public Health Image Library of the US Center for Disease Control and Prevention, PHIL.ID 6468)*

stains such as $KMnO_4$, methylene blue, malachite green, blue ink or toluidine blue.

Recently, laser scanning confocal microscopy has been shown to be useful in detecting bacilli in the tissue sections and smears stained with antibody-tagged fluorescent stains.[76] It is claimed that confocal microscopy can detect even a single bacillus in the specimen. [76]

Immuno-Fluorescent Stains

The diagnostic yield of fluorescent stains can be further improved by tagging them with specific antibodies against mycobacteria. These antibodies guide the staining chemical to the target cell avoiding organic debris in the background. Commonly used tagging antibodies are polyclonal anti-BCG antibodies (pAbBCG)[77] and anti-Mycobacterium Protein Tuberculosis-64 (MPT64) antibodies.[78]. MPT64 is highly specific to MTB and thus can differentiate it from other NTM. Immunofluorescent stains, instead of staining the entire cell wall surface of bacilli, simply bind a part of it. Thus immunofluorescent stains just locate the bacilli rather than revealing their actual structure. (Fig. 6) Presence of mycobacteria can only be inferred from the reddish brown dots of fluorescence rather

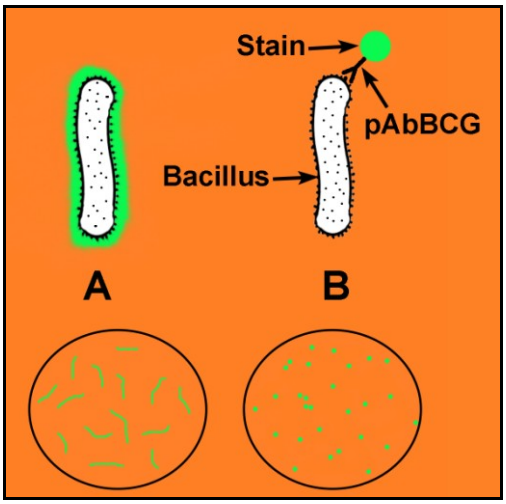

Fig 6. *Principles of regular fluorescence staining (A) and immunofluorescence staining (B). The top panel shows the mechanism of staining and the lower panel shows the pattern of microscopic appearance. pAbBCG - polyclonal anti-BCG antibody. (Courtesy of Elanthamizh)*

than by seeing the actual bacilli. Therefore, results are evaluated based on the intensity of staining.[78]

None of the aforesaid stains, except the MPT64 immuno-fluorescent stain, can differentiate MTB and NTM, as they both share the same cell wall structures.[79] The sensitivity of staining techniques varies depending on several factors, including the pathogen load and specimen processing protocols. It is important to note that all the staining methods simply indicate the presence of mycobacteria in the specimen without suggesting anything about pathogenicity or species identity.[21]

DEMONSTRATION OF BACILLI - CULTURE

The critical density of AFB that can be detected by Ziehl-Neelsen stain and fluorescent stains are 5000-10,000 AFB/ml and 500-1000 AFB/ml respectively. If the bacterial density of the clinical sample is less than these critical limits, it should be increased by culturing techniques before AFB can be recognized in smears. As little as 10-100 AFB/ml can be successfully cultured.[80] Further, culturing also allows species identification and testing of antimicrobial susceptibility. Hence, in 2007, the WHO declared culture as the gold standard of TB diagnosis.[81]

Several solid and liquid media are available for culturing mycobacteria[82] (Table 4) Among them the WHO now recommends Mycobacteria Growth Indicator Tube (MGIT)-960 liquid medium as it supports rapid growth and easy identification.[83] However, solid media are still widely used, as they are cost-effective.[84] AFB grows faster in the agar-based media than in the egg-based media.[85] The grayish or creamy glistening colonies are easily visible in the dark-red background of blood-agar or the green background of malachite containing egg-agar media. (Fig. 7)

Table 4. Mycobacterial culture media

Solid media
Blood-agar medium
Lowenstein-Jensen Egg-agar medium
MB Redox™ medium
Middlebrook medium*
Ogawa egg agar medium
Petragnani medium
Ribonucleic acid medium
Thin layer agar (TLA) medium
Liquid media
BacT/ALERT™
Bactec MGIT-960†™
Bactec MGIT-320™
Bactec 9000™
Bactec-460™
Bactec™ Myco/F
Dubos medium
Kirchner medium
Proskauer - Beck medium
Sauton medium
VersaTREK™

**7H10 and 7H11 are two modifications of Middlebrook medium*

† It is a modification of Middlebrook broth

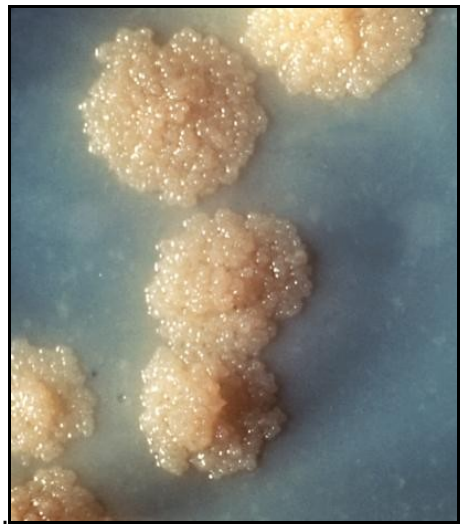

Fig 7. *Mycobacterial colonies in egg-based medium. Malachite green in the medium enhances the colour contrast for easy recognition of creamy glistening colonies. (Source: Public domain image from Public Health Image Library of the US Center for Disease Control and Prevention, PHIL.ID 6468)*

Various species of mycobacteria differ in their doubling time and they generally take 15-20 hr to complete one cycle of cell division.[69] Thus, visible growth in culture may take as long as 6-8 weeks, with an average of 14 days for liquid media and 25 days for Lowenstein-Jensen medium. The shortest duration is 9 days for the Bactec-460™ medium.[86] Overgrowth of contaminating commensals may mask the mycobacterial colonies. This is avoided by using selective media with added antibiotics to suppress commensals.

Indicator Media

Species identification of mycobacteria is done by their characteristic chemical reactions. Indicator media take advantage of this property and facilitate easy identification of MTB.[87] Indicators may be chromogenic (causing colour change) or non-chromogenic. For example, MTB turns the dark-blue colour of BIO-FM media into violet.[88,89] By bacterial oxy-reduction colorless tetrazolium salt in MB-Redox™ medium turns into pink, red or violet formazan.[90] In Bactec-460™ media, mycobacteria generate radioactive carbon dioxide from the radio-labeled carbon of palmitic acid and the resultant radioactivity is measured by a Geiger-Muller counter. Subsequent versions, such as the Bactec-9000MB™, are based on generation of non-radioactive carbon dioxide that is detected by spectrometry.[91] In Bactec MGIT™, the bottom of the tube is coated with oxygen-avid fluorochrome pigments. When oxygen present in the liquid media is completely utilized by mycobacteria, the uninhibited pigments start glowing brilliantly.[92] (Fig. 8) VersaTREK™ is based on detecting the pressure changes of the culture tube caused by fermented gas from bacterial action. A major disadvantage of all patented indicator media is their prohibitive cost.

Fig 8. *Bactec MGIT™ culture media showing brilliant fluorescence at the bottom of the tubes indicating the presence of mycobacteria. (Courtesy: Prof Thasneem Banu, Chennai)*

Animal Inoculation

Diagnostic animal inoculation with rabbit, monkey, guinea pig or hamster was done in the past for growing MTB and testing its drug susceptibility.[93] However, this is no longer practiced due to the complexity of the procedure, high cost and ethical concerns.

DETECTION OF GENETIC MATERIAL

DNA and RNA fragments of mycobacteria have several signature sequences such as rpoB (RNA polymerase-β subunit),[94] 16S-rRNA gene,[95] hsp-65 (heat-shock protein-65) gene,[96] 32-kDa protein gene and ITS (internal transcribed spacer)[97] Detecting these unique nucleotide sequences is diagnostically as accurate as demonstrating the whole organism. These molecular techniques are quick, easy to do and reliable; but are costly.

The DNA and RNA fragments are shed by the dead or dividing bacteria into the infected body fluids from which they can be isolated by centrifuging the sample. As the DNA or RNA fragments thus retrieved will be too miniscule to be identified, they need to be amplified before being detected by agarose gel electrophoresis technique. Polymerase chain reaction (PCR), real-time reverse transcription PCR (RT-PCR), loop-mediated iso-thermal amplification (LAMP) and cartridge-based nucleic acid amplification test (CB-NAAT) are some of the molecular techniques used in amplifying nucleic acid segments.

Polymerase Chain Reaction (PCR)

PCR is the traditional and reliable technique of detecting the genetic material of mycobacteria.[98] DNA extracted from the clinical sample is added to a PCR mixture which contains probes (a short-chain nucleotide tagged with a fluorescent stain that binds the amplified target-DNA fragment and helps in measuring them), primers (another short-chain nucleotide that binds to the segment of interest in the target-DNA template and initiates elongation of the synthesized complement nucleotide sequence), deoxy-nucleoside tri-phosphate (dNTP - the building block of nucleic acid chain), Taq DNA polymerase (the enzyme needed to add dNTP to the growing chain of nucleic acid from the primer), nuclease-free water, buffer and $MgCl_2$. The process of nucleic acid amplification involves the following steps: (1) Denaturation (unwinding of the bacterial double stranded DNA into single strand templates), (2) Annealing (attachment of primer to the template DNA segment of interest) and (3) Polymerization (synthesis of new DNA segments that is complement to the template DNA strand by the adding dNTP to lengthen the original primer segment). (Fig. 9) These molecular events are externally controlled by heating and cooling the PCR mixture. At optimal temperature, approximately 1000 dNTP units can be polymerized per minute. A set of temperature fluctuations that results in the synthesis of one complete set of new DNA strands is called one thermocycle. By repeating the thermocycles, more and more copies of the DNA strands can be generated. Typically with each thermocycle, the target DNA fragments in the PCR mixture get doubled by geometric proportion. Usually, 30-40 thermocycles are required to produce a sufficient amount of DNA segments that can be easily detected. Thus, 40 thermocycles will generate 1,099,511,627,776 copies (2^{40}) of the original double-stranded target-DNA segment. These amplified copies of DNA should be separated from other impurities by gel electrophoresis. Probes with fluorescent stains (e.g. SYBR-Green™, TaqMan™) bind the amplicons (multiplied DNA copies) and make them visible as bright fluorescent dots under ultraviolet transillumination or Southern blotting. [98-100]

Nested PCR is a technique in which two sequential PCR reactions are carried out to amplify the target DNA segment.[101] It has greater sensitivity and specificity than conventional single-step PCR. Line probe assay (LPA) is a variant of the PCR in which the amplicons are recognized by naked eyes when they react with probe chemicals on a membrane strip and cause color precipitates.

Liquid specimens such as sputum, cerebrospinal fluid (CSF), bronchial lavage, pleural fluid, urine and gastric aspirates are ideal for PCR.[98] The commonly used primers are TB_{41} or TB_{42} (targeting IS6110 sequence; probed with TB_{43}) and MT_1 or MT_2 (probed with MT_3).[98] Appropriate selection of primers, probes and thermal fluctuations

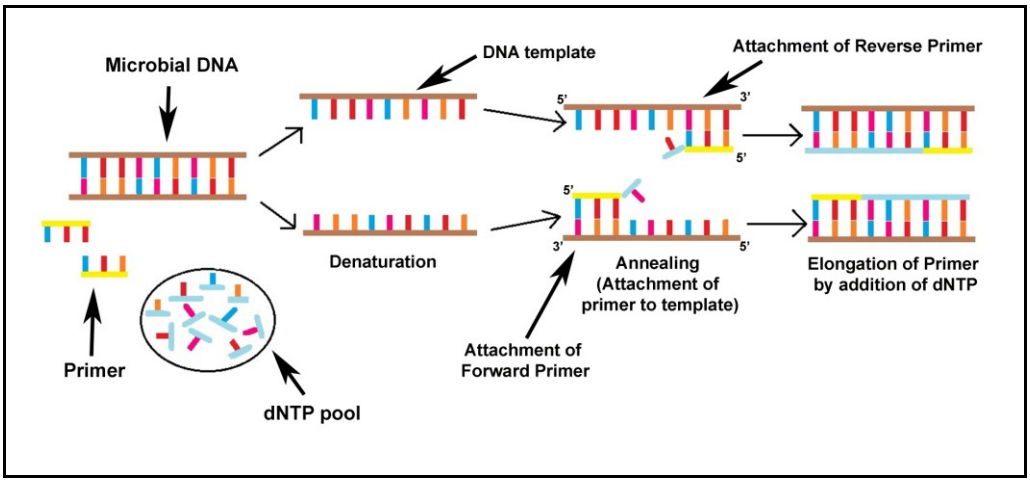

Fig 9. *Schematic diagram showing the principle of Polymerase Chain Reaction (Courtesy of Srinidhi)*

are essential for accurate results. With excessive heating or cooling, the primer will bind the target-DNA template at a wrong place, thus causing false negatives. PCR inhibitors (Table 5) such as hemoglobin and urea interfere with the polymerase reaction, resulting in false negativity.[102] Hence, blood and urine samples are generally considered unsuitable for PCR studies. However, newer protocols of specimen preparation annul these inhibitor effects. For example, use of citrate as anticoagulant in blood samples effectively replaces EDTA or heparin which are PCR inhibitors.[102] Similarly, bile salts in stool samples can be neutralized by adding activated charcoal.[102] PCR of blood, urine and stool samples are now considered as reliable diagnostic tools for childhood tuberculosis.[103] As PCR multiplies the template DNA fragment several billion times within few hours, it will also amplify contaminating DNA fragments leading to false positivity. Hence, extreme caution is needed to avoid contamination during sample handling and preparation of the PCR mixture.

Real-Time Reverse Transcription-PCR

In PCR, signature DNA copies of the template DNA fragments in clinical samples are multiplied. In real-time reverse transcription polymerase chain reaction (RT-PCR), complement DNA (cDNA) strands are reverse transcribed from the messenger RNA (mRNA). The cDNA is simultaneously amplified by PCR for easy detection.[104] Template RNA extracted from centrifuged clinical samples is mixed with RT-PCR mixture containing primer, probe, manganese diacetate,dNTP, reverse transcriptase enzyme, DNA polymerase, uracil nucleotide glycosidase and EZ buffer. The reaction takes place in a thermocycler and subsequent steps of identification of the cDNA are similar to PCR technique.[105] Its sensitivity and specificity are 82% and 99% for PTB; 70% and 99% for EPTB.[106]

Table 5. List of PCR inhibitors

Bile salt	Lactoferin
Calcium ions	Lipids
Collagen	Melanin
Detergents	Myoglobin
Drugs like acyclovir	Phenol
EDTA anticoagulant	Plasmin
Glycogen	Polysaccharides
Hemoglobin	Proteinase
Heparin	Sodium salt
Hormones	Urate
Immunoglobulin G	Urea

Source: Schrader [102]

Loop-Mediated Isothermal Amplification (LAMP)

LAMP is another technique of nucleic acid amplification that differs significantly from conventional PCR. Unlike PCR, where thermal fluctuations are used to control polymerization reaction, in LAMP nucleic acid synthesis occurs at a constant temperature.[107] Instead of one primer as in PCR, LAMP uses 4-6 primers (inner and outer primers). This increases its specificity and reduces reaction time. LAMP can synthesize 10^9 copies of the target DNA segment within 1 hr, while the same would require 5-6 hr in conventional PCR.[107] LAMP uses special polymerization enzymes that have high strand displacement activities besides replication. LAMP can be used to amplify both DNA and RNA. Concurrent usage of more than one primer and probe causes a peculiar problem of false positivity from primer-primer or primer-probe polymerization.[108]

Cartridge Based Nucleic Acid Amplification Test

Even nano-level contamination of environmental nucleic acid debris during the preparation of PCR mixture may lead to false positivity. To overcome this disadvantage Cepheid company, in collaboration with Foundation for Innovative New Diagnostics (Geneva), developed automated cartridges containing PCR mixtures. This cartridge-based nucleic acid amplification test (CB-NAAT) is also known by its brand name Gene-Xpert™ MTB/RIF (RIF stands for Rifampicin sensitivity). Like conventional PCR, Xpert is intended to detect rpoB gene that is linked with rifampicin sensitivity. This gene is present in all bacteria; but its length and nucleotide sequence differ between various species. GeneXpert MTB is intended to detect MTB specific rpoB gene, thus implying the presence of mycobacteria. In addition, recognized mutations of the gene will predict the bacterial resistance to rifampicin therapy. Xpert MTB has several technical variations such as Xpert MTB/RIF Ultra (a 6-color method) and Xpert MTB/XDR (a 10-color method).

As the reagents are readily available in cartridges and the process is automated, GeneXpert™ results can be obtained in just 45 min as compared to 4-6 hr with conventional PCR. Pre-prepared cartridges annul environmental contamination and enhance specificity by reducing false positives. Hence, the WHO recommends CB-NAAT as initial diagnostic test of choice in pediatric TB.[109] CB-NAAT is also suitable for stool samples and gastric aspirates in children.[110] They are suitable for both PTB and EPTB.[111,112]

False positive results may occur due to sampling error, detection of NTM DNA (which share similar sequence with MTB) or small amount of contaminating MTB DNA from previous samples.[25] False-negative results may occur due to low bacterial load ($<$0.25 CFU/ml),[113] presence of PCR inhibitors in the sample,[102] polymerization between primers and probes, and certain specific mutations in rpoB region.[114]

PATHOGEN-BASED BIOMARKERS

Mycobacteria release their surface antigens and secrete certain specific proteins into the host circulation. They may also get excreted in urine depending on their filtration size. By detecting these substances in blood or urine, the presence of mycobacteria can be inferred. Lipoarabinomannan (LAM), 38-kiloDalton (kDa) antigen, 16-kDa antigen and MTB12 are promising biomarkers in TB diagnosis.[115]

Lipoarabinomannan (LAM)

LAM is a glycolipid that forms the cell wall of MTB. They are shed into the host circulation when the bacilli undergo cell division or death.[116,117] LAM is 17.4kDa in size which is less than the 30kDa cutoff value of glomerular filtrates. Hence, LAM is easily excreted in urine irrespective of the organ affected. Detection of LAM more than $>$0.615 ng/ml in urine[118] or $>$2.29 pg/ml in blood samples[119] is considered diagnostic of TB. In children, urinary LAM assay is appealing in the background of difficult sample collection in that age group. Urinary LAM value is directly proportional to the bacterial

load.[120] LAM is highly elevated in disseminated disease and immuno-compromised patients.[121] In the late stages of HIV infection, impaired function of podocyte in nephrons also increases the urinary excretion of LAM. In paucibacillary disease such as pediatric TB and LTBI, LAM is generally considered unreliable.[120] However, urinary LAM detection using chemi-luminescent immunoassay (e.g. Fuji LAM™, Alere-Determine-LAM™) instead of using the Enzyme-linked immuno-sorbent assay technique has been found to increase the diagnostic yield in children and HIV negative patients.[122-124]

CONCLUSION

Diagnosis of TB in children is often challenging because of low bacterial load. The critical bacterial density necessary for detection is 5000-10000 AFB/ml for conventional Ziehl-Neelsen staining, 500-1000 AFB/ml for fluorescent staining, 10-100 AFB/ml for cultures while 0.25 CFU/ml is sufficient for nucleic acid amplification tests. Hence, the WHO recommends CB-NAAT (Gene Xpert MTB/RIF Ultra™ or Gene Xpert MTB/XDR™) as the preferred first-line investigation of TB in children. CB-NAAT is also advantageous in predicting drug resistance to rifampicin. Several host and pathogen based biomarkers are currently under investigation which may facilitate point-of-care diagnosis of TB in the future.

Addendum

Tests based on host reaction to invading mycobacteria will be reviewed in the part-2 of this article. It includes histopathology, fine-needle aspiration cytology, radiological imaging, antibody-based tests, host-based biomarkers and indicators of inflammation.

APPENDIX-1

Abbreviations

AFB - Acid-fast bacilli
AIDS - Acquired immuno deficiency disease
ATT - Anti-tubercular treatment
BCG - Bacillus Calmette-Guérin
CB-NAAT - Cartridge based nucleic acid amplification test
CD - Cluster of differentiation
CT - Computed tomography
DNA - Deoxy-nucleic acid
dNTP - deoxynucleoside triphosphate
ELISA - Enzyme-linked immuno-sorbent assay
EPTB - Extrapulmonary tuberculosis
FNA - Fine-needle aspiration
HIV - Human immunodeficiency virus
LAM - Lipoarabinomannan
LAMP - Loop-mediated isothermal amplification
LPA - Line Probe Assay
LTBI - Latent tuberculosis infection
MGIT - Mycobacterial growth indicator tube
MRI - Magnetic resonance imaging
MTB - *Mycobacterium tuberculosis*
MPT64 - anti-Mycobacterium Protein Tuberculosis-64
NTM - Non-tubercular mycobacteria
pAbBCG - Polyclonal anti-BCG antibodies
PCR - Polymerase chain reaction
PTB - Pulmonary tuberculosis
QFT- QuantiFERON TB Gold test™
RNA - Ribonucleic acid
RT-PCR - Reverse transcription polymerase chain reaction
TB - Tuberculosis
Truenat™ -Taqman RTPCR based nucleic acid test
WHO - World Health Organization

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Clinical Study

Pediatric Appendectomy in a Resource-Limited Setting: Laparoscopy Versus Laparotomy

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Keywords
Appendectomy
Comparative trial
Laparoscopic surgery
Open laparotomy

Abbreviations
HIC - High-income country
LIMC - Low, middle-income country

Abstract

Introduction: *Laparoscopy has increasingly become popular in the treatment of acute appendicitis. Despite its many advantages, it is not yet a routine practice in low-income countries like Senegal. Scarcity of research papers from Africa on the comparative benefits of laparoscopy has prompted the present study.*

Methods: *This is a descriptive and analytical prospective study over 24 months, from January 2022 to December 2023, in the pediatric surgical units of La Paix Hospital and of the Regional Hospital of Ziguinchor.*

Results: *This study includes 64 appendectomies (29 laparoscopy and 35 open). The mean age was 12 years (range 5-15 yr). There were 41 males and 23 females. The appendix was in the classic position in 77% of cases. The mean delay of therapeutic intervention was 16 hr for laparoscopy and 8 hr for laparotomy ($p=0.001$). The mean operating time was 87 min for laparoscopy and 46 min for laparotomy ($p<0.001$). Significant postoperative pain was noted in 2 patients after laparoscopy and in 7 after laparotomy ($p=0.126$). The mean hospital stay was 36 hr for laparoscopy and 65 hr for laparotomy ($p<0.001$). There were no complications after laparoscopy while 5 complications were registered after laparotomy, representing 14% ($p=0.043$).*

Conclusion: *Laparoscopic appendectomy in children appears to have considerable advantage over laparotomy in a resource-limitted setting.*

INTRODUCTION

Appendectomy is one of the most common surgical procedures done in children.[1] The two most widely used surgical techniques are laparotomy through a Lane's or McBurney's incision and laparoscopy.[1] Although laparotomy is safe, effective, simple and associated with a low morbidity and mortality rates, it is being replaced by laparoscopy which offers more advantages in terms of operating time, hospital stay, post-operative pain, time to resume activities, aesthetic appearance of scars and post-operative complications.[1-4] Many randomized controlled trials were conducted to determine the best surgical approach.[2,5,6] Laparoscopy is preferred in high-income countries (HIC), while it is still not available in many low- middle-income countries (LMIC), where most of the institutions still do open appendectomy.[7]

The adoption of laparoscopic surgery in LMIC has been sporadic for various reasons. Some of the obstacles are intrinsic of the health care system (e.g. inadequately trained personnel) while others financially driven (e.g. non-availability of equipment). The cost of initial setting-up and maintenance of laparoscopic surgery equipment has been reported in some studies as the main inhibitory factor for minimally invasive surgery in LMIC.[7] Moreover, in many LMIC it is difficult to implement new approaches in surgery, not only among patients but also among local surgeons.[8] Only a few studies have been done in Africa on the pediatric laparoscopy. Therefore, we intended to assess the role and benefits of laparoscopy in our establishment.

PATIENTS AND METHODS

Study Design and Setting

We conducted a descriptive and analytical prospective study over 24 months, from January 2022 to December 2023, in the pediatric surgical units of the La Paix Hospital and the Regional Hospital of Ziguinchor.

Population Study

All patients under 16 years of age whose had clinical and sonographic features of acute uncomplicated appendicitis were included in this study. We excluded all those who were found to have complicated appendicitis on surgical exploration and those with negative histology for appendicitis.

Surgical Technique and Post-operative Protocol

Laparotomy was performed through a 3 to 4 cm transverse, muscle preserving incision at the right iliac fossa. Ligation-section of the mesoappendix was done with 3-0 polyglactin. After exposing the appendicular base, 3 Kocher's camps were applied at the basis and section of the appendix was done between the 2 proximal forceps. Appendicular stump was ligated with 2-0 polyglactin and the exposed mucosa was ablated with electrocautery.

Laparoscopy was performed using 3- and 5-mm trocars. Telescope was inserted through the 5-mm umbilical trocar (T1) and two working 3-mm trocars were inserted through the right (T2) and left (T3) iliac fossae. Grasper through T2 held the tip of the appendix and forceps or bipolar coagulating scissors thorugh T3 was sued to section the mesoappendix. The appendicular base was tied with extracorporeal knots using 2-0 polyglactin. Section of the appendix was done with a scissors between the two ligatures through T3. Afterwards, the appendix was extracted through the umbilical port using an endobag.

Post-operatively, all patients received antibiotics (amoxicillin plus clavulanic acid and metronidazole) for 7 days and two analgesics (paracetamol and tramadol) for 7 days. Enteral feeding was started 12 hr after surgery in both groups. Criteria of discharge included tolerance of full enteral feed, absence of nausea or vomiting, normal range of vital signs, clean operative wound or absence of pus discharge after the treatment of surgical site infection.

Data Collection and Statistical Analysis

The parameters studied were age and sex of patients, anatomical location of the appendix, time delay of surgical intervention, operative time, and outcome data such as postoperative pain, length of hospital stay and complications.

Data collected from medical records and operating room registers were entered in Excel spread sheet (Microsoft Office 2013) and analyzed using SPSS (Statistical Package for Social Sciences) version 18. Comparisons between the laparoscopy and the laparotomy groups were done using Pearson's chi-square test or Fisher's exact test for discrete data and Analysis of Variance (ANOVA) for continuous data. Statistical significance was defined as P value <0.05.

RESULTS

We had done 64 appendectomies (29 laparoscopy and 35 laparotomy). The mean age was 11.9 $\pm$ 2.7 years (range 5-15 yr). There were 41 males and 23 females (sex ratio of 1.78). The appendix was paracecal in 76% of cases. (Fig 1)

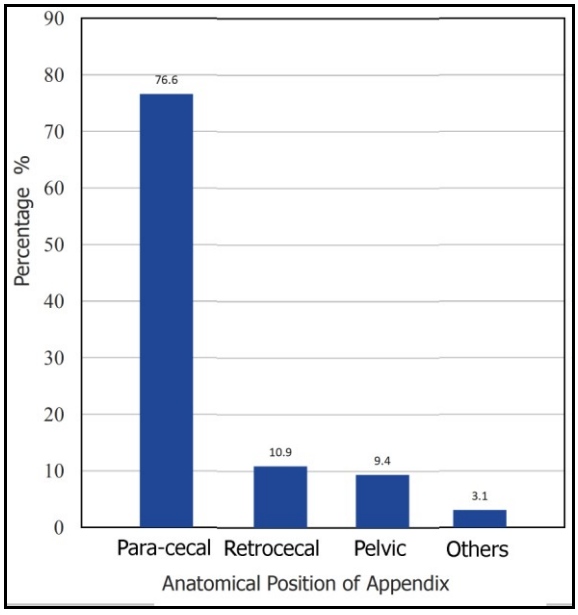

Fig 1. *Anatomical position of the appendix*

Comparison of laparoscopic and open appendectomy is summarized in Table-1. The mean delay of surgical intervention and the mean operative time were shorter for open surgery. Postoperative pain and mean length of postoperative hospital stay were signioficantly more for open suregry. All the five postoperative complications were seen in open surgery group (Table-2).

Table 1: Comparison between laparoscopic and open appendectomy

Parameters	Technique		P-value
	Lap	Open	
Mean delay of surgery (hr)‡	16	8	0.001
Operative time (min)‡	87	46	< 0.001
Post-operative pain (n)*	2	7	0.126
Post-operative stay (hr)‡	36	65	< 0.001
Complications (n)†	0	5	0.043

*‡ANOVA, *Pearson's chi-square test, †Fisher's exact test*

.

Table 2: Complications according to Clavien-Dindo classification

Category	n	%
Grade II	3	8.6
Surgical site infection	3	8.6
Grade IIIb	2	5.8
Adhesive small bowel obstruction	1	2.9
Incisional hernia	1	3.9

DISCUSSION

Over the last two decades, laparoscopic appendectomy in children has become the gold standard in HIC. However, it is still not widely unavailable in LMIC.

In this study, laparoscopy rate was 45% which is similar other published reports from LMIC.[9] In HIC, laparoscopy is the standard approach for

suspected acute appendicitis.[10] We did less laparoscopy, especially in emergency services, due to non-availability of surgeon or operating room staff trained in laparoscopy. This could also explain the long delay before doing laparoscopic surgery as compared to open appendectomy.

Most of the study subjects were adolescents, with mean age of 12 years, matching with the peak age of childhood appendicitis.[11,12] Doing laparoscopic appendectomy in young children poses challenges in our setting due to lack of instruments suitable for this age group, thus frequently necessitate conversion to open surgery. The sex ratio of 1.78 in our series is similar to the published data.[12,13] Although gender was not a criterion for the selecting the surgical modality in our center, laparoscopy appears to be more advantageous in girls for differential diagnosis of adnexal pathologies.

According to the literature,[14] the paracecal position is the most common anatomical position of appendix, followed by retrocecal and pelvic positions. We found the same proportion in our series. Laparoscopic may be more advantageous in the background of these anatomical variations, allowing easy access without extension of parietal wall incision.[10] Complete exploration of the abdominal cavity is possible with laparoscopy that may reveal Meckel's diverticula and other associated anomalies.[13] However, the benefits of laparoscopy are debatable when the intensity of inflammatory processes hinders dissection, leading to an increase in operative time and especially if extraction of the appendix requires enlarging an port site orifice.[1]

The time to treatment varies depending on the context.[1] In our study, the mean time delay of therapeutic intervention was significantly longer with laparoscopy. In our settings, preparing for laparoscopy takes more time due to the need of mobilizing a surgical team trained in laparoscopy. Additionally, since the operating room is occupied for longer time during laparoscopy, it had to be scheduled in consideration of the other emergency operations. However in HIC, the mean time delay of treatment was similar for both groups.[4]

The longer operative time is a frequently cited disadvantages of laparoscopy.[15] It is attributable to initial setting-up time and any subsequent instrument malfunctioning or troubleshootings during the procedure.[16] Meta-analyses[3,16] have shown that even though laparoscopy takes longer time than open surgery, this was not statistically significant. Longer operative time with laparoscopy was also observed in our series. However, some studies showed minimal[3,4] or no difference[16] in operating time of the two modalities. Some of the authors have even claimed shorter operating time with laparoscopy.[6] These differences may be due to selection bias and experience of the operating surgeon.

Postoperative analgesic requirement is considerably reduced after laparoscopy.[17] Studies have reported less pain with laparoscopy[18,19]. In our series, though postoperative pain was less with laparoscopy, it not statistically significant.

For children undergoing surgery, the time taken for returning to normal activities such as attending school is of paramount importance. It also reduces the long-term psychologic consequences of prolonged hospitalization.[16] The postoperative hospital stay is consistently shorter with laparoscopy.[13] Meta-analyses[1,16,20] have confirmed this observation. Laparoscopy has a lower rate of ileus and postoperative pain, allowing early mobilization and a shorter hospital stay.[1]

Laparoscopy is also reduces wound infections and postoperative adhesive bowel obstruction.[21] In our series, 5 patients operated by laparotomy had complications. Surgical site infection was seen 3 cases, followed by 1 case of adhesive small bowel obstruction and 1 case of postoperative incisional

hernia. There were no complications in the laparoscopy group. These differences were statistically significant. However, most of the complications of open surgery were minor (Clavien-Dindo Grade-II). Only two complications (Grade IIIb) required surgery, one of which was an emergency.

Despite limitted resources of our settings, laparoscopy appears to be more advantageous than laparotomy, with a reduction in hospital stay and post-operative complications. To reduce the time delay of surgical intervention and operative time, it is essential to strengthen coordination between the emergency room and operating room personnels.

STUDY LIMITATIONS

The small sample size is a limitation of this study. Furthermore, the surgeons' level of experience in laparoscopy was not taken into account. It would have been pertinent to do cost-analysis and to compare the outcomes between beginners and experienced surgeons.

CONCLUSION

Laparoscopy has considerable advantages over laparotomy, even in a resource limitted setting with limited expertise. It should be adopted in all pediatric surgery departments where laparoscopy expertise and equipment are available.

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Clinical Study

Challenges and Outcomes of 46,XY Disorders of Sex Development: An Analysis of 30 Cases from Senegal

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Keywords
46,XY DSD
Disorders of sex development
Intersex disorders
Male pseudohermaphrodite
Masculinizing genitoplasty
Micropenis
Posterior hypospadias
Testicular descent

Abbreviations
DHT - Dihydro-testosterone
DSD - Disorders of sex development
HCG - Human Chorionic gonadotropin
PMDS - Persistent Mullerian duct syndrome

Abstract

Introduction: *Optimal management of 46,XY disorders of sex development (DSD) has numerous challenges. The aim of this study was to evaluate the epidemiological, diagnostic, therapeutic and prognostic aspects of 46,XY DSD in Senegal.*

Methods: *A retrospective, descriptive study of patients with 46,XY DSD was done between May 2017 and April 2022. Study parameters included incidence, age at diagnosis, phenotype, etiologies, assigned sex, treatment outcome and morbidity.*

Results: *There were 30 new patients of 46,XY DSD. It represented 28% of all DSD cases, with a hospital frequency of 6 new cases per year. The mean age at diagnosis was 46 months. Female or ambiguous phenotypes were found in 3 cases each. The etiologies were androgen insensitivity (n=5), persistent Mullerian duct syndrome (n=4), gonadal dysgenesis (n=3), male adrenal hyperplasia (n=2), testosterone deficiency (n=2), ovotestis (n=2) and uncertain (n=3). The initially assigned sex was retained in 29 cases (97%). One patient required reassignment to male sex. Psychological support (n=3) and medical treatment (n=4) were needed in a few cases. Gonadal surgery and masculinizing genitoplasty were done in 13 (43%) patients. Post-genitoplasty morbidity was observed in 6 cases (46%).*

Conclusion: *46,XY DSD are rare disorders of diverse etiologies. Proper management with a multidisciplinary team can improve treatment outcomes.*

INTRODUCTION

Disorders of Sex Development (DSD) refer to a group of congenital conditions in which there is a discrepancy between chromosomal, gonadal, and phenotypic sex.[1] These disorders are classified as per the Chicago Consensus into 3 categories based on karyotype: sex chromosome DSD, 46,XY DSD and 46,XX DSD. This study specifically focuses on 46,XY DSD characterized by male chromosomal pattern with atypical male genitalia.

The clinical presentation of 46,XY DSD can vary widely, ranging from severe forms of ambiguous genitalia (e.g. female-like external genitalia with intra-abdominal testes) to more subtle manifestations such as hypospadias. The variable phenotypic expression contributes to the discrepancies in the reported prevalence rate of 46,XY DSD, as its definition vary depending on the inclusion of certain forms, such as hypospadias, in different clinical frameworks.[2]

Scientific research on 46,XY DSD has lead to better understanding of their pathogenesis.[2] Etiologically, 46,XY DSD can result from genetic aberrations affecting the formation of the testes, abnormalities of testosterone secretion, defects in the synthesis of dihydro-testosterone (DHT), or mutations in androgen receptors leading to partial or complete androgen insensitivity.

The management of 46,XY DSD is complex and requires a multidisciplinary approach involving pediatric surgeons, clinical psychologists, endocrinologists, geneticists and community nurses. This 'team-based care' model ensures both the medical and psychosocial needs of the patient are adequately addressed, fostering optimal outcomes. Still, management of these conditions poses numerous challenges, particularly in Africa, where diagnostic delays are common due to financial and sociocultural barriers. This disorder remains an enigma to many medical practitioners that early diagnosis is often severely affected. Consequently, many children may already have been raised as females by the time of first consultation with a specialist. This poses significant challenges in deciding the future sex of rearing. Surgical treatment is often necessary in this context, with anatomical correction being the primary concern of adolescent boys and their parents. Management of DSD remains intricate, relying on the definitive etiological diagnosis, functional capacity of the genital organs, feasibility of surgical reconstruction and the need of long-term hormonal supplements. Additionally, factors such as the age at therapeutic intervention, financial resources and sociocultural environment must be carefully considered. 46,XY DSD also pose a significant psychological burden to the affected children and their families. In our settings, DSD remains a psychosocial emergency.

The aim of this study was to explore the demographic, diagnostic, therapeutic and follow-up aspects of 46,XY DSD in pediatric patients at the Albert Royer Children's Hospital, Senegal.

PATIENTS AND METHODS

We conducted a retrospective descriptive study spanning over five years, from May 2017 to April 2022. Patients aged 0 to 16 years, treated for 46, XY DSD in the Department of Pediatric Surgery at Centre Hospitalier National d'Enfants Albert Royer (CHNEAR) were included in the study. A karyotype was done for all included patients, confirming the diagnosis of 46,XY DSD. The etiologies of DSD were classified using the Chicago Classification. Diagnostic workup of the study group is shown in the table-1. Those who did not have minimum essential assessment and those who did not give consent (n=8) were excluded.

Demographic parameters studied were frequency of diagnostic categories, age at the recognition of anomaly, circumstances of the discovery of abnormality, age at initial consultation, geographical location of patients, and assigned sex. *Diagnostic parameters* covered personal and family medical

histories, signs of physical examination, hormonal profiles, features of abdominopelvic ultrasound, diagnostic findings of surgical explorations, histopathological examinations following biopsies, and identified etiological factors. *Therapeutic parameters* included the delay before surgery and nature of surgical intervention (gonadal surgery, genitoplasty or other surgeries). *Evaluation parameters* focused on the types of complications observed during follow-up.

Table 1. Diagnostic work-up of 46,XY DSD†

- Peripheral blood karyotyping
- Abdomino-pelvic ultrasonography
- Hormonal assays
  - Testosterone
  - Follicle Stimulating Hormone (FSH)
  - Luteinizing Hormone (LH)
  - Anti-Mullerian Hormone (AMH)
  - Cortisol
  - 17-OH progesterone
- HCG Stimulation tests*
- Genitography*
- Diagnostic Laparoscopy ± Gonadal biopsy*
- Genital endoscopy (prior to feminizing genitoplasty)

DSD-Disorders of sex development; HCG-Human Chorionic Gonadotropin.
** Done in selected cases when indicated*
† Ratio of Testosterone to Dihydroxy-testotserone was not done in our center due to financial constraints. Thus, we could have missed some of the 5α-reducatse deficiency disorders

RESULTS

Demographic aspects

Thirty patients with 46,XY DSD were enrolled over a period of five-year period, averaging 6 new cases per year. This represented 28.3% of all DSD cases diagnosed during this period. Genital abnormality was noticed at birth in 26 cases (87%) and at a later age (one each at 5, 7, 8 and 9 years) in 4 cases. The anomaly was identified by parents in 20 cases (67%) and by medical or paramedical staff in 10 (33%). The mean age at first consultation was 46 months (range 3 days - 16 years).

Fourteen patients were from Dakar (the capital city and the location of our hospital), 15 were from other regions of Senegal, and 1 was from another country.

At birth, 23 patients (77%) were assigned with male-sex and 7 (23%) with female-sex. Later, two were reassigned to male-sex by their parents even before medical consultation.

Consanguinity among parents was present in 11 cases (37%), including first-degree consanguinity in 2 (7%), second-degree in 7 patients (23%) and unspecified linkage in 2 (7%).

Table 2. Clinical features at presentation in 46,XY DSD patients

Parameter		**n (%)**
Phenotype	Male	24 (80%)
	Female	3 (10%)
	Ambiguous	3 (10%)
Penile size	Micropenis	20 (67%)
	Well-developed*	10 (33%)
Genital Orifice	Single	27 (90%)
	Two	3 (10%)
Urethral Meatus	Apical	1 (3%)
	Peno-scrotal	21 (70%)
	Perineal	8 (27%)
Cryptorchidism	Unilateral	17 (68%)
	Bilateral	8 (32%)
	Inguinal	12 (48%)
	Intra-abdominal	13 (52%)
Penile Curvature		12 (48%)
Asymmetric Genital Folds		2 (8%)
Scrotal Cleft		19 (63%)
Signs of Puberty		3 (10%)

** Four had penile curvature*

Diagnostic Aspects

Clinical features at presentation and final diagnosis are summarized in Tables 2 and 3 respectively. All the patients underwent abdomino-pelvic ultrasound, which identified Mullerian remnant in 4 (13%). Hormone assay was performed in 16 cases (53%), with elevated plasma levels of testosterone being the most frequently observed abnormality that was present in 6 patients (37%). Diagnostic surgical exploration was done in 13, including seven laparoscopic explorations. (Fig.1) There were 2 cases of ovotestis. (Fig.2)

Table 3. Final diagnosis of 46,XY DSD

Etiology*	**n (%)**
Gonadal Dysgenesis	3 (10%)
Androgen Insensitivity	5 (17%)
Persistence of Mullerian Remnants	4 (16%)
Testosterone Synthesis Disorder	2 (7%)
Ovotestis	2 (7%)
Adrenal Hyperplasia	2 (7%)

** See footnote of Table-1 regarding the diagnosis of 5α-reducatse deficiency disorders.*

Therapeutic Aspects

One patient (3%), who was initially raised as a female, required sex reassignment at one month of age. Initially assigned sex was retained in 29 cases (97%). Psychological support was provided to 3 patients (10%). In 2 cases, parents faced challenges in choosing the sex of rearing.

Four patients (13%) received medical treatment in the form of hormonal supplements that include hydrocortisone plus fludrocortisone in 1, β-HCG in 1, gonadotropin in 1 and testosterone in 1 patient.

Surgical treatment was needed in 26 (87%) cases. The mean time delay of surgical treatment was 18 months (range 3-36 months). Gonadal surgery in the form of orchidopexy and partial gonadectomy were done in 11 and 2 cases respectively. Masculinizing genitoplasty was performed in 13 (43%) patients. Techniques included onlay urethroplasty in 6 patients (46%), Duckett's operation in 1 (8%), Koyanagi's repair in 2 (15%), and two-stage Bracka's operation in 4 (31%). Feminizing genitoplasty and vaginoplasty were performed for the children raised as girls. Endoscopic exploration was used to locate the origin of the uro-genital sinus.

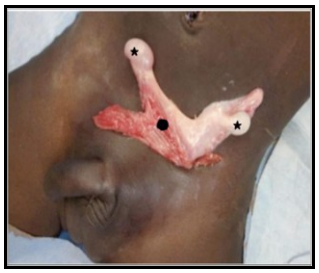

Fig 1. *Crossed testicular ectopia with persistent Mullerian remnant (*Testes; •Mullerian remnant)*

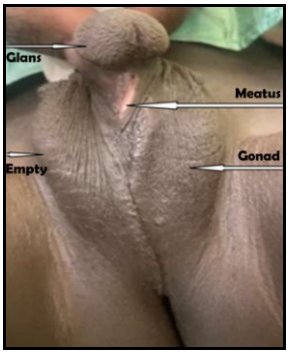

Fig 2. *External genitalia of a 46, XY ovotestis DSD patient showing asymmetric scrotal sac*

Pre-penile scrotum (n=2), penile torsion (n=1) and bifid scrotum (n=4) were also corrected. Hormonal substitution was tailored to the needs of individual patients. Estrogen replacement therapy was started after gonadectomy and testosterone injections are used to support virilization before masculinizing genitoplasty. We do not have access to topical dihydro-testosterone cream in Senegal. Hydrocortisone and fludrocortisone were admini-

stered in 2 boys with congenital adrenal hyperplasia. Human chorionic gonadotropin (HCG) was used to stimulate hormone production in cases of defective testosterone synthesis.

Evaluation Aspects

Postoperative outcomes following masculinizing genitoplasty were favorable in 7 patients. Complications were noted in 6 patients (46%), including fistula in 4, and suture dehiscence in 2. Androgen therapy resulted in an increase of penis size.

DISCUSSION

Demographic Aspects

The frequency of 46,XY DSD varies across studies. In our study, they represented less than a third of all DSD cases. In some published series, a predominance of 46,XY DSD is found to the tune of 53% to 98%.[3,4] These discrepancies may be related to different nosological frameworks. Indeed, anterior hypospadias is not considered a DSD in our center. In our cohort, consistent with several reports, the anomaly was usually discovered at birth.[5,6] But, we noted a delay in consultation that could be explained by delayed referral of patients and socio-cultural factors. In our communities, limited financial resources and the taboo of dis-cussing sex often constrain families from seeking timely medical care.

Diagnostic Aspects

The predominance of male-sex assignment in 46XY, DSD is consistent with the common practice of sex assignment in children with a male phenotype. However, the need of sex reassignment and the challenges associated with it underscore the need for a more early and accurate diagnosis.

Hormonal assay was conducted in 53% of the patients. Plasma testosterone levels were the most common abnormality, present in one third of the patients. Higher percentages are reported in other studies.[4] This discrepancy may be attributed to the fact that our analyses were not necessarily conducted during the mini-puberty period, which is the optimal time for such tests. Delayed diagnosis might have led to hormonal assay being done outside this critical window period, potentially resulting in testosterone levels that are difficult to interpret accurately.

Diagnostic surgical exploration, preferably laparoscopy, is not routinely done in the assessment of 46,XY DSD. However, it is to be done when biopsy of gonads is necessary, especially if ultrasound demonstrates Mullerian remnant.[10,11] Endocrine abnormalities predominate among 46,XY subjects, particularly in those with androgen insensitivity syndrome.[4,6,12,13] Our results are consistent with this observation as there were 5 cases (17%) of androgen insensitivity syndrome. The diagnostic work-up is often suboptimal due to unavailability of surgical facilities and high cost of care. In some cases, the etiology remains unknown due to inadequate workup consequent to the non-availability of genetic and molecular diagnostic tools in our region.

Therapeutic Aspects

In our cohort, only 1 case required reassignment to male sex at 1-month of age. Other pediatric surgeons have reported a reassignment rate of 4 to 12%.[6,14] Psychological support was provided to the parents of 3 patients when they faced the challenges of choosing the sex of rearing. In our communities, however, this concept is often poorly understood or accepted; highlighting the need for healthcare providers to improvise their clinical approach and to collaborate with support groups to provide emotional and social support.[4,15] Lifelong hormonal treatment necessitates meticulous education of patients and their families to ensure treatment compliance.

The mean delay of surgical intervention was often more than a year, which is considered unacceptably long for DSD which has significant psychosocial

impact in our country.[6,15,17] Techniques such as onlay urethroplasty, two-stage Bracka's operation, Koyanagi repair, and Duckett's procedures were used during masculinizing genitoplasties, as per the literature recommendations.[15]

Feminizing genitoplasty was done for the children raised as girls. However, no routine vaginal dilatation was performed at this stage, as they all are young children without a sexual life to maintain the dilations. Vaginal dilatation is planned for the future when it becomes appropriate.

Partial gonadectomy was performed in cases of ovotestis to remove the part of the gonad that did not correspond to the assigned sex. We chose to perform partial gonadectomy rather than total gonadectomy because life-long hormonal treatment is costly and unaffordable for our patients. Although we are aware that partial gonadectomy may be less effective in 46,XY DSD and, that the remaining gonadal tissue may still be at risk of cancer, we opted for partial gonadectomy as an initial approach. We closely monitor them for any complications or malignancy and provide appropriate follow-up care

Evaluation Aspects

In our series, favorable outcome after genitoplasty was noted in more than 50% of cases. However, complications, including suture dehiscence and fistulas, were common and it is consistent with the findings of other studies.[4,18]

MERITS AND DEMERITS

The present study has a few demerits. Firstly, the cohort size is very small. Secondly, we did not estimate the ratio of testosterone to DHT due to non-availability of technology and financial limitations. Thirdly, we do not have long-term follow-up data on sexual function, sperm production, fertility rate and psychological satisfaction with the assigned sex. However, we are intended to follow-up our patients and present the long-term outcome later at an appropriate point of time. Despite these demerits, the present study appears to the first report on 46,XY DSD from Senegal that provides some insight and elementary data necessary for further planning.

Current international standards recommend postponement of the final sex assignment until after puberty when the child can understand and take active part in decision-making. However, in our setting, sex assignment is heavily influenced by socio-cultural factors. Pubertal virilization and the possible need for gender reassignment later were discussed with families on a case-by-case basis, taking into account the available resources. These decisions were always made through multidisciplinary discussions. The goal was to ensure that all stakeholders were fully informed, coordinated and decisions were made consistent and unanimous. This approach is aimed to prioritize the best interests of the child while respecting social, cultural and financial considerations of the family.

CONCLUSION

46,XY DSD is a rare anomaly in Senegal. Its etiological investigations are lengthy and complex. Masculinizing genitoplasty needs a multidisciplinary approach and the therapeutic plan should be tailored to the needs of individual patients. Reconstructive surgery is often necessary, for both functional and psychological reasons. Involvement of commitment health-care professionals as well as patient family is essential for optimal outcome.

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Surgical Hypothesis

Mega-choledochus - Is it pathologically Similar to Megacolon?

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Keywords
Aganglionosis
Bile duct pathology
Choledochal cyst
Congenital megacolon
Enteric nervous system
Etiopathogenesis

Abbreviations
CDC - Choledochal cyst
CBD - Common bile duct
CHD - Common hepatic duct

Abstract

The traditional classification and etiopathogenic theory of choledochal cyst (CDC) has recently been challenged. A 16-month-old baby girl presented with jaundice, abdominal distention and clay colored stools for 2 weeks. Investigations revealed a Type IVA CDC. At laparotomy, a hugely distended biliary apparatus with an apparent blind distal end was noted. Excision of the CDC and Roux-en-Y hepatico-jejunostomy was performed. Her recovery is marked by a transient ascites for just 2 weeks. Histopathology of the excised distal bile duct showed hypertrophied nerve bundles similar to Hirschsprungs disease. Ultrasonography after 4 mo of surgery revealed complete regression of intra-hepatic duct dilation. From these, it appears that Todani Type I and Type IVa CDC may be just variations of the same disease.

INTRODUCTION

The traditional concept of choledochal cyst (CDC) and its anatomical classification by Todani have recently been challenged.[1,2] According to modern view, CDC is part of a larger spectrum of a fibro-cystic liver disease complex that includes a group of distinct disease entities with diverse etiologies, clinical manifestations, natural courses, complications and therapeutic options.[2] This report adds yet another dimension to the pathogenesis of CDC as a disorder of enteric nervous system.

CLINICAL EVIDENCE

A 16-month-old baby girl with a birth-weight of 2.6 kg had abdominal distension, jaundice and clay colored stools for the past 2 weeks. Previously she was normal except for a short spell of physiological jaundice during the first 2 wk of life that resolved with observation. Meconium history and the stool color were normal at birth.

On examination, there was a huge cystic mass in the abdomen extending from the epigastrium to the pelvis. Hemoglobin was 6.6 g/dl and leukocyte count was $22.5x10^9$ cells/l. Serum levels of total bilirubin 80.9µmol/l (serum direct bilirubin 70.3 µmol/l), albumin 25 g/l, globulin 36 g/l, alkaline phosphatase 2466 IU/l, aspartate transaminase 402 IU/l, alanin transaminase 321 IU/l and gamma glutamyl transferase 1921 IU/l. Computed tomography and ultrasonography showed hugely dilated intra-hepatic ducts, common hepatic ducts (CHD), gall bladder, cystic duct and common bile duct (CBD). (Fig. 1) The diameter of intra-hepatic ducts was 2.1-1.6 cm and that of the extra-hepatic ducts was 6 cm.

She was resuscitated with antibiotics, packed red blood cell transfusions and albumin infusions. On laparotomy ascites and a huge cyst occupying the entire abdomen were noted. About 300 ml of thick bile was aspirated from the cyst to deliver it into the wound. The cyst was arising from the CBD. The grossly dilated gallbladder, cystic duct, CBD, and CHD were dissected. The distal end of the CBD was apparently blind ending (Fig 2). Entire cyst was resected. The bile duct was transected at the bifurcation of the CHD and a Roux-en-Y hepatico-jejunostomy was done. Histology of the lower end of the cyst wall showed hypertrophied nerve bundles without a well-demarcated muscularis propria. (Fig. 3)

She tolerated oral feeds from the day-3 of surgery. Post-operatively she developed ascites (not leak) that required spironolactone and frusemide for 2 wk. She was discharged on the 11th day of operation. Liver enzymes reverted to normalcy within 2 wk. An ultrasonography after 4 months showed near normal caliber of the intra-hepatic ducts. (Fig. 4)

DISCUSSION

The exact etiopathogenesis of CDC is not clearly understood. According to the most widely accepted congenital theory of Babbitt, CDC is caused by an anomalous pancreato-biliary duct junction in which the pancreatic duct joins the CBD at a point 1-2 cm proximal to the sphincter of Oddi.[3] Other theories of pathogenesis include, weakness of the CBD wall, congenital or acquired ductal obstruction and dual theory (weakness of CBD wall cum ductal obstruction).[2,3]

Rolleston[4] (1905), Weber[5] (1934) and Saltz[6] (1956) speculated that CDC may be due to defective intra-mural neurons similar to Hirschsprung disease; but they did not provide any histopathological proofs.[4-6] Kusunoki[7] proposed that oligoganglionosis in the narrow portion of distal CBD results in proximal dilation similar to achalasia cardia and Hirschsprung disease. By manometric studies, Devenport and Basu[8] suggested that the round or fusiform choledochal cysts (Todani type-1) were congenital cysts with distal obstruction due to aganglionosis and proximal dilation similar to Hirschsprung disease. Histological evidences of our case supports these views.

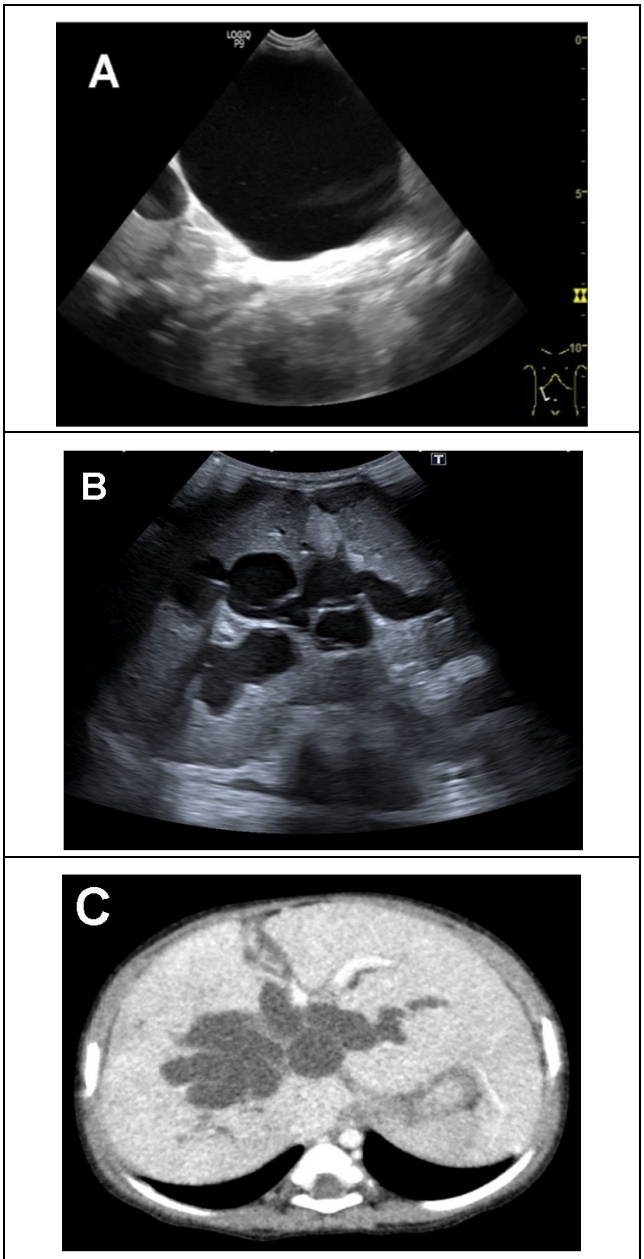

Fig 1. *Imaging studies of choledochal cyst. (A) Ultrasound showing dilated common bile duct. Ultrasound (B) and computed tomography (C) showing dilated intrahepatic biliary radicals.*

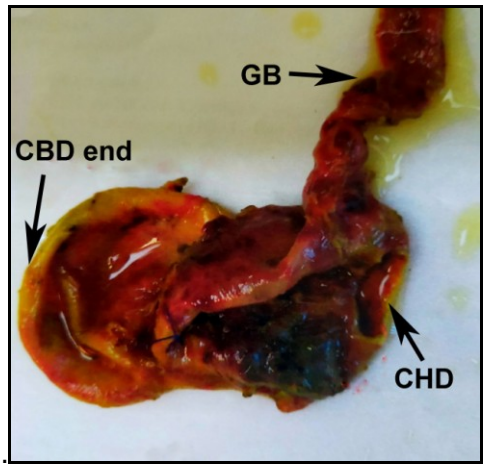

Fig 2. *Excised specimen of choledochal cyst showing dilatation of the gall bladder (GB), common hepatic duct (CHD) and the apparently blind ending dilated common bile duct (CBD)*

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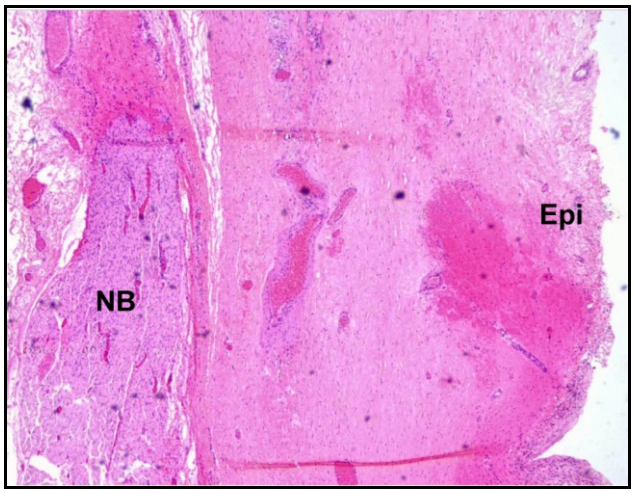

Fig 3. *Histology of the wall of choledochal cyst showing ulcerated epithelium (Epi) and hypertrophied nerve bundles (NB). Magnification 4 X, Eosin - Hematoxylin stain*

Complete regression of intra-hepatic duct dilation after hepatico-jejunostomy in our case supports the views of Visser[9] that type I and IVA cysts are variation of the same disease and the degree of intra-hepatic dilation defining one type versus the other was arbitrary. Complete occlusion of the distal end of the CDC in our case supports the

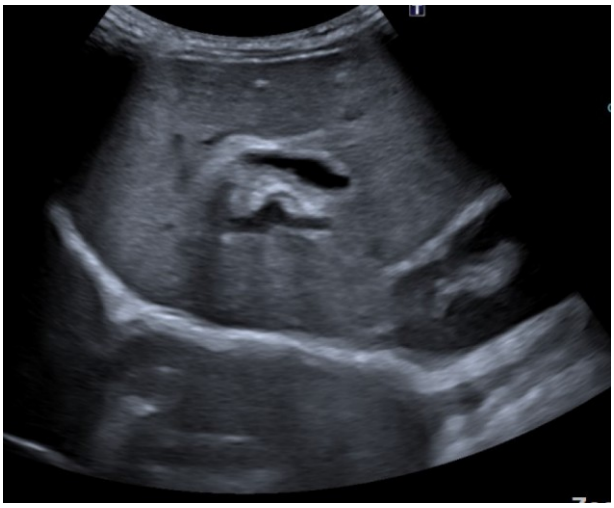

Fig 4. *Ultrasonography after 4 months of operation showing near normal caliber of the intra-hepatic ducts*

view of Diao[10] that ligation of the narrow distal stump of CDC may not be necessary.

CONCLUSION

Blind ending distal CBD may be due to segmental absence of ganglion cells with chronic infection similar to Hirschsprung disease. Complete regression of dilation of intra-hepatic ducts after surgery supports this etio-pathogenesis. More focus on Histopathology of CDC and revision of classifications need to be considered.

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Case Report

Esophageal Atresia of Kluth Type-13: Management of a Rare Variant

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Keywords
Congenital malformation
Esophageal atresia
Neonatal pathology

Abbreviations
EA - Esophageal atresia
POD - post-operative day
TEF - *Tracheo-esophageal fistula*

Abstract

A full-term low birth-weight female newborn presented with clinical features of esophageal atresia. Investigations revealed Kluth type-13, an extremely rare varient of esophageal atresia without fistula, in which the upper pouch is long and ends blindly just above the diaphragm near the gastro-esophageal junction. She was managed with esophagostomy and feeding gastrostomy in the neonatal period, followed by gastric tube esophagoplasty at 2 years of age. At 18 months of follow-up she is thriving well and asymptomatic.

INTRODUCTION

Esophageal atresia (EA) is a congenital anomaly in which the continuity of the esophagus is disrupted with or without persistent luminal communication with the trachea. Its incidence is approximately 1 in 3500 live births.[1] The most common type is an esophageal atresia (EA) with a distal tracheoesophageal fistula (TEF) (84%), while pure EA is much less common (6%).[1] Pure EA is commonly found in the upper one-third of the esophagus and is characterized by a wide gap between the two atretic ends.

Kluth classified EA into 10 different types with 96 sub-types based on: (i) the presence, location and number of fistulae, (ii) the gap between the atretic ends, (iii) the shape of the upper pouch, (iv) the presence of cyst, stenosis, strands, membranes and duplications, (v) associated abnormalities of the trachea, (vi) broncho-esophageal communication and (vii) esophago-laryngo-tracheal fissure. Kluth type-13 is a rare EA with a long upper esophageal blind pouch and agenesis of the distal esophagus.[2] We report a rare variant of the Kluth type-13 in which the distal esophageal segment was atretic rather than being totally absent.

CASE REPORT

A 4-day-old female neonate, born normally at full-term with a birth-weight of 1.45 kg, presented with drooling of saliva, regurgitation of feeds and non-passage of meconium since birth. She had had intra-uterine growth restriction. On examination, the abdomen was soft with no distention. Infant feeding tube could not be insertion and it coiled in the lower esophagus. Radiographs showed gasless abdomen and blind ending esophagus at the level of the diaphragm. (Fig. 1) Sonography of the spine and urinary system, and a 2D-echocardiography were normal.

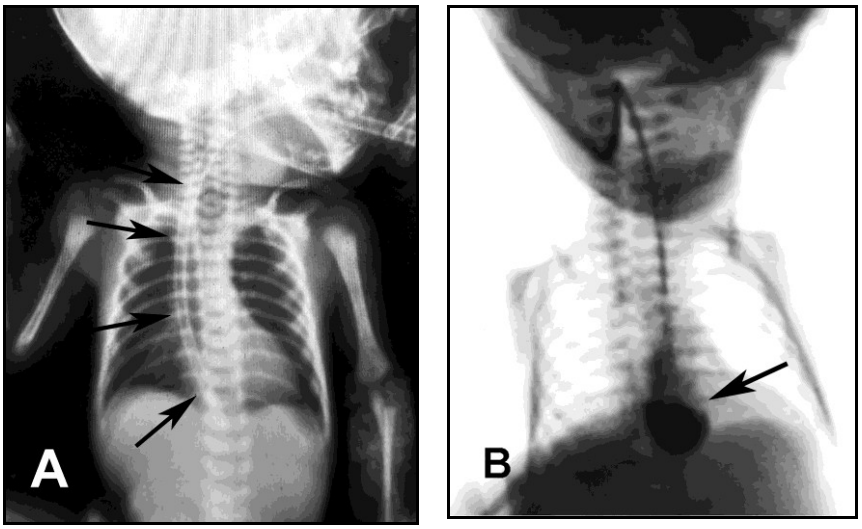

Fig 1. (A) *Plain radiograph showing an esophageal a red-rubber tube in situ (arrows) and a gasless abdomen; (B) Contrast esophagogram showing a long upper esophageal blind pouch that reaches upto the diaphragm (arrow). Gasless abdomen suggests atretic esophagus without fistula.*

She was diagnosed with EA without tracheo-esophageal fistula. After brief resuscitation, a laparotomy was done by a midline incision. The stomach was found to be small. The esophagus was atretic at gastro-esophageal junction with a 0.7-1 cm gap between the blind ends. Stamm's feeding gastrostomy along with a cervical loop esophagostomy were done. An infant feeding tube could not be passed retrogradely into the distal esophagus from the gastric lumen.

Persistent apneic spells during the post-operative period necessitated mechanical ventilatory assistance for 3 days. Feeding through gastrostomy tube was started on the postoperative day-10. After ensuring adequate weight gain, she was discharged on the 16th postoperative day (POD).

She was followed-up regularly as outpatient and a definitive operation was done at 2 years of age. The gastrostomy was reversed by laparotomy. The distal esophageal segment attached to the gastric fundus was atretic and measuring 4 cm in length. (Fig. 2) Gastric tube of 5 cm length was created from the greater curvature of the stomach. (Fig. 2) Tension free esophago-gastric tube anastomosis was done over a trans-anastomotic 12Fr Freka's tube. Oral feeds were started on the POD-5 and the Freka's tube removed on POD-10. She recovered uneventfully and was discharged on the 12th POD. At 18 months of follow-up, she is asymptomatic and thriving well.

DISCUSSION

In 1697, Thomas Gibson reported the first case of EA confirmed at post-mortem examination.[3] The diagnosis of EA is suspected by the inability to pass an infant feeding tube into the stomach due to bind ending of the upper esophagus. The resistance is generally felt at about 10 cm from the lower incisors.[4] If the infant feeding tube passes beyond this distance and then meets resistance, the possibilities of perforation of the upper pouch, a distal web or a stenosis should be suspected.[1] A gasless abdomen on X-ray in case of EA suggests the absence of a distal TEF.[4] Differentials include pure EA or EA with a proximal TEF. Our case was distinct as the patient had atresia of the distal esophagus without fistula.

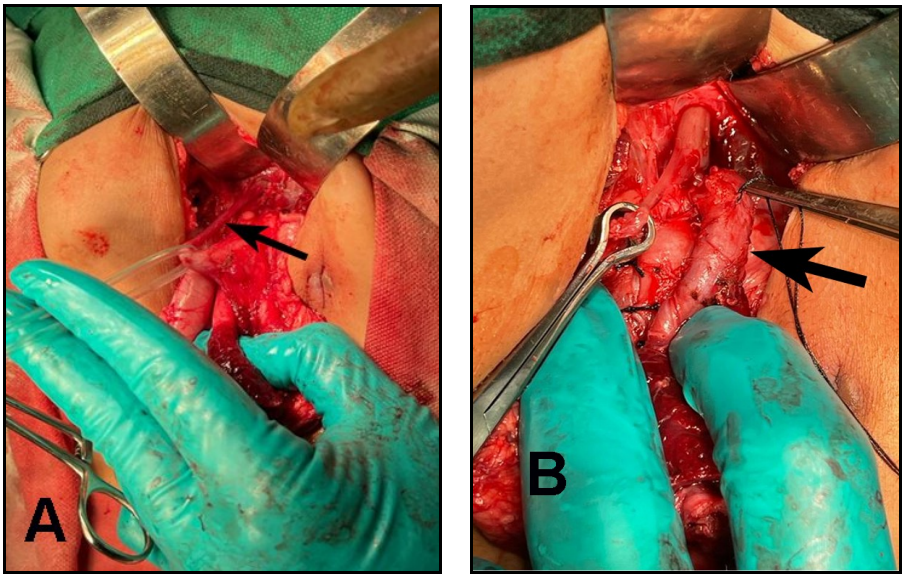

Fig 2. *Intraoperative photographs showing (A) atretic lower segment of the esophagus (arrow) and (B) the reconstructed gastric tube (arrow).*

Various theories have been put to explain EA with or without TEF. One of them holds that the trachea initially grows as a part of the undivided foregut and then becomes an independent structure due to the separation process that starts at the level of the lung buds proceeding in a cranial direction.[5] This is associated with a precise temporo-spatial pattern of expression of the key developmental

It is possible to measure the gap between the two ends of the atretic esophagus in terms of vertebral body heights. This requires insertion of a radio-opaque catheter in the proximal esophagus and injecting radio-opaque contrast or passing a bougie via gastrostomy site into the lower esophagus. Where the gap is less than the height of 2 vertebral bodies, immediate primary anastomosis can be done. Delayed primary repair can be done for a gap of 3-6 vertebral length. For a gap of more than 6 vertebra esophagostomy and gastrostomy should be done.[6]

Kluth classified EA into various sub-types depending upon the anatomical features.[2] The type-13, i.e. long upper esophageal blind pouch with total agenesis of the distal esophagus, is a rare variety of EA. Our case can be a further variant of Kluth type-13 as distal esophagus was atretic rather than being totally absent.

Gupta et.al reported 2 cases of Kluth type-13 EA. One of them was a 2-day-old term neonate 2.2 kg who underwent feeding gastrostomy and esophagostomy and the second one succumbed before any surgical intervention.[7] Shawyer and Flageole reported a case of intra-abdominal EA without TEF, wherein a primary esophageal anastomosis was done by an abdominal approach.[8]

Our patient had a birth weight of 1.45 kg and was at high risk for survival. We did cervical esophagostomy and feeding gastrostomy as a primary lifesaving procedure and scheduled the definitive repair at 2 years of age. We emphasize that all pediatric surgeons must be aware of this rare variant of EA for optimal outcome.

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Case Report

Successful Medical Management of Pediatric Gastroparesis

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Keywords
Abdominal distension
Domperidone
Erythromycin
Gastrointestinal paralysis
Gastroparesis
Intestinal motility disorder
Prokinetic agents

Abstract

Pediatric gastroparesis is characterized by delayed gastric empyting in the absence of any mechanical obstruction. This case report describes the successful use of domperidone and erythromycin in managing refractory gastroparesis in a 7-year-old girl. Owing to its rarity and shared symptomatology with other common gastrointestinal conditions, the diagnosis of gastroparesis is often delayed. In resource-limited centers without scintigraphy, the diagnosis may be made based on the clinical features and contrast radiography.

INTRODUCTION

Gastroparesis is an uncommon condition characterized by delayed gastric emptying in the absence of any mechanical obstruction.[1] The symptoms include nausea, vomiting, early satiety, epigastric bloating, weight loss, and abdominal pain.[2] Diagnosis and treatment are challenging. Management is often multimodal, including dietary changes, prokinetic medications and occasionally surgical interventions. An identifiable cause is often absent though it is more common in girls and is linked to diabetes, infections or surgery.[3] This report is intended to draw the attention of practicing pediatric surgeons to this uncommon problem.

CASE REPORT

A 7-year-old girl presented to emergency department with abdominal pain, distension, and obstipation for 2 days. Her parents reported a long-standing history of abdominal bloating without constipation over the preceding 2 yr. She was born by normal vaginal delivery at full-term, with a birth weight of 3.5 kg. There was no significant maternal or antenatal history. During the perinatal period, she had neonatal jaundice and septic ileus that were treated conservatively.

At the age of 2 yr, she had a similar presentation with post-prandial abdominal pain, bloating and constipation for 2 weeks. Dietary modifications and laxatives relieved her symptoms. On further probing, she was found to have intermittent upper abdominal fullness since infancy, particularly after large meals with no history of vomiting, nausea, diarrhea, or fever. Stool consistency ranged from Type IV to III on the Bristol Stool Chart. Described as a 'picky eater,' she frequently consumed Milo™ and junk foods.

On physical examination, he was afebrile and well hydrated. She had moderate upper abdominal distension with no palpable fecaloma. Digital rectal examination was unremarkable.

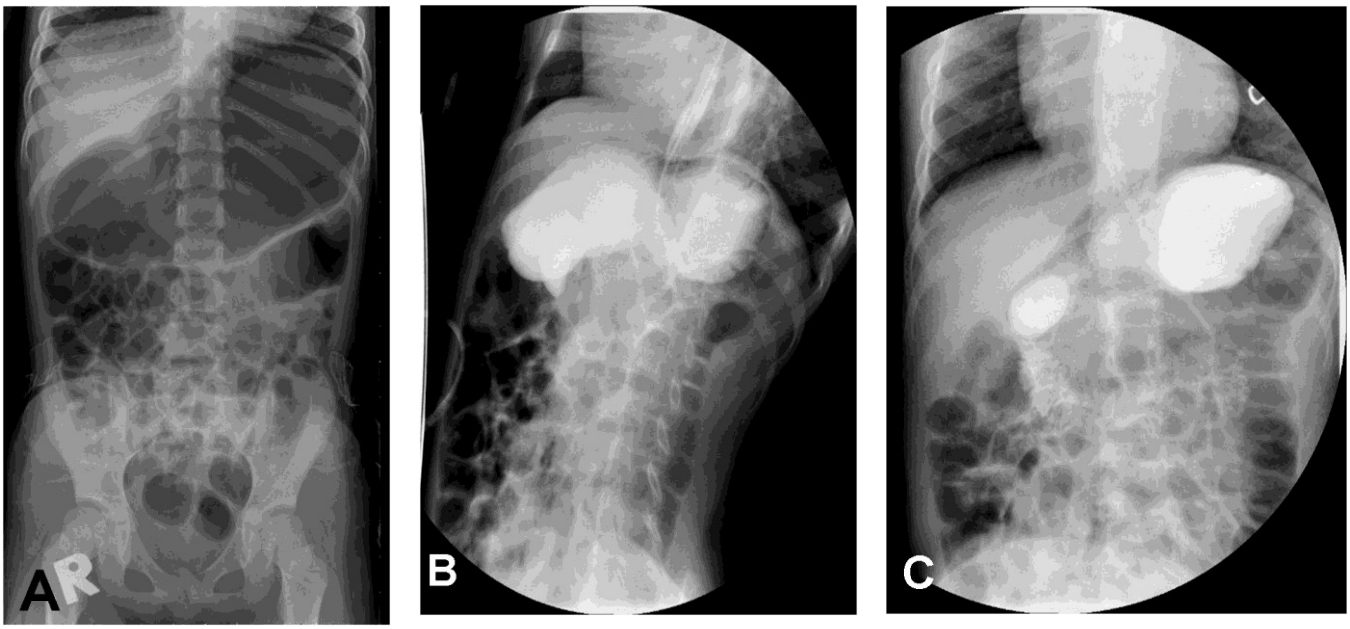

Fig 1. *Imaging studies. (A) Plain radiograph showing hugely distended stomach, (B) Upper gastrointestinal contrast study showing distended stomach, (C) Delayed contrast film showing retained contrast in the stomach even after 120 min.*

On admission, she was treated with nil per mouth, intravenous fluids and gastric decompression by a nasogastric tube. Blood work-up was unremarkable and an abdominal radiograph showed significantly dilated stomach without fecal loading. (Fig. 1) Over the next 2 days, her abdominal distension improved and oral feeding was initiated. Suspecting gastroparesis, she was given domperidone (0.5mg/kg, t.i.d) and Erythromycin (2mg/kg, t.i.d).

Upper gastrointestinal contrast study showed a distended, baggy stomach without gastric outlet obstruction or rotational anomalies. A significant amount of the contrast was found to be retained in the delayed film at 120 min. (Fig. 1)

The diagnosis of gastroparesis and its long-term treatment plan were discussed with the parents. By day-6 of admission, she was relieved of the symptoms and was discharged with domperidone, erythromycin and bisacodyl (5mg, o.d) and advice on dietary modification.

At 2 mo of follow-up, her symptoms had resolved. Bisacodyl was discontinued, and gradual weaning of other medications was planned. Erythromycin and domepridone were stopped after 6 mo and 9 mo respectively. She was well at 3 mo after stopping all medications.

DISCUSSION

Gastroparesis is diagnosed primarily by clinical features. Gastric emptying scintigraphy is the gold standard for confirmation.[1] When scintigraphy is unavailable, as it is in our case, upper gastrointestinal contrast radiography may be helpful. It aims to rule out other causes of gastric outlet obstruction and demonstrate a significant gastric residue even after 120 min.

Managing gastroparesis is challenging, particularly in chronic cases. First-line intervention includes dietary modifications such as low-fibre diet, small frequent meals and avoiding dairy products. While no medication is standardized, prokinetic agents and antiemetics are commonly used for sympto-

matic relief. Surgical treatment includes gastrostomy, pyloromyotomy, intra-pyloric injection of botulinum toxin, feeding jejunostomy and implantation of a gastric pacemaker.[1] The wide variety of treatment options underscores the lack of a consensus in the management of gastroparesis.

The aims of medical management are to relieve symptoms and to address malnutrition.[4,5,6] This case report highlights the usefulness of a combination therapy with domperidone and erythromycin. Previous studies have focused only on erythromycin;[5,6] but we noted that combining it with domperidone for 3-6 months gives a better result. As chronic gastroparesis is characterized by perio-dic exacerbations and remissions caution is need-ed in attributing the cure to any particular medication. Recurrence of symptoms in future cannot be ruled out and they can be treated with the same strategy. In addition to pharmacological stimulation of gastric peristalsis, addressing any concurrent constipation is essential during gastroparesis treatment. Factors that influence the resolution of symptom include the host response to treatment, timing of treatment initiation, duration of symptoms and the underlying cause of gastroparesis. In most of the cases, including our patient, response to prokinetic agents is rapid despite long duration of symptoms.

CONCLUSION

Owing to its rarity and shared symptomatology with other common gastro-intestinal conditions, the diagnosis of gastroparesis is often delayed. In resource-limited centers without scintigraphy, the diagnosis may be made based on the clinical and contrast radiography features. Combination treatment with domperidone and erythromycin seems to be effective.

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Technical Note

Techniques of One-Lung Ventilation (Lung Isolation) in Children

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Keywords
Anesthesia technique
Lung isolation technique
One-lung ventilation
Bronchial intubation
Thoracic surgery

Abbreviations
CPAP - Continuous positive airway pressure
DLT - Double lumen tube
ETT - Endotracheal tube
FOB - Fiberoptic broncho scope
OLV - One-lung ventilation
V/Q - ventilation-perfusion

Abstract

One-lung ventilation (OLV) in pediatric patients, especially those under 8 years of age, poses significant challenges due to anatomical constraints. However, the need for lung isolation is increasing with advancements in surgical techniques such as thracoscopy. The availability of newer bronchial blockers and innovative methods of their placement have made OLV more feasible. This article briefly reviews the recent developments in pediatric OLV. Technique such as double lumen tube, bronchial blockers and endobronchial intubation of single lumen tube are discussed. Technical tips of using Bronchial blockers such as Fogarty catheters, Arndt blocker, uniblocker and univent tube are described.

INTRODUCTION

One-lung ventilation (OLV) (also known as lung isolation technique or single-lung intubation) in children, especially below the age of 8 years, is challenging for anesthesiologists due to anatomical constraints of the pediatric airway.(1) However, the need for lung isolation is increasing due to the popularity of thracoscopic approach. The availability of newer bronchial blockers and innovative approaches to enhance the successful placement of the blockers makes pediatric OLV feasible. This article, briefly reviews the challenges, available options and technical considerations of achieving successful OLV.

CHALLENGES

Anatomical Challenges

OLV in children has several anatomical considerations. Firstly, the smaller size of the pediatric airway necessitates the availability of a wide range of airway devices. Secondly, the diameter of the left main bronchus in children is smaller (roughly 0.66 times of the trachea) than that of the right main bronchus (0.86 times).(2) Also, in infants of age 0-3

months, the left bronchus might be too small even for a 3.0 uncuffed tube. Thirdly, in many children, the distance between the tracheal carina and the right upper lobe bronchus is less than 1 cm, posing a risk of over-insertion of tube past the opening of the right upper lobe bronchus. The distance from the carina to the origin of the left upper lobe bronchus is usually 3 times greater, providing a better margin of safety while intubating the left main bronchus. Fourthly, the right main stem bronchus is angulated less acutely with trachea than its left counterpart. Understanding the tracheo-bronchial anatomy is essential for optimal placement of lung isolation devices and doing successful fibreoptic bronchoscopy. During pre-operative assessment, all the available chest imaging should be assessed for the exact nature of the pathology, the presence of airway narrowing and the diameters of the trachea and bronchi in order to choose an appropriate size tracheal tube.

Physiological Challenges

Pliable cartilaginous rib cage, compression of the dependent lung by the mediastinal structures in lateral positions and upward displacement of the diaphragm by the abdominal viscera will reduce the compliance of the dependent lung. This causes significant ventilation-perfusion (V/Q) mismatch, leading to hypoxia. The smaller size of the lungs leads to less effective shunting of blood from the non-dependent to the dependent lung, worsening the V/Q match that is caused by the hydrostatic gradient between the two lungs in lateral position.

Availability of Equipment

Selecting an appropriate size fiberoptic bronchoscope (FOB) is essential. It should be smaller than the intended endotracheal tube (ETT), allowing easy passage through the ETT. The size of the selected bronchoscope should allow ventilation even when it is inserted through the ETT. With a bronchial blocker and a bronchoscope inside the ETT, ability to manipulate the blocker must be checked before performing the procedure on the patient.

INDICATIONS FOR PEDIATRIC LUNG ISOLATION

Indications of pediatric lung isolation are: [3-5]

1. Facilitation of surgical access to a hemithorax: Lung decortication, Resection of pulmonary, mediastinal or chest wall lesions, and anterior access to thoracic spines or neural structures.
2. Facilitation of ventilation: Repair of bronchial injury and broncho-pleural fistula.
3. Prevention of contaminating spillage of infected secretions from the diseased lung into the healthy side: Lung abscess and hemorrhage

AVAILABLE OPTIONS

1. Double-lumen tubes (DLT)
2. Bronchial blockers
   (a) Low-pressure cuffs (e.g. Arndt blockers and Uniblocker tube)
   (b) High-pressure cuff (off-label use) - Vascular balloon catheters
3. Endobronchial insertion of single lumen ETT
4. Intra-operative usage of lung retractors by surgeons to collapse the ipsilateral lung

The choice of lung isolation technique is often dictated by the availability of suitable size FOB and the type of bronchial blocker.

SINGLE LUMEN ENDOTRACHEAL TUBE

It involves selective insertion of an ETT into the contralateral bronchus (healthy side). It is simple, quick and can be used in any age group. It is the preferred option in children less than 6 months of age. Placement of an ETT on the right side is easier than that of the left side. However, there is a high risk of occlusion of the right upper lobe bronchus because of its low level opening into the trachea. Although the technique can be done blindly, FOB will facilitate correct positioning of the ETT. Disadvantages of using ETT for OLV are inadequate

collapse of the lung and inability to apply suction or continuous positive airway pressure (CPAP) of the operating lung.

BRONCHIAL BLOCKERS

Bronchial blockers can be classified as: (1) low-volume, high-pressure blockers (e.g. off-label use of vascular balloon catheter) and (2) high-volume, low-pressure cuffs (e.g. Arndt blocker and Uni-blocker). (Fig. 1) Blockers can be inserted through the ETT (coaxial technique) or outside it (parallel technique). (Fig. 2) Coaxial technique is preferred in the age group of 6 m to 2 yr. Parallel technique is preferred in 2–8 yr of age. (Table 1)

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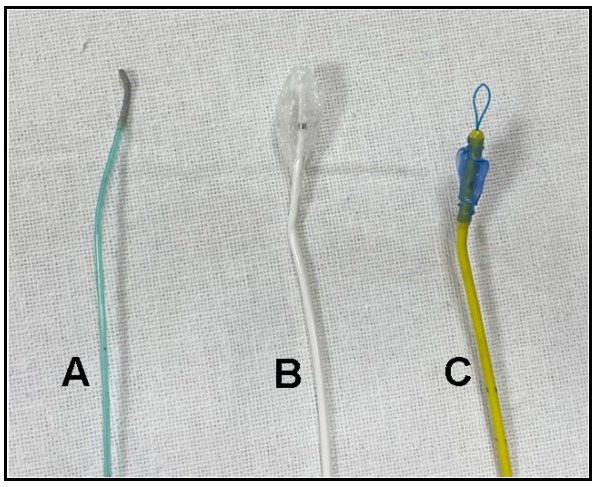

Fig 1. *Bronchial blockers. (A) Fogarty catheter, (B) Atrial embolectomy catheter, (C) Arndt blocker*

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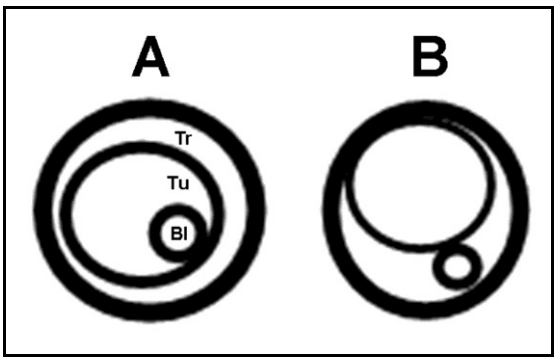

Fig 2. *Coaxial (A) and parallel (B) techniques of inserting bronchial blockers. Tr-Tracheal lumen, Tu- Lumen of endotracheal tube, Bl - Bronchial blocker*

Vascular Balloon Devices

Fogarty and atrial septostomy catheters have been used as bronchial blockers. Fogarty catheters of 3-Fr and 4-Fr size come with a guide wire that can be angulated at the tip to facilitate insertion to the desired bronchus. Positioning it is usually done using FOB. As Fogarty catheters are with high-pressure cuff, it is important to confirm the position of the cuff before inflating it under vision to avoid bronchial rupture or mucosal damage. The atrial septostomy catheter has a predesigned bend at the tip, which aids in directing the blocker to the desired side bronchus. However, it does not have a central channel to apply suction and to maintain CPAP of the operating lung.[6,7]

Arndt Blocker

Frequently a 5-Fr Arndt catheter is used in pediatric patients. It has a flexible long shaft with a central lumen, which houses a looped nylon wire, projects at the tip, and has a cuff at the tip. The looped wire projecting at the tip can be used to position the blocker using a FOB. If the nylon wire is removed, the central lumen can be used to apply suction and CPAP to the operating lung. It should be noted that the wire once removed, it cannot be reinserted, and repositioning will be difficult. A swivel connector with the blocker allows ventilation during placement.[8-9]

Table 1: Choice of lung isolation techniques

Age	EB Intubation	Prefrred bronchial blocker*	Univent	Double lumen tube
0-6 m	Preferable	NA	NA	NA
6m-2yr	Available	Parallel	NA	NA
2-6 yr	Available	Any one	NA	NA
6-8 yr	Available	Available	Available	NA
> 8 yr	Available	Available	Available	Preferred

NA - Not available, EB-Endobronchial

** The two available techniques are parallel or coaxial*

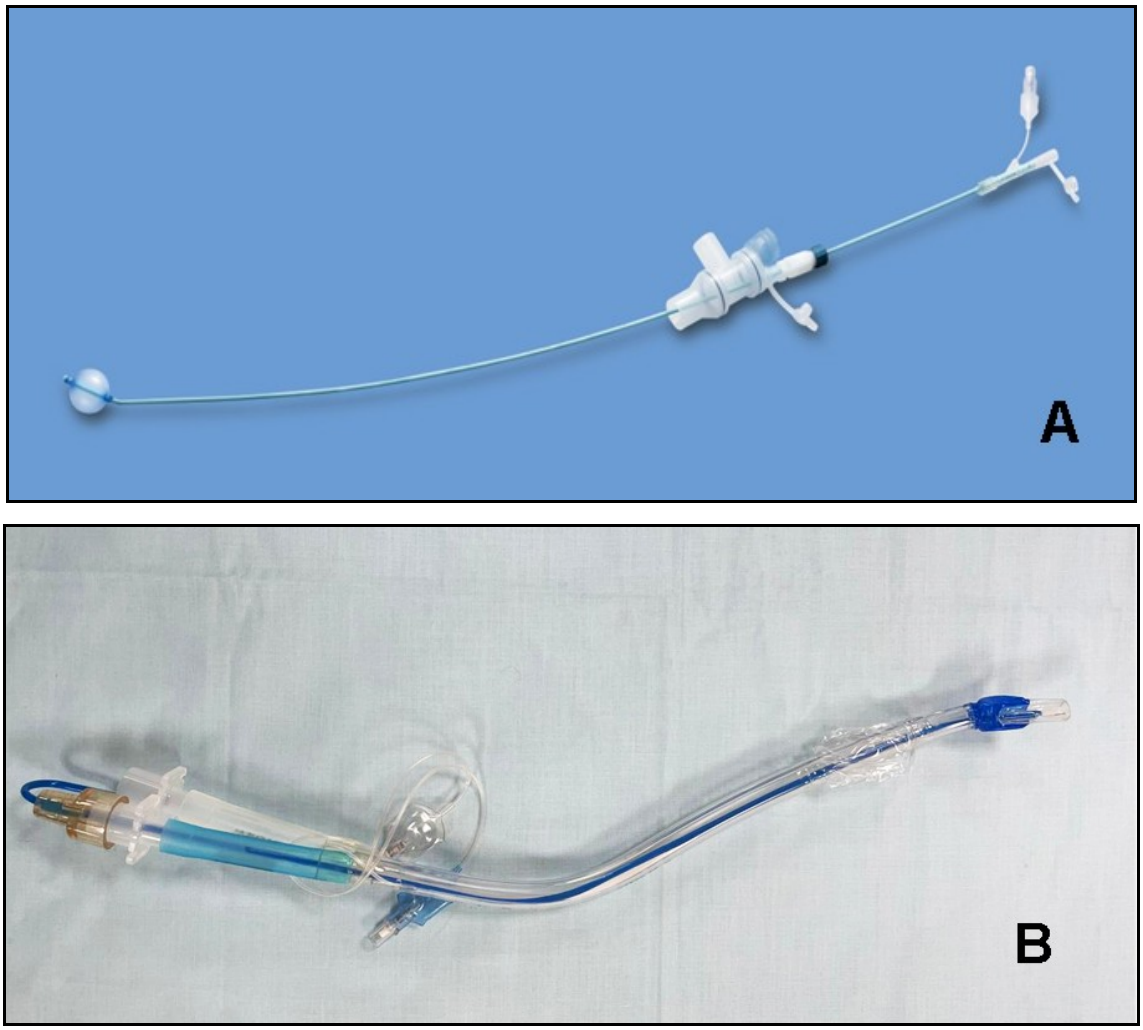

Fig 3. *(A) Fuji Uniblocker™ (Courtesy: Fuji Systems Corporation, Tokyo, Japan), (B) Double lumen tube*

Uniblocker (Fuji Uniblocker)

Fuji uniblocker has a stiff shaft with an angled tip to facilitate correct positioning. It is available with 5-Fr size for pediatric use. A swivel connector with the blocker allows ventilation during placement. (Fig. 3A) There is no central lumen in the shaft to apply suction or CPAP.[10]

Technical Considerations of Blockers

When 2 ml of air is injected, the cuff pressure is 710 cm H_2O for 5-Fr Fogarty, 690 for septostomy catheter, 340 for Arndt bronchial blocker and 330 for Uniblocker. Thus, the cuff inflation pressure of all these devices is always significantly greater than the normal systemic blood pressure (163 cm H_2O). Hence, cuff of bronchial blockers should be inflated with minimum volume required to seal the bronchus, and it should be done only under direct vision of FOB to avoid bronchial injury.[11]

To enable coaxial insertion technique, the combined outer diameter of bronchial blocker and bronchoscope must be less than 90% of the inner diameter of the ETT. No more than 50% of the ETT lumen should be blocked in order to ensure ventilation during bronchoscopy. This is feasible with the currently available devices. However, caution is needed in sick patients due to increased airway

resistance and decreased ventilation. The smallest fibreoptic bronchoscope (outer diameter 2.2 mm) and bronchial blocker (5 Fr, outer diameter 1.67 mm) with a 4.5 ETT (inner diameter 4.5 mm) can be used for patients as young as 2-years old.

For patients under 2-years of age, the bronchial blocker may be placed outside the ETT lumen by parallel insertion technique. The bronchial blocker inserted prior to intubation. Generally, a 3.5 or 4.0 ETT with a 5-Fr bronchial blocker outside the ETT can be used in infants aged 6 mo - 2 yr.

The following precautions should be taken while inserting a bronchial blocker:

1. The cuff of the blocker should be checked by inflating and deflating it prior to use
2. External tracheal manipulation or rotating the head to the contralateral side may be needed to direct the blocker towards the side intended to be blocked.[12-13]
3. The blocker should be inserted a little more inside than the intended length, because it may migrate outside while shifting the patient to lateral position.
4. Minimum volume of air should be used to inflate the cuff avoiding over-inflation in order to prevent pressure damage to the bronchus.
5. Ventilation should be stopped while inflating the cuff of the blocker to avoid the inspiratory volume being trapped in the isolated lung.
6. Micro-cuff tubes are preferabe to avoid leaks.

UNIVENT TUBE

The Univent™ tube is a special form of ETT with a side channel to insert a bronchial blocker. (Fig. 4) If double-lung ventilation is required, the deployed blocker may be deflated and withdrawn into the tracheal lumen. As the blocker balloon is at the distal end of the smaller lumen and is affixed to it, chance of accidental dislodgement is less. Univent tubes are available in two pediatric sizes, 3.5- and 4.5-mm internal diameter. Tubes larger than 4.5 mm internal diameter have an additional channel in the blocker that allows CPAP and suctioning of the operating lung. FOB should be used to position the bronchial blocker.[14]

The main disadvantage of Univent tubes is small cross-sectional diameter of the ventilating lumen. This increases airway resistance and prohibits the usage of FOB to position the blocker. It is important to remember that the size of a Univent tube refers to the internal diameter, and hence its outer diameter will be much larger than the equivalent sized single lumen ETT. The age range (6-8 yr) in which the Univent tube can be used is very narrow.

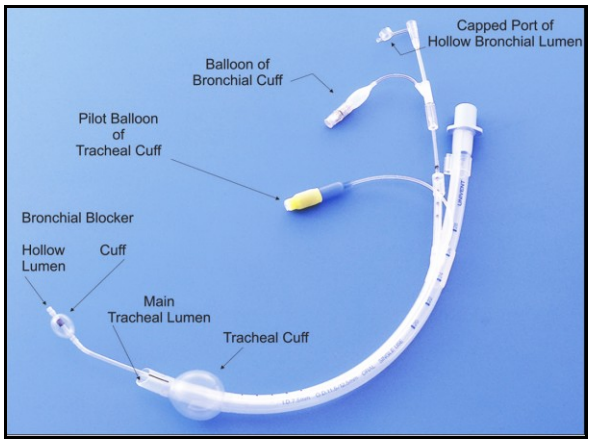

Fig 4. *Univent tube (Reproduced from Atul Prohit et.al, Indian Journal of Anaesthesia 2015 under CC-NC-SA-3.0 license; DOI: 10.4103/00195049.165855)*

Double-Lumen Tube

DLT is considered the gold standard for lung isolation in adults and is suitable for children older than 8 yr of age. (Fig. 3B) The smallest available DLT size is 26-Fr, which is generally suitable for children 8-10 yr of age. DLT has two tubes fused parallelly, of which one is angled and longer to facilitate inser-tion into the desired bronchus, while the shorter tube remains in the trachea. Both the tubes are cuffed so that single-lung and double-lung ventila-tion can be easily done by clamping and releasing the appropriate limb on the adapter piece.[15]

CONCLUSION

The lung isolation techniques in children have evolved over the years with the development of ultra-thin bronchoscopes and newer varieties of bronchial blockers. However, the choice and technique of pediatric OLV are greatly influenced by the availability of resources, provider preferences and skill level.

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Clinical Study

Long-Term Evaluation of Transanal Pull-Through For Hirschsprung Disease: A Prospective Study of 18 Cases from Senegal

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Keywords
Colonic aganglionosis
Congenital megacolon
Continence evaluation
Fecal continence
Hirschsprung disease
Transanal pullthrough

Abbreviations
HD - Hirschsprung disease
TAP - Transanal pull-through

Abstract

Introduction: *Distal colonic aganglionosis is increasingly been treated with trans-anal pull-through that avoids a laparotomy. This study is intended to evaluate the results of this approach in a resource-limited setting.*

Methods: *This is a descriptive study done prospectively between 2016 and 2023 at the Albert Royer Children's Hospital, Dakar, Senegal. It includes 18 children operated upon exclusively by De la Torre-Mondragon's technique of trans-anal pull-through for Hirschsprung disease. Morbidity and anal continence were evaluated using the simplified Holschneider and Krickenbeck scores.*

Results: *The mean follow-up duration was 6 yr (range 4-7 yr). Immediate complications were diaper rash and anal fissures. According to the Holschneider scoring system continence was normal in 11 patients (61%), good in 5 (28%), and satisfactory in 2 (11%). However, occasional soiling was noted in 56%. According to the Krickenbeck score, continence was noted in 16 patients (89%), while 10 patients (56%) suffered from fecal incontinence and 4 patients (22%) from constipation. Three patients (17%) reported restricted social life as a direct consequence of impaired bowel function.*

Conclusion: *Transanal colonic pull-through may lead to long-term morbidity, such as soiling, which can significantly affect the quality of life.*

INTRODUCTION

Several surgical techniques have been described in the treatment of Hirschsprung disease (HD), the latest of which is the transanal approach of Torre-Mondragon and Ortega-Salgado.[1] This approach avoids a laparotomy and its complications. It also reduces hospital-stay and is a scarless surgery. For these reasons, it is now gaining more popularity. The present study was conducted to evaluate the long-term outcome of exclusive transanal pull-through (TAP) in HD.

METHODS

This prospective, single-center, descriptive study was conducted over a period of 7 yr, from 1 March 2016 to 28 February 2023, in the department of pediatric surgery at the Albert Royer Children's Hospital, Dakar, Senegal. Children, who were diagnosed with HD based on clinical or radiological features, underwent exclusive TAP. Only those with a minimum follow-up of 4 yr were included. There were 14 boys and 4 girls, with a sex ratio of 3.5. All the children were operated on using the same surgical technique. (Fig. 1) Anal canal was exposed using guide threads and Farabeuf retractors. Circumferential dissection of mucosal sleeve was followed by myectomy or myotomy.

The studied parameters included the age at the time of surgery, the length of the resected colon, operative difficulties, operating time, short-term morbidity, mortality, and the evaluation of anal continence using the simplified Holschneider and Krickenbeck scores.

RESULTS

The mean age of the patients at the time of surgery was 47 months (range 2m-13yr). There were 7 infants (39%) aged 1-30 months. Five patients (28%) were operated after the age of 5 yr and two after the age of 10 yr. At the time of continence evaluation, all the children were over 3-yr of age.

The mean length of the resected colon was 29 cm (range 15-35 cm). Intra-operative difficulties were encountered in 2 cases (11%). The mean duration of surgery was 102 min (range 70-150 min). In the immediate postoperative period, minor complications (e.g. diaper rash and anal fissures) occurred in 7 cases (39%). Histopathological examination of the surgical specimen confirmed HD in all the children. Inadequate resection margin necessitated surgical revision in 2 patients.

Table 1. Anal continence results according to the modified Holschneider score

Parameter	Score	n	(%)
Stool Frequency			
Normal (1-2 /day)	2	11	61
Often (3-5 /day)	1	7	39
Abnormal (>6 /day)	0	0	0
Stool Consistency			
Firm (Solid)	2	9	50
Loose (Semi-solid)	1	7	39
Liquid	0	2	11
Ability to Retain Stools			
Minutes	2	16	89
Seconds	1	2	11
None	0	0	0
Soiling			
None	2	8	44
Sometimes	1	4	22
Always	0	6	34
Use of Laxatives			
None	2	15	83
Sometimes	1	3	17
Always	0	0	0

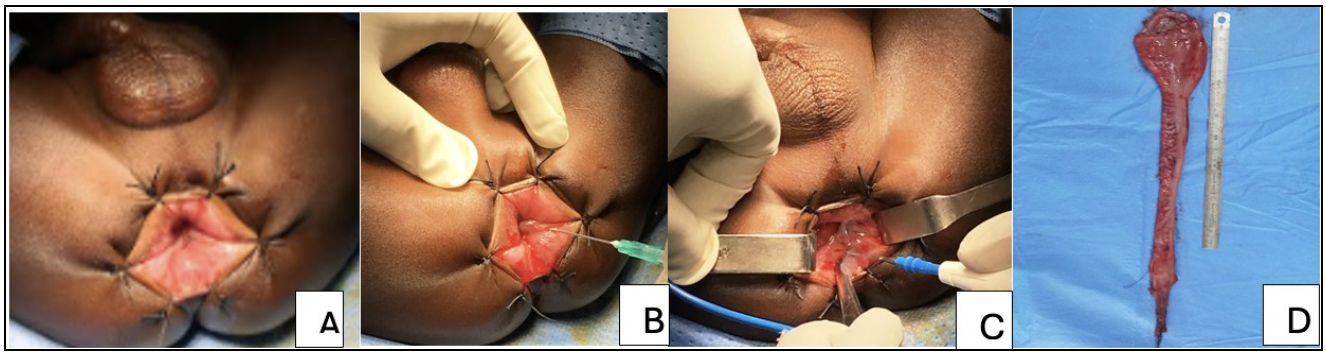

Fig 1. *Different Steps of Transanal Pull-Through: (A) Setup and exposure of the anal canal; (B) Submucosal infiltration with adrenaline-laced lidocaine; (C) Dissection of the anal mucosa; (D) Resected colonic specimen demonstrating the transition zone*

Long-term evaluation was done after a mean follow-up of 6 yr (range 4-7 yr). All the patients were aged more than 3yr at the time of continence evaluation. Stool continence, evaluated by modified Holschneider score, was normal in 11 cases (61%), good in 5 (28%) and fairly satisfactory in 2 (11%).(Table 1) Stool continence according to the Krickenbeck questionnaire was satisfactory in 16 children (89%) while 10 (56%) reported soiling. Fecal soiling occurred daily in 6 (33%), with significant social impact in 3 of them. Finally, 14 (78%) did not report any constipation.

DISCUSSION

Exclusive TAP for HD has revolutionized the treatment of this condition, especially the rectal and rectosigmoid forms.[1,2] This technique has several advantages. It can be done without covering colostomy or abdominal approach, and can even be performed during the neonatal period.[3,4] But, in our practice, the mean age at surgical intervention was higher (47 months), than that reported from developed countries.[5] In infants and young children, TAP facilitates dissection with reduced intraoperative bleeding.

In our experience, mobilization of the rectum in infants was easy with less blood loss.[2] In older children, dissections were difficult probably due to adhesions from previous episodes of enterocolitis and prior rectal biopsies.[6] Our patients did not have prior biopsies. Clinical presentation and barium enema were used to diagnose HD and the extent of aganglionic colon.

The mean operating time in this series was 102 min. The duration of TAP depends on the age, of patients, being longer in those over one year of age. Maturation of the mesenteric vascular system, huge colonic dilation and frequent preoperative episodes of enterocolitis contribute to difficult dissections and hence prolonged operative time.[2]

The immediate postoperative outcomes of TAP are generally straightforward.[7-9] Common complications include soft-tissue abscess, perianal excoriations, mucosal prolapse and anal stenosis.[10,11,12] In this study, diaper rash and anal fissures due to frequent postoperative stools were the common post-operative complications, which resolved with local treatment.

Long-term functional outcome of HD surgery is concerned with persistence of fecal incontinence and constipation. In our study, the common long-term complaint was significant soiling, with social impact in some children. Constipation was less frequent, likely due to the routine myotomy or myectomy done during the TAP. This suggests that soiling was due to true incontinence rather than overflow incontinence. Fecal continence depends

on several factors: anal sphincter function, colonic motility, and anorectal sensitivity, all of which can be affected by transanal surgery, leading to soiling.[13,14,15] Soiling rates of 29-65% have been reported in various studies.[5,16,17]

Concerns exist regarding the impact of the TAP on the anal sphincter due to prolonged exposure and increased traction on the anal canal.[16,18,19] To minimize these effects, some authors recommend a laparoscopic-assisted TAP rather than an exclusive transanal approach.[14,20] Fig. 2 depicts some of the published outcomes of colonic pull-through for HD in terms of constipation.

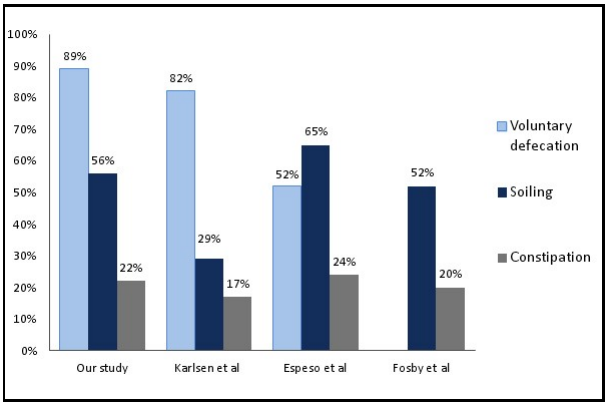

Fig 2. *Continence rate after transanal pull-through reported by various authors*[5,16,19]

CONCLUSION

Long-term follow-up of patients undergoing TAP for HD reveals that fecal incontinence persists in many patients despite a technically successful operation. TAP done with initial laparoscopic mobilization is an option to minimize the operative damage to the anal sphincter. Nevertheless, when the facilities of minimally invasive surgery are not available, forceful retraction of the anal sphincter should be limited during the operation.

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PST PEDIATRIC SURGERY IN TROPICS

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Clinical Audit

Burns in Children: Epidemiological, Clinical, Therapeutic and Outcome Aspects at the Albert Royer Children's Hospital in Dakar

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Keywords
Burn wound
Domestic accident
Thermal injury
Wound care

Abbreviations
TBSA - Total body surface area

Abstract

Introduction: *Childhood burns are common injuries that carry significant morbidity. In this article, the outcome of pediatric burns in Senegal is audited.*

Methods: *This is a retrospective, descriptive study carried out over 20 months, from May 1, 2021, to December 31, 2022, at the pediatric surgery department of the Albert Royer Children's Hospital in Dakar. Demographic and clinical parameters were studied.*

Results: *During the study period 78 skin burns were treated as in-patients. This formed 10.02% of all hospital admissions during that period. The mean age was 43 months (range 6mo - 15yr). The sex ratio was 1.16. Burns occurred in the morning in 38% of cases. The mean delay of medical consultation was 72 hr. Spillage of hot liquid was the commonest etiology in 85% of cases. Transportation had been done by non-medical vehicles in 95% of cases. The mean extent of burns was 11% of total body surface area. All of them were second degree burns. Multiple body parts were burnt in 83% of patients. The mean length of hospitalization was 9 days. Anemia was found in 29.5% of children. The mortality rate was 6.4%.*

Conclusion: *Skin burns are common in Senegalese children, and are most often due to domestic accidents. In our resource-limitted setting, the morbidity and mortality remains high. Preventive measures appear to be the practical way of reducing them.*

INTRODUCTION

Despite improvements in burns care in the recent years, the frequency and severity of these injuries remain a real challenge in certain areas, particularly among young people. The number of children burned worldwide is estimated to be more than 500,000 per year.(1) Burns is a global public health problem. However, its incidence varies in different

countries depending on the socio-economic status. According to the W.H.O, burns causes more than 250,000 deaths each year worldwide, and more than 90% of which are in low- and middle-income countries.[2]

In sub-Saharan Africa, the incidence of burns is one of the highest in the world with an incidence of 245 cases per 100,000 people, and it is 3 times the global average incidence.[3] Mortality due to burns is also high, at an estimated rate of 10% in East Africa.[3] In Senegal, a study on domestic accidents showed that burns were the second most common injury following fractures.[6] Its relative frequency remains high and is 13-24% of all recorded accidental injuries.[4-7] The objective of this work is to report the clinical profile of pediatric burns and its therapeutic outcome in a resource-poor setting.

METHODS

We conducted a retrospective, descriptive study over a period of 20 months, from the May 1, 2021 to the December 31, 2022. All children hospitalized for burns in the pediatric surgery department of the Albert Royer National Children's Hospital in Dakar were included. Demographic parameters studied were the frequency of burns, age, sex, circumstances, time and place of accident, location, extent and depth of the burns, nature of treatment, morbidity, and mortality.

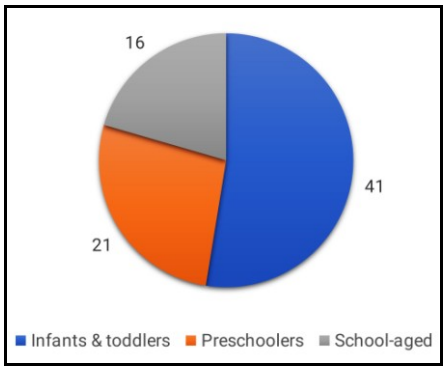

Fig 1. *Age distribution of burns*

RESULTS

Epidemiological Aspects

During the study period, 78 cases of burns were enrolled, representing 3.4 cases per month and 10% of hospital admissions during the period. There were 42 boys (54%) and 36 girls (46%) with a mean age of 43 months (range 6mo – 15yr). Infants represented 53% of patients. (Fig. 1)

Clinical Aspects

In 30 patients (38%), the injury occured between 6 a.m and 12 noon. The mean delay in seeking medical consultation was 72 hr (range 30 min-60 days) and 30 patients (38%) consulted within 3 hr of the injury. The domestic accident was the cause in 77 cases (99%), and a work place accident (1%) was noted. The burns were of thermal origin in 76 patients (96%) and electrical in 2 patients (4%). Spillage of hot liquid was the etiology in 66 (85%) patients. (Fig. 2)

Twenty-four patients (31%) were referred from another facility and 75 (95%) were shifted by non-medical transportation. The mean extent of burns was 11% of total body surface area (TBSA) (range 1-40%). Fig.3 depicts the extent of burns. All of them were second-degree burns, superficial in 9 (12%) and deep in 69 (89%) In 65 cases (83%), the lesions affected multiple sites, the isolated locations were the limbs in 5 cases (6%), the thorax, buttocks, and face in 2 cases each (3%), the abdomen, head, and neck in 1 case each (1%).

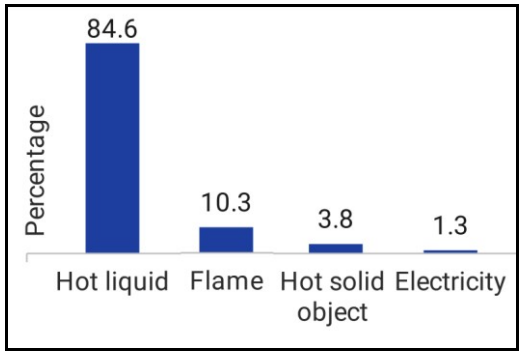

Fig 2. *Etiology of burns*

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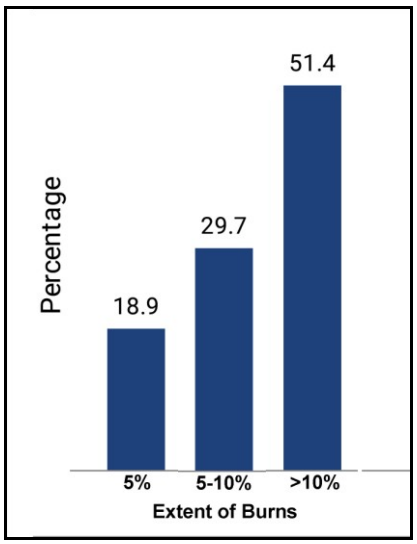

Fig 3. *Extent of burns*

Therapeutic and Follow-up Aspects

All patients received local wound care along with analgesics. Capillary refilling time was monitored in children with greater than 10% TBSA burns. Wound dressing was done daily in 69 patients (89%). The dressing was occlusive in 42 patients (55%) and exposed in 18 patients (23%). Splinting was needed in 10 patients (12%) and physiotherapy in 4 (5%). Systemic antibiotics were used in 88%, and blood transfusion in 9% of cases. Surgical treatment (4%) consisted of skin graft, blepharoplasty, and release of scar contracture.

Table 1. Post-burn complications

Complications	n (%)
Anemia	34 (44%)
Local infection	8 (10%)
Malnutrition	6 (08%)
Metabolic complication	4 (05%)
Scar Depigmentation	8 (10%)
Scar Contractures	8 (10%)
Hypertrophic scar	8 (10%)
Septic shock	2 (03%)
Others	5 (06%)

The mean duration of hospitalization was 9 days (range 1–59 days). At a mean follow-up of 5 mo (range 2–24m), a total of 59 complications were recorded. (Table 1) There were 5 deaths (6.4%).

DISCUSSION

Burns care is an important component of pediatric surgical practice. In 2021, we reported that burns was the second commonest domestic accident.[6] In our series, the hospital frequency of burns was 10% of all admissions to pediatric surgery department. This is slightly lower than the frequency of 14% reported by others.[8]

In our study, infants were the most commonly affected, with a mean age of 43 months. Our results are consistent with literature data wherein the average age of burn victims is reported to be 3-5.5 years.[9-12] This age-specific high frequency can be explained by the characteristic features of that age-group such as imcompletely developed psychomotor skills, tendendy to explore environment and remaining at home without attending school.[13]

The sex ratio of 1.16 in our study corroborates with that of published literature.[1,14,15] Male predominance appears to be due to greater physical activity of boys who often engage in adventurous games.[7]

In our series, the majority of accidents occurred inside the house, mainly in the kitchen (42%) which is similar to published literature.[1,15-17] This could be linked to the fact that in large families with limited resources, the same room is shared for several activities thus allowing toddlers to play around in the kitchen. Sub-optimal cooking equipment due to poverty may also lead to increased domestic accidents.

Similar to published reports burn accidents often occur in the morning and evening times.[16,18-20] In our culture, these periods correspond to meal

preparing time and household activities. Consistent with general observation, in our series, thermal burns were the commonest injury, occuring in 96% of cases.[10,16,21-26]

The mean extent of burns in our series was 11% TBSA. Langer[27] from Germany also reported a mean extent of 11.9% TBSA. Other have reported a mean extent of 4-10%.[1,10,16,21,26,27] We noted deep second degree in 89%. Other African studies reported second degree burns in 92 - 94%.[16,21] This is explainable by the fact that spilt hot liquids seldom produce third degree burns. Lack of knowledge of first aid and long delay in seeking medical treatment may have also contributed to this.

Initial resuscitation must be intensive if the extent of burn exceeds 10% TBSA. In a setting where sophisticated monitoring gadgets are unavailable, capillary refilling time is a useful prognostic indicator. Patients with impaired capillary refilling are at the risk of renal failure, sepsis, and death.[28] Antibiotic therapy in our setting was empirical rather than been guided by culture sensitivity of bacteria. Empirical antibiotics, though not ideally recommended, are not uncommon in Africa.[29,30] Non-availability of 24/7 culture facilities, transportation to hospital in commercial vehicles with possible contamination and delayed clinical presentation with established wound infection justify empirical antibiotics in out settings.

In our series, the mean duration of hospitalization was 9 days. Rafik from Morocco reported a mean hospital stay of 8 days.[21] On the other hand, Ada et al[18] from our center previously reported a mean stay of 14.5 days. The length of stay could be influenced by the rate of healing, depth and extent of burns, long delay in seeking medical care, and the occurrence of complications.

In our series, as in several other studies,[23,25] anemia, wound infection and malnutrition were the most common complications. At a mean follow-up of 5 mo, 18.5% of burn victims developed sequelae, the most common of which was scar depigmentation (10%). The frequency of hypertrophied scar and keloids was similar to the published literature.[31] They frequently depend on the depth and location of the lesions and the quality of wound management.

Mortality from burns is a real problem throughout the world, especially in developing countries with limited resources.[32] In our series, 5 patients died, giving an overall mortality of 6.4%. This rate is lower than the range found in the African literature, which varies between 9.3 - 41.2 %.[16,21,23,25] Yet, our mortality is higher than that of reported from developed countries,[19] which is typically 0.49 - 9.08 %.

CONCLUSION

Pediatric burns forms 10% of our practice and it mainly affects infants. Most of the injuries were deep second-degree due to spilt hot liquids. Morbidity and mortality of our series is still high as compared to that of the developed countries. Awareness and the creation of pediatric burn care services are expected to improve the prognosis.

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