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EDITOR'S COMMENT

Dear Colleagues

Welcome to the 15th edition of the *AfSPID Bulletin*.

This edition begins with an update on community acquired pneumonia (CAP). Notwithstanding the reduction in the incidence of pneumonia due to advances in vaccination and management, CAP remains one of the common causes of death especially in under-fives. The article keeps us abreast of changes in the causes, diagnosis, management and prevention of pneumonia.

Tuberculosis (TB) features prominently in this edition. There is an extensive review on the routine investigations used in the diagnosis of childhood TB as well as an article that discusses the recent research findings on the duration of treatment for drug-susceptible TB (DS-TB) and their implications for paediatric practice.

On the 24th of March every year, World TB Day is celebrated. The theme this year was "Invest to End TB. Save Lives" which highlights the urgent need to invest resources for TB prevention, diagnosis, and treatment to meet with the commitments made by the global community to end the disease.

Noteworthy also was the release of the new *WHO consolidated guidelines on tuberculosis; Module 5: management of tuberculosis in children and adolescents, 2022*.¹ Numerous studies that evaluated the impact of various interventions related to diagnostic approaches for TB, treatment for DS-TB, drug-resistant TB (DR-TB) and TB meningitis (TBM), as well as models of TB care, relevant to children and adolescents were utilised in formulating the new guidelines. Varying levels of certainty of evidence for the diagnostic approaches and treatment guidelines were provided.

The highlights of the guidelines include TB screening in children using integrated treatment decision algorithms to diagnose pulmonary TB, use of Xpert MTB/RIF Ultra on gastric aspirate or stool to diagnose pulmonary TB and rifampicin resistance, treatment shortening in children and adolescents with non-severe drug-susceptible TB, use of bedaquiline and delamanid in children aged below 6 years of age with drug-resistant TB and treatment of TB meningitis in children and adolescents.^{1,2} Models of care for TB case detection and TB prevention in high TB burden settings were also included. Priority areas where identified which have the potential to inform the development of future research questions that can improve TB prevention and care.

Here is a question to ponder on: What constitutes non-severe TB?

The guideline defines non-severe TB as: Peripheral lymph node TB; intrathoracic lymph node TB without airway obstruction; uncomplicated TB pleural effusion or paucibacillary, non-cavitary disease, confined to one lobe of the lungs, and without a miliary pattern. The guideline goes on to say that children and adolescents who do not meet the criteria for non-severe TB should receive the standard six-month treatment regimen (2HRZE/4HR), or recommended treatment regimens for severe forms of extrapulmonary TB.

An identified research gap is the feasibility of making a diagnosis of non-severe drug-susceptible TB in settings with no access to diagnostic tools, especially chest radiology or where other healthcare workers other than doctors are involved in the care of children and adolescents with TB.

I hope you will find these and other contributions in this edition of the bulletin interesting.

Regina Oladokun, deputy-editor

References

1. WHO consolidated guidelines on tuberculosis; Module 5: management of tuberculosis in children and

- adolescents. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.
2. WHO operational handbook on tuberculosis. Module 5: management of tuberculosis in children and adolescents. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.

SOCIETY NEWS

APPOINTMENT OF NEW EDITORIAL BOARD MEMBERS

We welcome Dr Julie Copelyn, Dr Colleen Bamford, Dr Mulugeta Naizgi Gebremicael and Dr Mohammad Issack to the editorial board.



Figure 1: New editorial board members, Dr Julie Copelyn (top left), Dr Colleen Bamford (top right) Dr Mulugeta Naizgi Gebremicael (bottom left) and Adjunct Professor Mohammad Issack (bottom right)

Julie Copelyn is a paediatric infectious diseases sub-specialist. She received her MBBS from the University of Sydney in 2007, before returning home to South Africa. She holds an MSc in Paediatrics and Child Health (Global Health) from University College London and is a member of the founding committee of Young WSPID. Her interests include paediatric HIV and TB, vaccine preventable illnesses and antimicrobial stewardship.

Colleen Bamford is a clinical microbiologist. After some years of experience in general and paediatric medicine in resource limited settings, she specialised in medical microbiology at the University of Cape Town, obtaining her FCPATH (Microbiology) and MMed (Medical Microbiology). She subsequently worked as a consultant in the National Health Laboratory Service and headed the diagnostic laboratory at Groote Schuur Hospital for 5 years.

She is currently working in East London, in the Eastern Cape province of South Africa. She is an honorary Associate Professor in Medical Microbiology at the University of Cape Town, a member of the Working Group of the South African Antibiotic Stewardship Programme (SAASP), a past chair of the South African Society for Clinical Microbiology (SASCM) and current member, and an active examiner in medical microbiology and the

microbiology component of Clinical Pathology for the Colleges of Medicine of South Africa.

She has a wide range of interests in clinical microbiology including the rational use of laboratory diagnostics, antimicrobial resistance, and antimicrobial stewardship.

Mulugeta Naizgi Gebremicael is a paediatric infectious diseases consultant at Ayder Comprehensive Specialized Hospital, Mekelle, Tigray, Ethiopia, and an Asst. Professor at the School of Medicine, Mekele University, Tigray, Ethiopia. Currently, he is involved in research on HIV drug resistance & infection prevention at Ruhr-university, Bochum, Germany.

He completed his subspecialty training in paediatric infectious diseases at the Red Cross War Memorial Children's Hospital, South Africa, in 2021.

He is a founding member of the Young World Society of Paediatric Infectious Diseases Committee.

He is a project coordinator for Ayder Hospital in the joint project training and research on infection prevention and drug resistance of HIV infection between Ayder Hospital / Mekele University, Ethiopia, and Ruhr-university, Bochum, Germany.

His research interests include infection prevention, neglected tropical diseases, and vaccine-preventable diseases. He has several publications in this field.

He has a special interest in antimicrobial stewardship and is a member of the task force that is developing an antimicrobial guideline for Ayder Hospital.

Mohammad Issack is a clinical microbiologist and a fellow of the UK Royal College of Pathologists. He obtained his medical degree from the University of Leeds in 1988 and specialised in clinical microbiology in the UK. He worked as a registrar in medical microbiology at Guy's Hospital from 1991 to 1995 and obtained his MRCPATH in 1996. He is currently a consultant at the Central Health Laboratory in Mauritius where he has been heading the Department of Bacteriology since 1997. He has also been a part-time lecturer at the University of Mauritius since 1998 and was appointed Adjunct Professor in the Faculty of Medicine and Health Sciences in 2020.

He has been a member of the University of Mauritius Research Ethics Committee from 2006 to 2010 and from 2018 to 2020.

He is a member of the Mauritius National Immunisation Technical Advisory Group. He is also currently a member of the WHO Advisory Group on Critically Important Antimicrobials for Human Medicine.

His main scientific interests include surveillance of antimicrobial resistance, food-borne infections and vaccine-preventable diseases and he has several publications in these fields.

FROM A NEWSLETTER TO A JOURNAL

The *AfSPID Bulletin* started out as a newsletter in April 2013. From the outset members were encouraged to submit articles. Over the ensuing period, a wide variety of news, opinion pieces, conference reports, case reports, medical images, commentaries, reviews, and the occasional research article were published.

Expansion of the editorial board gathered momentum in December 2020. Currently, the editorial board comprises

30 members including a deputy editor and six associate editors. Peer-review of all commentaries, reviews, research papers, case reports and medical images started from September 2021 and the first peer-reviewed articles were published in the November 2021 edition of the *AfSPID Bulletin*.

An important decision taken by the editorial board at the second editorial board meeting in August 2021 was to transform the newsletter into a journal. **Thus, as of this edition, the *AfSPID Bulletin* becomes the official journal of The African Society for Paediatric Infectious Diseases.**

This development heralds the start of an exciting period for the publication. Further development of the journal during the next few months and years will include application for official registration, the commencement of new sections of the journal, further expansion of the editorial board, adoption of additional journal-specific standards and the capacitation of editorial board members with technical skills needed to fulfil their responsibilities.

WSPID 2022 REVIEW

The 12th World Society for Pediatric Infectious Diseases (WSPID) congress was held virtually from 20 to 24 February 2022. The conference was meant to take place in Cancun, Mexico in November 2021 but because of the COVID-19 pandemic, was deferred until late February 2022. It had a strong focus on Central and South American issues, and featured a wide range of excellent speakers including Central and South American speakers.

Close to 1800 participants from 103 different countries attended the conference. The programme included 128 invited speakers and chairs from all regions of the world, 61 oral abstracts and 148 e-posters covering a range of infectious diseases research projects. Although conducted on Mexican time, the daily start and end times varied so as to accommodate as many time zones as possible.

The conference was preceded by a research workshop, an important educational initiative of WSPID aimed at junior researchers. This year's research workshop was named the Sally Gatchalian Research Workshop in honour and memory of Professor Sally Gatchalian who was the co-convenor of the research workshop that preceded the 11th WSPID conference in Manila in November 2019, and who sadly succumbed to COVID-19 in March 2020.

The conference featured a spectrum of symposia that addressed developments in a range of important infectious diseases topics relevant to the practice of paediatric infectious diseases in Africa, including measles, prudent antibiotic use, lessons learned from the COVID-19 pandemic, innovations in infectious diseases, community-acquired bacterial meningitis and viral encephalitis, malaria, pneumonia in low- and middle-income countries, viral hepatitis, skin infections, diagnostic issues in paediatric infectious diseases, HIV infection, tuberculosis, and RSV infection and vaccination.

Society symposia also featured and AfSPID hosted a symposium on severe COVID-19 in children across Africa. It featured four speakers, Regina Oladokun from Nigeria and representing West Africa who spoke on COVID-19 among children in a Nigerian setting, Maha Hamdi from Egypt and representing North Africa, who addressed MIS-C epidemiology and management, Sabrina Bakeera-Kitaka from Uganda and representing West Africa who discussed the challenges of diagnosis, treatment and follow-up of MIS-C in low-resourced settings, and Mary-Ann Davies from South Africa and representing Southern Africa who

compared paediatric outcomes in the 4th Omicron-driven wave with previous waves in the Western Cape province of South Africa.

Despite the organisational challenges the 12th WSPID congress was a highly successful event, characterised by cutting-edge science. In 2023 the WSPID conference moves to Durban, South Africa where participants can look forward to another excellent conference.

COMMENTARIES & REVIEWS

UPDATE ON COMMUNITY ACQUIRED PNEUMONIA IN AFRICAN CHILDREN

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Abstract

Recent medical advances have led to a drop in the global incidence of pneumonia. Despite this global drop, pneumonia remains the number one cause of childhood mortality outside the neonatal period, especially in low-to-middle income countries. The purpose of this review is to give an update on the causes, diagnosis, management, and prevention of community acquired pneumonia (CAP) in African children.

Due to increased immunisation coverage, viruses have become the most common cause of CAP (respiratory syncytial virus being the most common virus), while *staphylococcus aureus* and non-typeable *Haemophilus influenzae* are the most common causes in fully immunised children.

Extensive investigations are not warranted in most cases, as a result, investigations to be carried out will be dependent upon the clinical condition and local protocol. In light of the COVID-19 pandemic all cases of CAP must be screened for COVID-19.

Antimicrobial treatment is determined by, clinical severity, local antibiotic resistance patterns, presence of complications, the causative organism, and local protocols. Broad-spectrum antibiotics such as amoxicillin-clavulanic acid or a 2nd or 3rd generation cephalosporin are normally sufficient. Special attention needs to be paid to immunocompromised children as well as those with sickle cell disease, as additional pharmacological cover is recommended.

Notwithstanding the significant burden posed by CAP in low-to-middle income countries, there remains a paucity of data on CAP from Africa, therefore, it is of paramount importance that further epidemiological data be collected from African countries to optimise the understanding, prevention and management of CAP in Africa.

Introduction

Notwithstanding the drop in the incidence of pneumonia due to advances in vaccination, diagnostics and therapy,

pneumonia remains the number one cause of childhood mortality outside the neonatal period.^{1,2} Of note, most childhood pneumonia deaths occur in low to middle income countries (LMICs), particularly in sub-Saharan Africa.² In 2017 pneumococcal pneumonia was estimated to be the leading cause of death due to lower respiratory tract infections, followed by respiratory syncytial virus pneumonia, *Haemophilus influenzae* type B pneumonia and influenza.¹

In 2019, after neonatal causes, lower respiratory tract infections were the leading cause of morbidity in the 0–9-year age group, accounting for 11.6% (IQR 10.5–12.6) of the disability-adjusted life-years (DALYS).³

Childhood pneumonia has been affected by the global coronavirus disease 2019 (COVID-19) pandemic. This pandemic has complicated routine child health care, including reduced routine childhood immunisation and diversion of resources to the COVID-19 response.^{4,5} Unfortunately, the impact that this has made on childhood pneumonia may only be seen in the coming years and has the potential to negatively impact the progress that has been made over the past decades.

Considering the significant burden that pneumonia poses, particularly in LMICs, it is important that we keep abreast with the changes pertaining to the causes, diagnosis, management, and prevention of pneumonia.

Definition

Community acquired pneumonia (CAP) is an acute lower respiratory tract infection of the lung parenchyma which forms part of the spectrum of lower respiratory tract infection (LRTI) in childhood.⁶ LRTI encompasses infections that variably affect the airways and parenchyma depending on the organism and host response. CAP refers only to pneumonia acquired in the community and is distinct from other defined pneumonias such as hospital acquired pneumonia, ventilator acquired pneumonia and congenital pneumonia. CAP in African children will be the focus of this review.

Causative organisms

CAP can be caused by bacteria, viruses, mycobacteria, and fungi. Prior to widespread pneumococcal and *Haemophilus influenzae* B vaccination, the most common causes of CAP were *Streptococcus pneumoniae*, *Haemophilus influenzae* type B and respiratory syncytial virus.⁷ Due to increased immunisation coverage, the cause of pneumonia has changed over recent years with viruses now the most common cause of CAP in African children, while *Staphylococcus aureus* and non-typeable *H. influenzae* have become the most common bacterial causes in immunised children.⁸⁻¹⁰ *Mycobacterium tuberculosis*, has also been recently identified as an important cause of acute pneumonia, especially in tuberculosis endemic countries.^{9,11,12} Furthermore, polymicrobial infections have been documented, particularly in severe CAP.¹⁰

The type of organism is not only determined by patient vaccination status and local immunisation coverage but also by the age (Table 1) and immune status of the patient.

Table 1: Causes of community acquired pneumonia in children at different ages

Age group	Causative organisms
Neonates	Bacteria <ul style="list-style-type: none"> Group B Streptococcus <i>Escherichia coli</i> <i>Listeria species</i>
	Viruses

	<ul style="list-style-type: none"> Respiratory Syncytial Virus Cytomegalovirus Herpes simplex virus
1 – 6 months	Viruses <ul style="list-style-type: none"> Respiratory Syncytial Virus Influenza Adenovirus Parainfluenza Bacteria <ul style="list-style-type: none"> <i>Streptococcus pneumoniae</i> <i>Haemophilus Influenzae</i> <i>Staphylococcus aureus</i> <i>Moraxella catarrhalis</i> <i>Bordetella pertussis</i> <i>Chlamydia trachomatis</i> <i>Ureaplasma urealyticum</i>
6 – 12 months	Viruses <ul style="list-style-type: none"> Respiratory Syncytial Virus Influenza Adenovirus Parainfluenza Rhinovirus Bacteria <ul style="list-style-type: none"> <i>Streptococcus pneumoniae</i> <i>Haemophilus Influenzae</i> <i>Staphylococcus aureus</i> <i>Moraxella catarrhalis</i> Mycobacteria* <ul style="list-style-type: none"> <i>Mycobacterium tuberculosis</i>
1 – 5 years	Viruses <ul style="list-style-type: none"> Respiratory Syncytial Virus Influenza Adenovirus Parainfluenza Rhinovirus Varicella zoster Bacteria <ul style="list-style-type: none"> <i>Mycoplasma pneumoniae</i> <i>Streptococcus pneumoniae</i> <i>Staphylococcus aureus</i> <i>Haemophilus influenzae</i> <i>Chlamydia pneumoniae</i> Mycobacteria* <ul style="list-style-type: none"> <i>Mycobacterium tuberculosis</i>
> 5 years	Viruses <ul style="list-style-type: none"> Influenza Adenovirus Epstein Barr virus Rhinovirus Bacteria <ul style="list-style-type: none"> <i>Mycoplasma pneumoniae</i> <i>Streptococcus pneumoniae</i> <i>Chlamydia pneumoniae</i> Mycobacteria <ul style="list-style-type: none"> <i>Mycobacterium tuberculosis</i>

*In high tuberculosis prevalence settings
Adapted from Paediatric pneumonia: a guide to diagnosis, investigation and treatment and Kendig's Disorders of the respiratory tract in children.^{13,14}

According to the Pneumonia Aetiology Research for Child Health (PERCH) study, ten pathogens were responsible for 79–90% of cases with severe pneumonia requiring hospital admission in HIV uninfected children aged 1–59 months.⁹ In this study respiratory syncytial virus was the most common cause contributing 31.1% (CI 28.4–34.2), with the following pathogens contributing more than 5% each, human rhinovirus, human metapneumovirus, parainfluenza, *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Mycobacterium tuberculosis*.⁹ Pertussis is an important cause in young children, particularly in the unimmunised or partially immunised child.^{15–17}

Immunocompromised patients such as those that are living with Human Immunodeficiency virus (HIV) and whose viral load is unsuppressed are prone to atypical organisms such as *Pneumocystis jiroveci* and cytomegalovirus.¹⁸

Clinical features and classification of pneumonia

Patients may present with fever, cough, tachypnoea, tracheal tug, use of accessory muscles, grunting, hypoxia and poor feeding.¹⁴ Older children may complain of chest pain or abdominal pain.¹⁴ According to the World Health Organization (WHO) CAP can be classified as severe or non-severe.¹⁹ Non-severe pneumonia in a child older than 2 months of age presents with fast breathing and/or lower chest indrawing.^{19,20} A child with severe pneumonia presents with a general danger sign (not able to drink, persistent vomiting, convulsions, lethargy or unconsciousness, stridor in calm child) or hypoxia or severe respiratory distress if less than 2 months of age or lower chest indrawing if malnourished and/or HIV infected.^{19,20}

Investigations

Investigations are helpful in confirming the diagnosis of CAP, determining the causative agent(s), grading the severity, and identifying complications.²⁰ However, extensive investigations are not warranted in most CAP cases as they do not change clinical management.

A chest x-ray should be done in all patients with CAP requiring admission. Those patients with CAP who can be managed as outpatients do not warrant a chest x-ray unless tuberculosis (TB) is suspected and/or they have not responded to initial empiric treatment.²¹ A lateral chest x-ray projection is not always necessary unless TB is suspected, or a complication that requires characterisation on the lateral projection is suspected, for example, diaphragm paresis or an abscess.^{20,22} It is important to note that chest x-ray cannot differentiate between viral and bacterial causes of CAP accurately.²¹

In addition to a thorough clinical examination, investigations such as pulse oximetry and arterial or venous blood gas measurement can help grade the severity of CAP. CAP with hypoxemia has a poorer outcome compared to CAP without hypoxemia.^{23,24} Pulse oximetry detects hypoxaemia, which can be used as a non-invasive indicator of hypoxia. Ideally, pulse oximetry should be available at primary health care level, but unfortunately this is not the case in many low-middle income countries. A study done in Malawi indicated that the availability of pulse oximetry may help in identifying more cases of potentially fatal pneumonia in an outpatient setting, that would otherwise be missed when using the WHO clinical referral guidelines alone.²⁵ Despite the small sample size, in this study oxygen saturations of less than 90% identified 6% (1/16) of deaths at community health worker level and 23% (3/13) of deaths at health centre level not identified by clinical signs.²⁵ In a similar but bigger study, absence of pulse of oximetry would have led to, 68.7% (390/568) severely hypoxaemic children at study health centres and 61.9% (52/84) severely hypoxaemic children

seen by community health workers being considered ineligible for referral to the next level of healthcare.²⁶ Highlighting the difficulty of accurately assessing severity on clinical signs alone and the critical role oximetry plays in reducing mortality from CAP. In light of the above findings African governments need to identify low cost and sustainable solutions that would enable availability of pulse oximetry at primary health care level in order to avoid preventable pneumonia deaths.

Arterial blood gas (ABG) measurement has the advantage over pulse oximetry in that it measures hypoxemia more accurately. It also measures carbon dioxide as well as other metabolic parameters that aid in assessing the severity of the child's illness. This is of particular importance in the child who is receiving non-invasive ventilation and yet continues to deteriorate, a child requiring invasive ventilation or a child that has multiple organ involvement. However, the blood gas machine and reagents are expensive, rendering them unavailable even in some tertiary care centres in LMICs.

Determining the exact cause of CAP in children can be challenging because CAP can be due to a single organism or multiple organisms^{10,27}; the challenges associated with obtaining an appropriate respiratory specimen; the difficulty between differentiating colonisation versus infection and the fact that reliable results are dependent on the laboratory capacity to process the sample.^{10,27,28}

Respiratory tract samples that may assist in detecting the cause include upper respiratory tract samples such as nasopharyngeal aspirates and cough swabs, and lower respiratory samples such as expectorated sputum or induced sputum. More invasive samples that may be obtained include bronchoalveolar lavage and tracheal aspirates. Respiratory samples are not required in all cases of CAP, but recommended in cases of suspected tuberculosis, outbreak scenarios, complicated CAP, severe CAP requiring intensive care treatment and patients with chronic or recurrent respiratory disease.^{20,21}

Table 2 describes the spectrum of respiratory samples that may be collected in different scenarios and the type of tests that can be performed on them.

Due to the COVID-19 pandemic it is important to screen all cases of CAP for COVID-19. Even though the SARS-CoV-2 virus has been associated with severe pneumonia, children are much less affected than adults, with fewer infections, very few hospitalisations and <1% of COVID-19 deaths globally, even in settings with high pneumonia risk factor prevalence. Upper or lower respiratory samples, such as sputum and tracheal aspirates, can be utilized for testing.²⁹ The most common sample being collected currently is the mid-turbinate swab. The laboratory technique of choice in making a diagnosis of COVID-19, is a COVID-19 polymerase chain reaction (PCR) test.²⁹ Other laboratory techniques that may be utilized, particularly as screening tests or in settings where PCR might be unavailable, include antigen detection tests and antibody detection tests, however they have a lower sensitivity compared to PCR.²⁹ The sensitivity of PCR is as follows, sputum (97.2%, 95% CI 90.3–99.7%), saliva (62.3%, 95% CI 54.5–69.6%), nasopharyngeal aspirate/swab and throat swab (73.3%, 95% CI 68.1–78.0%).³⁰ Specificity of PCR is 98.6% for a throat swab and 90.0% on sputum samples.⁽³⁰⁾ It is important to note that some patients will present with CAP with COVID-19 as a coinfection rather than the sole cause of the respiratory symptoms.

Table 2: Clinical scenario and suggested respiratory sample types and tests*, **, ***

Clinical scenario		Respiratory sample type	Tests
Non-severe CAP			
Severe CAP requiring ICU	NIV	Nasal pharyngeal aspirate	RV multiplex PCR
		Induced or expectorated sputum	RV multiplex PCR MCS
	IV	Tracheal aspirate	RV multiplex PCR MCS
		BAL	RV multiplex PCR MCS
CAP with suspected TB	Out-patient	Induced or expectorated sputum	Xpert MTB/RIF Ultra TB MCS
	NIV	Induced or expectorated sputum	Xpert MTB/RIF Ultra MCS TB MCS
	IV	Tracheal aspirate	Xpert MTB/RIF Ultra MCS RV multiplex PCR TB MCS
		BAL	Xpert MTB/RIF Ultra MCS RV multiplex PCR TB MCS
Immuno-compromised With severe CAP	NIV	Induced or expectorated sputum	MCS Xpert MTB/RIF Ultra TB MCS RV multiplex PCR <i>Pneumocystis jiroveci</i> PCR CMV VL on blood**** Fungal MCS
			IV

CAP with pleural effusion	No respiratory Support	Induced or expectorated	Fungal MCS MCS Xpert MTB/RIF Ultra TB MCS	
		Pleural fluid	MCS Xpert MTB/RIF Ultra TB MCS Bacterial PCR Cell count Biochemistry	
			NIV	Induced or expectorated Sputum
		IV	Pleural fluid	MCS Xpert MTB/RIF Ultra TB MCS Bacterial PCR Cell count Biochemistry
	Tracheal aspirate or BAL			MCS TB MCS Xpert MTB/RIF Ultra RV multiplex PCR
	Pleural fluid		MCS TB MCS Xpert MTB/RIF Ultra Bacterial PCR Cell count Biochemistry	

ICU: intensive care unit; NIV: Non-invasive ventilation; IV: invasive ventilation; RV multiplex PCR: respiratory virus multiplex polymerase chain reaction; MCS: microscopy, culture, and sensitivity; BAL: Bronchoalveolar lavage; CMV VL: cytomegalovirus viral load

* All patients to be screened for COVID-19 using the local protocol
 ** Performance of tests dependent on clinician expertise, patient stability, local protocol, resources, and laboratory capacity
 *** Additional tests such as CRP or blood cultures to be done according to clinical severity
 **** Test done on blood

Other investigations that may be used to identify the causative organism include lung aspirate, blood culture, urine, stool, and pleural fluid analysis.^{20,31} Blood cultures have a low yield, and hence not recommended routinely unless the patient has features suggestive of bacteraemia such as fever, chills or rigors, "toxic" looking, hypotension, altered level of consciousness and/or multiorgan involvement.^{21,27} Traditionally, pleural fluid analysis was noted to yield no bacterial growth as it tended to be done after antibiotic administration.^{21,31} However, the recent PERCH study demonstrated the value of culture and PCR testing on pleural fluid collected within 72 hours of

admission.³¹ Furthermore, the type of cells that predominate as well as the biochemistry may help support a bacterial cause, or in tuberculosis endemic areas, to support a diagnosis of tuberculosis. It may also be used to rule out non infective causes of pleural effusion.

Transthoracic lung aspiration, though not done routinely, is relatively safe.³¹ The specimen can be sent for culture, PCR testing and histology.³¹ Clinicians in Africa need to consider utilising this test further, particularly in children with non-responding chronic pneumonia.

Acute phase reactants such as procalcitonin and c-reactive protein (CRP) have not been found to be helpful in distinguishing between bacterial and viral infections, as a result they should not be done routinely in CAP and considered only in cases with multiorgan involvement or requiring intensive care treatment.^{20,21} Where resources permit, a CRP level of $\geq 40\text{mg/L}$ has been shown to be positively associated with bacterial pneumonia and negatively with RSV pneumonia.³² A CRP level of $\geq 100\text{mg/L}$ is even more specific for bacterial pneumonia, but is not as sensitive as the cut off of $\geq 40\text{mg/L}$.³² However, how CRP relates to viruses other than RSV, still needs to be investigated.

Point of care lung ultrasound (LUS) has recently gained interest in thoracic imaging. It has various advantages including lack of radiation exposure, it is non-invasive, it can be used to guide procedures in real time, and it can be repeated with minimal discomfort to the patient.³³⁻³⁵ Point of care LUS has been shown to be an accurate tool for the diagnosis of pneumonia.³³ In cases of pleural effusions it can help characterise the collection (simple versus complex) and hence guide the therapeutic option chosen.³⁴ In tuberculosis endemic areas, LUS has been found to be helpful in identifying mediastinal lymphadenopathy, it can also detect more abnormalities and has a higher inter-reader agreement when compared to chest x-ray.³⁵ Further studies especially on the role of LUS in LMICs are required.

Fortunately, chest computed tomography (CT) of the chest is rarely required. It is expensive, exposes children to radiation, in younger children requires general anaesthesia and requires expertise in its performance and interpretation. Chest CT may be considered in cases of complicated CAP such as necrotising pneumonia, abscess formation, and complex empyema.²⁰

Management

The management of the patient includes pharmacological and non-pharmacological management.

Pharmacological management depends on the clinical severity, local antibiotic resistance patterns, presence of complications, the causative organism, and local protocols. In the outpatient setting a five-day course of a broad-spectrum antibiotic such as high dose amoxicillin or amoxicillin-clavulanic acid is sufficient.^{14,20} In patients requiring admission who cannot tolerate oral antibiotics, broad-spectrum cover such as ampicillin and gentamicin, amoxicillin-clavulanic acid, or a 2nd or 3rd generation cephalosporin is recommended.¹⁴ When treating with ampicillin, in neonates or immunocompromised patients, adding gram negative cover with an aminoglycoside such as gentamycin is recommended.¹⁴ Once the patient responds to treatment and can tolerate oral antibiotics, they can be switched to oral antibiotics to complete 5-7 days.

Very ill immunocompromised patients such as those with HIV should also be treated for pneumocystis pneumonia (high dose cotrimoxazole and prednisone) and cytomegalovirus (ganciclovir). In general, neonates with CAP should be managed in hospital and not in the

outpatient setting.²⁰ Sickle cell disease is a common cause of pneumonia in several African regions. Unfortunately, there are no random controlled trials (RCTs) that have been done to recommend the best treatment for CAP in sickle cell disease.³⁶ Children with sickle cell disease are prone to CAP from encapsulated organisms such as *S. pneumoniae*, *Salmonella species*, *H. influenzae* type B, *C. pneumoniae* and *Mycoplasma pneumoniae*, as such, when they present with acute chest syndrome they must be covered for atypical organisms with a macrolide.³⁷

Table 3: Treatment guidelines for CAP^{14,19,20,37}

Characteristic	Suggested treatment*
Age <1 month	Ampicillin 50mg/kg IV 6-hourly Or benzylpenicillin 50 000 U/kg IV 6-hourly And gentamycin 7.5mg/kg IV daily Poor response in 48–72 hours change to Cefotaxime 50mg/kg IV 8-hourly Or Ceftriaxone 50mg/kg 12-hourly Switch to oral amoxicillin-clavulanic acid when tolerating orals and if cultures negative Complete 5 days total antibiotic duration
Age >1 month, outpatient	Amoxicillin 45mg/kg/dose orally 12-hourly for 5 days Poor response switch to Amoxicillin-clavulanic acid 45mg/kg/dose orally 12-hourly for 5 days
Age >1 month, inpatient	Amoxicillin-clavulanic acid 30mg/kg/dose IV 8-hourly for 5 days Or amoxicillin-clavulanic acid 45mg/kg/dose orally 12-hourly for 5 days Or Ampicillin 50mg/kg IV 6-hourly
Pertussis	Azithromycin 10mg/kg daily oral for 5 days Or Clarithromycin or erythromycin**
<i>Mycoplasma pneumoniae</i>	Azithromycin 10mg/kg daily orally for 5 days Or Clarithromycin or erythromycin**
<i>Chlamydia trachomatis</i>	Azithromycin 10mg/kg daily orally for 5 days Or Clarithromycin or erythromycin**
<i>Pneumocystis jiroveci</i>	Cotrimoxazole: Trimethopim 250mg/m ² stat then 150/m ² 8-hourly (<11 years), 12-hourly (>10 years). Switch to oral therapy once tolerating for a total of 21 days And prednisone 2mg/kg per day oral for 1 week, then 1mg/kg per day for 1 week then, 0.5mg/kg/day for 1 week
Cytomegalovirus	Ganciclovir 5mg/kg IV 12-hourly Switch to oral antibiotics once tolerating for a total of 6 weeks Valganciclovir 15mg/kg 12-hourly orally
Methicillin sensitive <i>S. aureus</i>	Amoxicillin-clavulanic acid 30mg/kg/dose IV 8-hourly Or Ceftriaxone 50mg/kg IV 12-hourly Or Cloxacillin 50mg/kg IV 6-hourly (maximum 1–2g) Switch to oral antibiotics once tolerating for a total of 2–4 weeks Amoxicillin-clavulanic acid 45mg/kg/dose orally 12-hourly Or Flucloxacillin 12.5–25mg/kg 6-hourly (maximum 500mg)
Methicillin resistant <i>S. aureus</i>	Vancomycin 25–30mg/kg stat then 15–20mg/kg 8-hourly Monitor levels, duration dependent on clinical picture
<i>Moraxella catarrhalis</i>	Amoxicillin-clavulanic acid 45mg/kg/dose orally 12-hourly for 5 days
Influenza	Oseltamivir: <38 weeks 1mg/kg/dose 12-hourly per os for 5 days >38 weeks–8 months 3mg/kg/dose 12-hourly per os for 5 days ≥ 9 months 3.5mg/kg/dose (maximum 75mg) 12-hourly per os for 5 days

HIV-infected and -exposed infants with severe CAP	<p>Empiric treatment:</p> <p>Ampicillin 50mg/kg IV 6 hourly Or benzylpenicillin 50 000 U/kg IV 6-hourly And gentamycin 7.5mg/kg IV daily</p> <p>Poor response in 48–72 hours change to Cefotaxime 50mg/kg IV 8-hourly Or Ceftriaxone 50mg/kg 12-hourly</p> <p>Switch to oral amoxicillin-clavulanic acid when tolerating orals and if cultures negative Complete 5 days total antibiotic duration</p>
	<p>Add <i>Pneumocystis jiroveci</i> cover in infants or severely immunocompromised</p> <p>Cotrimoxazole: Trimethopim 250mg/m2 stat then 150/m² 8-hourly (<11 years), 12-hourly (>10 years). Switch to oral antibiotics once tolerating for a total of 21 days And Prednisone 2mg/kg per day orally for 1 week, then 1mg/kg per day for 1 week then, 0.5mg/kg/day for 1 week</p>
	<p>Add cytomegalovirus cover*** Ganciclovir 5mg/kg IV 12-hourly Switch to oral antibiotics once tolerating for a total of 6 weeks Valganciclovir 15mg/kg 12-hourly orally</p>
Sickle cell disease	<p>Amoxicillin-clavulanic acid 30mg/kg/dose IV 8-hourly for 5 days And azithromycin 10mg/kg daily oral for 5 days or clarithromycin or erythromycin**</p> <p>Or amoxicillin-clavulanic acid 45mg/kg/dose orally 12-hourly for 5 days And azithromycin 10mg/kg daily per os for 5 days or clarithromycin or erythromycin**</p>

Adapted from Diagnosis and management of community-acquired pneumonia in children: South African Thoracic Society guidelines, Kendig's Disorders of the respiratory tract in children.^{20,14} WHO Guidelines Approved by the Guidelines Review Committee. Revised WHO Classification and Treatment of Pneumonia in Children at Health Facilities: Evidence Summaries and How I treat acute chest syndrome in children with sickle cell disease.^{19,37}

* Once the microbiological results are available use specific therapy according to the sensitivity of the organism

** Erythromycin contraindicated in neonates

*** Treatment can be stopped if the cytomegalovirus viral load is low

Cases of complicated CAP such as empyema, necrotising pneumonia and abscess require prolonged antibiotics and sometimes surgical management. The duration is usually a total of 2–3 weeks from the day the patient became afebrile, this can be completed as an outpatient.³⁸

Certain organisms require specific therapies. *Staphylococcus aureus* pneumonia requires a total of 2–4 weeks of anti-staphylococcal cover, which can be amoxicillin-clavulanic acid, 3rd generation cephalosporin or cloxacillin. In the event of methicillin resistant staphylococcus isolation then vancomycin instead is used. Atypical organisms such as pertussis, chlamydia and mycoplasma require cover with a macrolide such as azithromycin.^{14,20} Tuberculosis is treated with anti-tuberculosis drugs according to local protocols. Oseltamivir is recommended early in the treatment of influenza, but it is unavailable in most LMICs.

Supportive management is determined by the clinical severity and includes oxygen therapy, respiratory support (non-invasive ventilation and invasive ventilation), analgesia and antipyretics and nutritional support.²⁰

Non-invasive ventilation in the form of continuous positive airway pressure (CPAP) or high flow nasal canula (HFNC) improves survival in children with severe CAP in LMICs.³⁹ It has various advantages, including its potential to be used

even out of the intensive care unit setting in areas with a high burden of respiratory illness or limited resources.³⁹

Complications

Fortunately, complications in CAP are rare, they can be divided into acute and chronic and are dependent on the causative organism. Acute complications should be suspected in patients who remain ill, continue to be pyrexial or deteriorate despite at least 48–72 hours of appropriate therapy.^{21,38} Acute complications include local complications such as parapneumonic effusions, empyema, pyopneumothorax, pneumothorax, abscess formation, expansile pneumonia and necrotising pneumonia.^{21,38} Systemic complications include acute respiratory distress syndrome (ARDS), sepsis, multiorgan failure and disseminated intravascular coagulation.^{21,38} Though the course of complicated CAP tends to be protracted, most previously well children recover completely, although in all children, LRTI is associated with slightly reduced subsequent lung function; and so each episode of LRTI matters.^{38,40}

Chronic complications include bronchopulmonary fistula, bronchiectasis, bronchiolitis obliterans, lung fibrosis and persistent lung cavities.²¹ Chronic complications should be suspected in cases with recurrent and/or persistent symptoms. To prevent further lung damage clinicians must have a high index of suspicion in patients who do not recover completely after an episode of CAP.

It is in cases of acute or chronic complications of CAP where further imaging such as CT scan of the chest are beneficial.²⁰

Prevention

Prevention of CAP is related to preventing the known risk factors for CAP. Known risk factors include malnutrition, prematurity, immunosuppressed states including HIV, exposure to indoor and outdoor pollution, lack of breastfeeding, maternal smoking during pregnancy, incomplete or inadequate immunisation and poor socioeconomic status.^{8,20,41,42}

Immunisation has come to the forefront especially with the COVID-19 pandemic. Routine child immunisation particularly with pneumococcal vaccine and *H. influenzae* type B reduces the risk of CAP in children.^{20,43} Other vaccines that are of benefit include yearly influenza vaccination, COVID-19 vaccination and pertussis boosters every ten years and pertussis boosters for pregnant women.^{20,44,45}

Due to respiratory syncytial virus being the most common organism isolated in cases of CAP various modalities have been used to prevent infection and severe disease. The mainstay of prevention utilized has been universal precautions and immuno-prophylaxis in the form of palivizumab, a monoclonal antibody used in at risk infants, but it is very expensive and not routinely used in LMICs.²⁰ Recently maternal immunisation has been shown to be effective.²⁰ Furthermore, a long-term immune-prophylaxis option, nirsevimab, a monoclonal antibody, was shown to prevent respiratory syncytial virus infection. It is administered once during the respiratory syncytial virus season.⁴⁶

Chemoprophylaxis is recommended in certain at-risk populations. For example, cotrimoxazole prophylaxis in HIV infected children and other immunosuppressive conditions, as well as tuberculosis preventative therapy in children who are less than 5 years and/or are immunocompromised who have been exposed to active tuberculosis.²⁰

Conclusion

CAP causes significant morbidity and mortality in children. Accordingly, the following are key measures to reduce the impact of CAP on child health: prevention, accurate and early diagnosis and prompt management using best practice medicine.

As we experience medical advances, with improved science and technology, it is essential that clinicians continue to carry out robust clinical studies that lead to increased characterisation of this illness in LMICs as well as improvements in therapeutic options. Moreover, clinicians need to advocate for children, particularly in LMICs, to ensure access to appropriate and quality healthcare.

Finally, as noted in this review, there is a paucity of literature on CAP in Africa, with most of the literature emanating from the PERCH study and South African publications. The PERCH study had no sites in Central or North Africa. It is important that further CAP epidemiological data is collected from other African countries to improve understanding of CAP in African children and how prevention and management of CAP can be optimised.

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ROUTINE INVESTIGATIONS USED IN THE DIAGNOSIS OF CHILDHOOD TUBERCULOSIS

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Abstract

World Health Organization approved the use of Xpert MTB/RIF Ultra (Ultra) in children due to quick turn-around time, improved yield over smear microscopy, and ability to detect rifampicin resistance despite culture being the gold standard. This study reviewed published literature on childhood tuberculosis diagnostic modalities.

For childhood tuberculosis (TB) diagnostic modalities, PubMed was searched using Boolean terms OR/AND between childhood tuberculosis and words such as diagnosis, polymerase chain reaction, molecular, histology, imaging, and cultures. All abstracts were read, after which selected articles that met this article's objectives were thoroughly reviewed and referenced appropriately.

Ultra is an important diagnostic method for confirming TB in children even though mycobacterial culture, other molecular, and histology tests are used in the diagnosis of pulmonary and extrapulmonary TB. Modalities such as imaging and immunologic testing support the diagnosis of microbiologically unconfirmed TB.

Despite advances in the diagnostic tools for tuberculosis in children, the sensitivity and specificity of such tests are still relatively low. Clinical criteria of TB still play a role in deciding whether to treat children for TB.

Introduction

Globally, in 2021 there were approximately 9.9 million new cases of tuberculosis (TB), 11% of which were children. This drop from the 2020 global burden was attributed to the disruption of TB services from the covid19 pandemic.¹ However, the actual burden of TB in children is likely to be higher given the challenges in diagnosing childhood TB.²

Childhood tuberculosis typically presents with persistent or chronic cough greater than two weeks, fever unresponsive to conventional treatment, weight loss, failure to gain weight, failure to thrive, and fatigue or reduced playfulness or reduced activity. Generally, young children aged 0–4 years are the most vulnerable to the disease due to the vulnerability of their immune systems.³ Immunosuppression, commonly from human immunodeficiency virus (HIV) infection, multiplies the risk of progression from tuberculous infection to disease in children.⁴ Severe malnutrition has a strong association with childhood TB.⁵ Other risk factors known to be associated with TB infection in children include poverty, poor immunisation status (unvaccinated with BCG), low parental education, especially maternal education, overcrowding, high population density, contact with adult infectious TB cases, ingestion of unpasteurised milk, and chronic diseases.^{6–8}

Childhood tuberculosis and HIV have overlapping clinical manifestations, leading to missed or late diagnosis. HIV infection increases the incidence of TB in children by a factor of around 8, increasing with the degree of immunosuppression; ART reduces TB risk by about 70%, with protection continuing to increase over 1–2 years.⁹ Children living with HIV infection have an increased risk of TB-related morbidity and mortality.¹⁰

Children with TB present to health facilities just like any sick children. Children with respiratory symptoms are often misdiagnosed as pneumonia and offered multiple antibiotics. Those presenting with weight loss are managed with nutritional support by health care providers. The thought of HIV and TB often comes very late into managing such children leading to increased morbidity and mortality. The early diagnosis and initiation of treatment based on the susceptibility of the organism for children with tuberculosis can significantly reduce mortality in line with the aspirations of sustainable development goals (SDG) 3.^{11–13}

Mycobacterium culture is the gold standard for diagnosing confirmed tuberculosis and identifying drug-susceptible bacilli, but it takes relatively long (2-6 weeks) for growth to be observed. Children have paucibacillary compared to multibacillary disease, contributing to low yield on cultures compared to adults. Microbiological confirmation of

childhood tuberculosis is challenging due to the pathophysiology of childhood TB disease and for logistical reasons and, as a result, is uncommon.¹⁴ Respiratory specimens are difficult to collect in young children, and the reported bacteriologic yield is low.¹⁵ Nicol et al., in a study evaluating 452 children with a median age of 19.4 months that were admitted to hospital with suspected pulmonary tuberculosis (PTB) in 2009-2010 in Cape Town, found 27 children (6%) had a positive smear result, 70 children (16%) had a positive culture result, and 58 children (13%) had a positive Xpert MTB/RIF test (Xpert) result.¹⁶ Microbiology laboratory capacity is lacking in many African countries, and diagnosis frequently relies on a combination of symptoms, signs, radiological findings, a tuberculosis contact history and tuberculin skin testing.¹⁷

Confirmed TB is defined as microbiological confirmation of *Mycobacterium tuberculosis* by either culture or Xpert MTB/RIF Ultra on at least one respiratory specimen.¹⁸

Unconfirmed TB is microbiological confirmation NOT obtained AND at least 2 of the following:

- i. Presence of suggestive symptoms or signs of TB,
- ii. Chest radiograph consistent with TB,
- iii. A close TB contact or immunologic evidence of *M. tuberculosis* infection,
- iv. Positive response to tuberculosis treatment.¹⁸

Pulmonary tuberculosis (PTB) is any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or tracheobronchial tree.

Extrapulmonary TB (EPTB) is any bacteriologically confirmed or clinically diagnosed TB involving organs other than the lungs. Tuberculous intrathoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitutes EPTB.¹⁹

Childhood TB is often paucibacillary; thus, TB is usually microbiologically unconfirmed in childhood practice.

The purpose of this article was to review the literature on advances in routine investigations for diagnosing tuberculosis in children, including pulmonary and extrapulmonary disease

Methodology

In March 2021, a peer-reviewed literature search was done in PubMed with key search terms related to routine investigations used to diagnose childhood tuberculosis. The search was a simple, non-systematic literature review. Box 1 shows the words inputted into the search.

Box 1: Literature Review Search Terms

tuberculosis, investigations AND diagnosis, polymerase chain reaction, molecular, histology, imaging, and cultures.

Routine investigations

I. Investigations that provide microbiological confirmation

Mycobacterial culture

Lowenstein-Jensen (LJ), as a solid culture medium, had been the gold standard for the diagnosis of TB for over a century. Its median time for positivity is four to six weeks.

Commercial automated liquid culture methods, including the mycobacterial growth indicator tube (BACTEC MGIT 960 - Becton Dickinson USA), are widely used for routine TB diagnosis.²⁰

The BACTEC MGIT liquid culture system has a shorter turn-around time than the conventional LJ method for smear-positive and negative clinical specimens with a median detection time of 2 weeks.²⁰ In a study in which smear-positive specimens were also cultured, the yield of positive results was 66.7% and 87.4% on LJ and MGIT methods, respectively. On smear-negative specimens, the yield was 13.4% and 17.4% on LJ and MGIT methods, respectively.²¹ Mycobacterial culture is superior to Ultra for diagnosing PTB in children because childhood TB is often paucibacillary.²²

The microscopic-observation drug-susceptibility (MODS) assay is a liquid culture-based method for detecting living mycobacteria based on two well-known MTB characteristics. The growth in liquid medium is faster than that on solid medium and the microscopic visualisation of the unique cording of MTB in liquid culture.²³ It is a low-cost, low-technology tool for high-performance detection of MTB and multidrug-resistant TB (MDR TB).²⁴ Compared to smear microscopy (28.2%), MODS (39.7%) was more sensitive to detecting MTB in children.²⁵

Xpert MTB/RIF Ultra assay on a respiratory specimen

World Health Organization (WHO) in December 2010 approved the use of Xpert as a replacement for sputum smear microscopy, especially in settings with high rates of HIV-associated TB and MDR-TB.²⁶ It can detect *Mycobacterium tuberculosis complex* (MTBC) and simultaneously screens the β subunit of the mycobacterial ribonucleic acid (RNA) polymerase gene for the presence of mutations conferring rifampicin resistance.

More recently, the Xpert MTB/RIF Ultra (Ultra) assay was developed to overcome the limited sensitivity of Xpert in the detection of PTB, particularly in patients with a paucibacillary disease or HIV infection.²⁷ Dorman et al. in a study among adults with suspected TB who produced at least three sputum specimens in two days, the yield on Xpert and Ultra was 83% and 88%, respectively, on all culture-positive specimens. Among smear-negative, culture-positive specimens, the yield on Xpert and Ultra was 46% and 63%, respectively. Among HIV-infected patients with a culture-positive specimen, Xpert and Ultra yielded a positive result on 77% and 90%, respectively.²⁷

A South African study published in 2018 investigated the comparative accuracy of Xpert and Ultra on induced sputum for diagnosing PTB in children. Among 76 children with a positive Xpert, Ultra or mycobacterial culture, Xpert detected 63.2%, Ultra 73.7% and culture 82.9%, (P = 0.117 for comparison of Xpert and Ultra).²²

Xpert MTB/RIF Ultra assay on a stool specimen

Due to the challenges in collecting quality respiratory specimens for pulmonary tuberculosis diagnosis in children, researchers have been looking for alternative specimens that are easy to collect and process. Stool specimens are very easy to collect and could be a preferred alternative.

A study from Shanghai Public Health Clinical Centre evaluated the diagnostic efficacy of stool based Xpert MTB/RIF Ultra assay versus other assays for detecting paediatric PTB prospectively through a head-to-head comparative study. Samples were collected from children (< 15 years) with abnormal chest imaging (X-ray or CT scan) results for the following tests: Ultra on stool sample (Ultra-Stool), Ultra on respiratory tract sample (Ultra-RTS),

Xpert MTB/RIF assay (Xpert) on RTS (Xpert-RTS), acid-fast bacilli smear on RTS (AFB-RTS), and *Mycobacterium tuberculosis* (*Mtb*) culture on RTS (Culture-RTS). Against a composite reference standard, Ultra-RTS demonstrated the highest sensitivity (52%) and specificity (100%). Ultra-Stool showed 84.1% concordance with Ultra-RTS, demonstrating 45.5% sensitivity and 94.7% specificity ($\kappa = 0.65$, 95% CI = 0.51–0.79). The sensitivity of Ultra-Stool was similar to *Mtb* culture (45.5%, $p = 1.000$) and higher than AFB-RTS (27.3%, $p < 0.05$). Assay positivity was associated with age and infiltration range in chest imaging.²⁸

Sputum smear microscopy

Sputum smear microscopy is widely used to detect TB. Light-emitting diodes (LED) were developed to offer fluorescence microscopy benefits over conventional Ziehl-Neelsen (ZN) microscopy.²⁹ The ZN stain is for acid-fast organisms like *Mycobacterium*, which has large amounts of lipid substances within their cell walls called mycolic acids. The lipid capsule of the *Mycobacterium* takes up carbol-fuchsin and resists decolourisation with a dilute acid rinse. The organism stains as red bacilli under light microscopy. Conventional fluorescence microscopy has higher sensitivity than ZN. It is rapid, but uptake has been hampered by high cost due to expensive mercury vapour light sources, regular microscopy maintenance, and the requirement for a dark room. Light-emitting diode (LED) technology was developed to allow the benefits of fluorescent microscopy without the associated costs. It has some limitations, including low sensitivity, especially in HIV-positive individuals and children, and the inability to detect drug resistance.³⁰ With mycobacterial culture as the reference standard, Xpert identified twice as many cases (75.9%) as did smear microscopy (37.9%) in one study¹⁶ whilst in a systematic review and meta-analysis, the sensitivity of Xpert was 36–44% more than microscopy.³¹

II. Investigations used in the diagnosis of microbiologically unconfirmed TB

Tuberculin skin testing (Mantoux tests)

Short of demonstrating viable organisms in body tissues and fluids, the tuberculin skin test (TST) was the only method of detecting *Mycobacterium tuberculosis* (MTB) infection in an individual until the introduction of the interferon gamma-release assay (IGRA). Both tests are used to diagnose TB infection in individual patients and in epidemiological settings to measure the prevalence of tuberculous infection in populations.³²

Tuberculin skin testing is performed by the Mantoux method. The Mantoux test is affordable, but it cannot distinguish actual TB infection from TB disease. Neither can it differentiate between *Mycobacterium tuberculosis* from environmental non-*Mycobacterium tuberculosis* nor the effect of BCG vaccination. Briefly, 0.1 mL of 2 tuberculin units of purified protein derivative is administered intradermally with a short bevel needle. The result of a Mantoux test is read in millimetres of induration 48–72 hours after injection. The diameter of the indurated area is measured across the forearm (perpendicular to the long axis).

The interpretation is dependent on the immune status of the child. In an immunodeficient child (e.g., HIV-infected not on ART or malnourished), a Mantoux test is considered positive when the transverse diameter of the skin induration reaction is ≥ 5 mm. In an immunocompetent child, a response ≥ 10 mm is positive.¹⁹ False-negative results following Mantoux testing could be due to HIV/AIDS, malnutrition, following immunisation with live vaccines such as measles and rubella, zinc deficiency, and recent TB infection. Exuberant reactions are usually caused by MTB

infection but can result from nontuberculous mycobacterial infection and BCG vaccination.

Imaging modalities

Chest radiographic imaging is one of the oldest imaging techniques used for diagnosing respiratory conditions, including suspected pulmonary TB.

On chest radiography (CXR), a calcified Ghon focus or Ghon complex may be seen. Intrathoracic TB in infants and young children are frequently characterised by enlarged peripheral and hilar lymph nodes with resulting airway displacement, compression with/without lobar collapse consolidation.

Airspace disease with expansile lobar or diffuse TB bronchopneumonia can be seen on CXR. Lymph node disease is most common following primary infection before five years of age.³³ This, in addition to the small airway size, makes young children the most vulnerable group to develop lympho-bronchial TB.³⁴

Children older than five years develop TB hypersensitive pleural effusion or pericardial effusion, which may develop after a recent primary infection.³⁵ TB lung abscess is seen as an irregularly shaped thick-walled cavity with an air-fluid level. TB empyema is characterised by a thick pleura ring with dense and irregular parietal and visceral pleura calcification.

In older children (>10 years), an adult-type cavitating disease often follows a recent primary infection.³⁶ Adolescents and young adults with TB commonly present with apical consolidation, cavitation, fibrosis, and atelectasis.³⁷ Tuberculosis of the spine (Pott's disease) typically involves the thoracic vertebrae and may be detected on CXR with or without gibbus and TB paraspinal abscesses.³⁸

Miliary TB is diagnosed by the presence of a diffuse miliary infiltrate on CXR. Post TB fibrosis or bronchiectasis changes are seen as lung scarring.

A classification proposed by Marais et al, has helped classify intrathoracic TB in children into domains namely: lymph node TB (lympho-bronchial TB), air-space parenchymal TB (consolidation/atelectasis/adult-type), miliary TB, and pleural TB.³⁹

However, CXR is limited by its two-dimensional orientation and high inter-interpretor and intra-interpretor variability in identifying lymphadenopathy.^{40,41} Poor image quality and co-infections in children living with HIV reduce the specificity of CXR as a diagnostic tool. In some studies specificity was < 50%.^{42,43}

Imaging techniques other than chest radiographs are less widely available in African countries and require interpretation by radiologists. These techniques include ultrasonography (USG), computerised tomography (CT) and magnetic resonance imaging (MRI).

Ultrasonography findings of the abdomen suggestive of TB include lymph node enlargement greater than 1.5 cm and micro-abscesses in the liver and spleen with ascites as further supporting evidence. With additional history, USG findings as described above could suggest TB, especially in HIV-infected patients.⁴⁴ USG of the chest helps identify lymph nodes and effusions. Using the supra-sternal window, USG can detect lymph node abnormalities more frequently than radiography.⁴⁵

Computerised tomography scans and magnetic resonance imaging (MRI) are imaging modalities that provide cross-sectional and three-dimensional spatial information to

visualise multiple coexisting lesions, thus enhancing sensitivity and providing non-invasive monitoring for individuals.⁴⁶ The primary disadvantage to their routine use in developing countries context is cost.

Chest CT is superior for detecting lymphadenopathy, visualisation of airway compression, pneumonia, lymph node necrosis, and lung necrosis than CXR.^{47,48}

CT scan of the brain helps assess features and complications of TB meningitis (TBM), including hydrocephalus, parenchymal enhancement of tuberculous granulomata, contrast enhancement of basal leptomeningeal lesions, cerebral infarction, and focal or diffuse brain oedema.⁴⁹ These advances notwithstanding, lateral skull X-rays are still helpful in demonstrating communicating hydrocephalus after intrathecal injection of air (air encephalograms).⁵⁰

CT scanning is limited by exposure to radiation and the need for intravenous contrast to enhance visualisation.⁴⁷

On MRI, necrotic tuberculosis lesions, including lymph nodes, show low T2 signal.⁵¹ Three significant findings of spinal TB on MRI are endplate disruption, paravertebral soft tissue abscess, and increased signal intensity of intervertebral disc on T2-weighted image. It can identify abscesses, including extension into the psoas muscle and epidural space.⁵² Some techniques require sedation in young children.

III. Investigations used in the diagnosis of microbiologically confirmed or microbiologically unconfirmed TB

Fine needle aspiration versus excision biopsy

Lymph nodes may be sampled by fine-needle aspiration biopsy (FNAB), providing diagnostic material for mycobacterial culture and drug susceptibility testing, cytology, as well as nucleic acid amplification testing (NAAT).⁵³

About 30% of children with PTB also have an extrapulmonary disease, with tuberculous lymphadenitis as the most typical manifestation.⁵⁴ Tuberculous lymphadenitis is considered a local manifestation of the systemic disease, whereas lymphadenitis due to nontuberculous mycobacteria is truly localised disease.⁵⁵

A prospective study in Cape Town, South Africa, showed that FNAB using a combination of cytomorphology, autofluorescence, and ZN staining in high-risk populations provided a rapid and definitive diagnosis of mycobacterial infection, allowing initiation of therapy pending culture and sensitivity testing.⁵⁶ In a prospective diagnostic study in adults using fine-needle aspirates (FNA) at Groote Schuur Hospital, Cape Town, Ultra sensitivity was 75% using mycobacterial culture on FNA as reference.⁵⁷

Even though excision biopsy is more sensitive than FNA (94% vs 80%) in diagnosing tuberculous cervical lymphadenopathy, the need for theatre space, anaesthesia and potential complications from the procedure such as surgical site bleeding, haematomas, and surgical site infections make it a lesser preferred option.⁵⁸

Tissue histopathology

A key finding of *Mycobacterium tuberculosis*-infected tissue is necrotising granulomatous inflammation, composed of epithelioid histiocytes surrounding a central necrotic zone, and can be accompanied by a variable number of multinucleated giant cells and lymphocytes.⁵⁹

A histological finding of chronic granulomatous inflammation (CGI) concomitant with caseating necrosis (CN) from a peripheral lymph node excision biopsy or tissues of any organ system can be strong evidence of active TB even though not confirmatory.⁶⁰ Other infectious (e.g. cat scratch disease) and non-infectious (e.g. sarcoidosis) conditions produce CGI.⁶¹

Diagnostics on extrapulmonary fluids

A definitive diagnosis is based on the discovery of *Mycobacterium tuberculosis* in any pleural, peritoneal (ascitic) fluid, or CSF cell smears, bacterial culture, or polymerase chain reaction (PCR).

In a study by Jeren et al., which retrospectively reviewed 84 cases in ten years, cerebrospinal fluid (CSF) in patients with TB meningitis in the first ten days showed cytological changes with neutrophils predominated (60% to 80%) then mononuclear cells, such as lymphocytes, lymphoid cells, monocytoic cells and macrophages, became predominant. Plasmacytes (20%) were found in 30% of these cases from the third week of the disease.⁶²

The gold standard for diagnosing tuberculous pleural effusion (TPE) is the detection of *Mycobacterium tuberculosis* in pleural fluid or pleural biopsy specimens, either by microscopy or culture, the histological demonstration of caseating granulomas in the pleura along with acid-fast bacilli. Adenosine deaminase and interferon- γ in pleural fluid have been documented to be useful tests for the diagnosis of TPE.⁶³

In cases of TB peritonitis, peritoneal fluid analysis typically shows an elevated lymphocyte count with lymphocyte predominance, serum-ascitic albumin gradient of <11 g/L, and high protein levels (>2.5 mg/dL).⁶⁴

For abdominal tuberculosis, adenosine deaminase (ADA) helps make the diagnosis, specifically when levels are above ≥ 30 U/L.⁶⁵

Table 1 Other tests for TB diagnosis in children

LAMP⁶⁶	A nucleic acid amplification method designed to amplify a specific DNA region under isothermal conditions	User friendly Less infrastructure needed More sensitive than sputum smear microscopy	Less sensitive than Xpert MTB/RIF Ultra
Urine-LAM⁶⁷	Detects cell wall lipopolysaccharide lipoarabinomannan in urine	Commercially available as a POCT	More applicable in adult HIV patients with advanced disease
Immune response test			
ADA⁶⁸	An enzyme involved in T-cell proliferation	Supportive for TB pleural effusion	Variable cut-off values indicating a significant result
IGRA⁶⁹	Measures interferon (IFN)-gamma release in response to antigens present in <i>Mycobacterium tuberculosis</i>	Differentiates <i>Mycobacterium tuberculosis</i> infection from BCG	The test is performed using blood (invasive procedure) Expensive

LAMP-Loop-mediated isothermal amplification assay; LAM-Lipoarabinomannan; ADA- Adenosine Deaminase; IGRA- Interferon Gamma release assay; POCT-Point-of-care test; BCG-Bacillus Calmette-Guerin vaccine.

Other investigations

Table 1 shows other tests less frequently used in the diagnostic workup of children with suspected TB.

Limitations

The search was limited to PubMed and English language resources. This literature review and its conclusions may therefore be subject to publication bias.

Conclusion

This article reviewed investigations used in everyday clinical practice to support the diagnosis of childhood TB. All diagnostic modalities have limitations. Clinical criteria including the presence of symptoms consistent with childhood TB and a close contact history remain vital for establishing the diagnosis of childhood TB.

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ORGANIZATION & IMPLEMENTATION OF A HOSPITAL INFECTION PREVENTION AND CONTROL PROTOCOL

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Abstract

There has been a global rise in antimicrobial resistance and threats from epidemics and pandemics. These threats and the difficulties experienced while managing them have led to a global plan to improve infection prevention and control (IPC) practices, especially in the developing world, thus making them more effective. International health regulations have considered running an effective IPC programme as a critical strategy for dealing with public health threats of international concern. This review aims to survey IPC implementation practices through the global core components of IPC programmes, including monitoring, and then relate them to the practice in a hospital setting of a developing country. Global best practices on IPC from international health organizations were extracted and summarised. This information was then compared to the real-time situation in a developing country's hospital. An effective hospital IPC program is necessary to curb the devastating consequences of uncontrolled pandemics and antimicrobial resistance (AMR). However, the Nnamdi Azikiwe University Teaching Hospital in Nnewi, a hospital likened to that of other hospitals in developing countries, has yet to implement the core components of an organized IPC programme fully, and is thus at high risk of an outbreak.

Introduction

Nosocomial (healthcare-associated) infections are a subset of infectious diseases acquired in a healthcare facility. They are not related to the original clinical conditions that brought the patient to the hospital and were not incubating before admission; instead, they must develop at least 48 hours after admission.^{1,2}

Despite the advances in modern medicine and surgery, approximately 5-10% of patients admitted to hospital subsequently acquire an infection, thus, leading to increased awareness of the need for rational, scientifically based procedures to minimize this problem.^{1,2,3}

Concern about hospital-acquired infections has been increasingly echoed by patients and healthcare practitioners, thus highlighting the importance of infection control procedures.

Globally, it is recommended that every hospital should have an infection control team (ICT).^{1,2,3,4} The quality of a hospital infection control programme is a reflection of the general standard of care provided by that institution.^{1,2,3,4}

International health regulations like the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) have considered running an effective IPC programme as a key strategy for dealing with public health threats of international concern.⁵ These international organizations have outlined several minimum requirements as the core components to achieve a successful IPC practice in healthcare facilities.⁵ This review aimed to survey the global IPC best practices and then relate them to what is available in a hospital setting in a developing country.

Organizing an effective hospital infectious disease protocol

To properly organize an effective infectious disease protocol, the national health organizations, IPC programme, and other relevant bodies should coordinate and support the implementation of the following core components of IPC practices at the facility level.

IPC programme

Every nation's health care system must establish active, stand-alone, national IPC programmes with clearly defined objectives, functions and activities. These programmes can then be adopted and modified to suit individual hospitals' infectious disease situations, with a dedicated, trained team in each acute health care facility.⁵ The programme's purpose will be to give general guidelines on preventing healthcare-associated infection (HAI), promoting patient safety and combating antimicrobial resistance (AMR) through IPC best practices.

A dedicated IPC programme should be in place at the national level, including at least one full-time focal person trained in IPC and a dedicated budget for implementing IPC strategies. However, recommendations at the facility level will depend on the type of facility in focus.

For example, a tertiary healthcare facility should have at least one full-time trained IPC focal person with dedicated time per 250 beds, an IPC programme aligned with the national programme and

with a dedicated budget, multidisciplinary team and access to the microbiology laboratory.^{5,6}

IPC guidelines

The recommended IPC guidelines should be evidence-based, Ministry-approved guidelines adapted to the local context and reviewed at least every five years.^{5,6,7} These include evidence-based facility-adapted standard operating procedures (SOPs) and monitoring based on the national IPC guidelines at the primary care facility. The minimum requirement at this level includes hand hygiene, decontamination of medical devices and patient care equipment, environmental cleaning, health care waste management, injection safety, healthcare worker (HCW) protection, aseptic techniques, triage of infectious patients, basic principles of standard and transmission-based precautions. It also requires regular monitoring of the implementation of some basic IPC guidelines / standard operating procedures (SOPs).^{5,6}

All primary healthcare facility level requirements apply at the secondary and tertiary healthcare facilities. In addition, SOPs on standard and transmission-based precautions should be included. For example, SOPs for the prevention of airborne pathogen transmission, the aseptic technique for invasive procedures, occupational health-specific SOPs.^{5,6,7}

Education on IPC practices

The WHO recommendations for IPC education states that there should be a national law requiring that all health facilities conduct training and retraining of their staff on IPC practices. This training should be in place for all HCWs by using team and task-based techniques that are participatory and include bedside and simulation training to reduce the risk of Healthcare-Associated Infections (HAIs) and AMR. The IPC team should monitor and evaluate training, and the training of HCW should be conducted annually.^{5,7,9}

At the primary care level, it is recommended that IPC training for all front-line clinical staff and cleaners upon hiring must be conducted, including training on IPC guidelines / SOPs. The training should also include all IPC link persons in primary care facilities and IPC officers at the district level.^{5,7,8}

All IPC training described in the primary care levels and specific IPC training for IPC staff should be done at the secondary and tertiary healthcare facilities. In addition, the IPC staff should receive the IPC training for the tertiary healthcare facilities annually.^{7,8,9}

Surveillance for healthcare-associated infections

The WHO recommends that HAI surveillance programmes and networks that include mechanisms for timely data feedback should be designed to reduce HAI and AMR. Timely feedback of surveillance results to HCWs and stakeholders is also necessary.^{7,7}

Healthcare-associated infection surveillance is not a minimum requirement at the primary facility level. Still, if available, it should follow national or sub-national plans (for example, detection and reporting of outbreaks affecting the community are usually included in national plans).^{5,7,10,11}

Secondary care HAI surveillance is required and should follow national or sub-national plans. The HAI

surveillance must be active for tertiary care facilities, including information on AMR. There should also be timely and regular feedback to key stakeholders to lead to appropriate action, particularly to the hospital administration.^{5,8}

Implementation of IPC activities using multimodal strategies

It is recommended that multimodal strategies are used to implement priority IPC interventions. For example, the facility should implement the very least interventions like improving hand hygiene, safe injection practices, decontamination of medical devices and instruments, and environmental cleaning at the primary health facility. In addition to interventions mentioned for primary care facilities at the secondary health facility, multimodal strategies should also be employed for implementing interventions to improve the standard and transmission-based precautions and triage. Tertiary care facility interventions should then include improvement of each of the standard and transmission-based precautions, triage, and those targeted at reducing specific infections (for example, surgical site infections or catheter-associated infections) in high-risk areas / patient groups, in line with local priorities.^{6,8,9,12}

Monitoring, evaluation, auditing and feedback

Effective monitoring of IPC structural and process indicators should be set up at all levels of care.⁶ Through this component of IPC practice, the IPC team, can determine if the job has been done correctly and if there need to be further interventions.

This monitoring should be based on IPC priorities identified in the other components of IPC practices mentioned above at the primary care level. In addition, monitoring and evaluation require decisions at the national level and implementation support at the subnational level.

An individual should be responsible for the periodic or continuous monitoring of selected structural process indicators for secondary and tertiary care facilities, informed by the facility's priorities or the country's priorities. Timely and regular feedback must be provided to key stakeholders to take appropriate action, particularly the hospital administration.^{5,8}

Workload, staffing and bed occupancy

The panel set up by the WHO to look into IPC recommends that the following elements should be adhered to reduce the risk of HAI and the spread of AMR:

- The bed occupancy should not exceed the standard capacity of the facility
- Healthcare worker staffing levels should be adequately assigned to suit patient workload.

At the primary healthcare facility, the focus should be to reduce overcrowding. There should be a system for patient flow, a triage system (including a referral system), and a system for the management of consultations should be established according to existing guidelines. The staffing levels should also be optimized, considering the various categories identified when using WHO / national tools and developing an appropriate plan.^{13,14}

For secondary and tertiary care facilities, standardization of bed occupancy should be done by establishing a system to properly manage space in the facility and establish the standard bed capacity. The hospital administration should ensure that the developed system is enforced, no more than one patient per bed, spacing of at least one metre between the edges of beds, and overall occupancy should not exceed the designed total patient bed capacity of the facility.^{5,10} The same minimum requirements as for primary health care is required to reduce overcrowding and optimize staffing at these levels.^{5,8,10}

Buildings, environment, materials and equipment for IPC

Patient care should be undertaken in a clean and hygienic environment that facilitates practices related to preventing and controlling HAI and AMR, including all elements around water and sanitation hygiene (WASH) infrastructure and services and the availability of efficient IPC materials and equipment. The WHO panel also recommends that materials and equipment to perform proper hand hygiene should be readily available at each point of care.^{5,9}

For primary care facilities:

- Clean water should always be available from a source on the premises to perform basic IPC measures.
- A minimum of two functional, improved sanitation facilities should be available on-site, one for patients and the other for staff. In addition, both should be equipped with menstrual hygiene facilities.
- Functional hand hygiene facilities should always be available at points of care / toilets and include soap, water and single-use towels (or, if unavailable, clean reusable towels) or alcohol-based hand rub within 5 metres of the toilets.
- Sufficient and appropriately labelled bins to allow for health care waste segregation should be available and used (less than 5 metres from the generation); waste should be treated and disposed of safely via autoclaving, high-temperature incineration (850° to 1100°C), and buried in a lined, protected pit.
- The facility layout should allow adequate natural ventilation.
- Sufficient and appropriate IPC supplies and equipment (for example, mops, detergent, disinfectant, personal protective equipment) and power / energy should be provided for performing all basic IPC measures according to minimum requirements / SOPs.^{15,16}

Secondary and tertiary care facilities

- A safe and sufficient quantity of water should be available for all required IPC measures and specific medical activities, including drinking and piped inside the facility at all times.
- A minimum of two functional, sanitation facilities that safely contain waste for outpatient wards, and one facility per 20 beds for inpatient wards should be available; all should be equipped with menstrual hygiene facilities.
- Efficient hand hygiene facilities should always be available at points of care, toilets and service areas
- Waste segregation and disposal are the same as for primary health facilities.
- The facility should be designed to allow adequate ventilation (natural or mechanical, as needed) to prevent transmission of pathogens.
- Sufficient and appropriate supplies and equipment and reliable power/energy should be available for

performing all IPC practices, including standard and transmission-based precautions, according to minimum requirements/SOPs.

- The facility should have a dedicated space for decontamination and reprocessing medical devices according to minimum requirements/SOPs.
- The facility should have adequate single isolation rooms or at least one room for sorting patients with similar infectious disease syndromes if the number of isolation rooms is insufficient.^{15,16}

Cost of establishing an infection control programme

The cost of setting up the significant portion of an infection control programme (90%) is minimal; the cost of attaining one hundred per cent is much higher. Therefore, it is prudent, to begin with, programmes designed to achieve the first 90% and gradually build up the final 10% as revenue savings are realized.^{1,9,10,17}

The cost involved in setting up an infection control programme includes:

- Predictable costs include staff costs, protective clothing, monitoring equipment, data surveillance equipment, maintenance of equipment, laboratory test for routine monitoring of specialized areas, stationery, office furniture
- Unpredictable costs include costs for individual patient episodes, unforeseen outbreaks

Responsibilities of the infection control team

The infection control team (ICT), which comprises the infection control doctor, infection control nurse, the administrator and the community health physician, make up the core of the ICT. Other healthcare personnel, including pharmacists, laboratory staff are also part of the team.^{7,9,16}

The Meeting of the ICT should be monthly, but inspection of the hospital should be done weekly. The ICT reports directly to the infection control committee (ICC).^{9,11}

The ICC is responsible for developing policies and procedures related to infection control in the hospital and acting as a source of expertise on matters relating to infection. The committee advises the hospital's chief executive through the infection control doctor.⁷

Infection prevention and control implementation activities in Nnamdi Azikiwe University Teaching Hospital (NAUTH)

Structure

Although there had been some level of infection control practice ongoing in NAUTH from the hospital's inception, the official IPC structure involving an ICC and an ICT was set up in 2012. From the time the IPC in NAUTH received official recognition by the hospital management in 2012, the team has slowly but steadily improved in the hospital's IPC processes, evidenced by progressive reductions in HAI rates. For example, in 2012, the NAUTH ICT reported an unpublished surgical site infection (SSI) rate of 22%. However, when the same rates were reported in 2020, an SSI rate of less than 13% was observed.

In NAUTH, the ICC comprises members from the management and staff of the hospital, including management, clinical microbiology, nursing, and other medically related fields. A top management staff member, the chairman of the medical advisory committee, leads the ICC for obvious reasons, including policymaking and the seamless approvals of requests and recommendations made by the ICT. This committee was scheduled to meet at least once every quarter.

The ICT, being the subset of the ICC that carries out the actual day to day surveillance and responses to occurrences or outbreaks in the hospital, is led by a consultant clinical microbiologist. Several other doctors from diverse disciplines serve as infection control doctors. In addition, we currently have two infection control nurses who relate with other nurses in the hospital wards to get the IPC job done as swiftly as possible. The hospital recently employed a specialist infectious diseases physician, and we hope to have him join the team as soon as possible.

Implementation of the IPC core components by the NAUTH infection control committee

The hospital is not at its best regarding implementing all the core components of an effective IPC programme, but there is gradual and steady progress. For instance, an IPC programme is available with a dedicated, trained team to prevent HAI and combat AMR. However, the hospital still depends on national guidelines for implementing the IPC programme. Staff receive basic training on IPC practices, but this is not as regular as it should be.

Several surveillance drives for endemic and sometimes epidemic infections have been conducted, including ongoing surveillance coordinated by the hospital in collaboration with the Nigerian Center for Disease Control (NCDC) on causes and prevalence of acute febrile illnesses (including COVID 19). There are also occasional point prevalence surveys on antimicrobial stewardship.

The roles currently carried out by the IPC team in NAUTH include but are not limited to the following:

- To help coordinate the IPC programme activities and develop, revise, and implement the set policies (this involves the review of all the compliance, process and outcome indicators collected during the periods before the policy is established. This process is ongoing but not yet optimal.
- To regularly train hospital staff on the basic understanding of IPC principles and practices (the last hospital-wide training conducted by the team was done in 2020).
- To organize surveillance for HAI and outbreaks (currently ongoing).
- To carry out quarterly point prevalence surveys for antimicrobial use and resistance (currently done yearly due to limited resource availability).
- To coordinate antimicrobial stewardship programmes, including daily rounds in the hospital.
- To audit the quality and effectiveness of the hospital environmental cleaning, including disinfection and sterilization practices.
- To implement local and international best practice guidelines for preventing infection transmission in the hospital.
- On clinician adherence to IPC policies, the committee has continued to engage clinicians on the need to comply with IPC guidelines. A holistic policy document on IPC practices specific for the hospital is pending review and approval by the management. We believe that when this document is finally released, clinicians will give IPC compliance the required seriousness and dedication it deserves.

Challenges

We have experienced some challenges in our centre regarding fully implementing all the set policies / core components for a successful IPC programme. The hospital community's general lack of interest is the top on the list. Unfortunately, this is also witnessed in many other hospitals in the country. Another major challenge is limited funding of IPC activities and reduced zeal by team members resulting from a weak incentive system. Some team members believe that the IPC job is an addition to their regular duties, hence it should come with specific incentives.

Case scenarios

An interesting occurrence was experienced in the hospital's neonatal intensive care unit (NICU) in 2015. An out-born neonate was admitted to the NICU for neonatal sepsis and extensive Staphylococcal scalded skin syndrome (SSS), having a temperature of about 40°C. The managing team managed the patient with meropenem, but the temperature remained sustained. Based on this occurrence, the clinical microbiologist was invited to review the patient's condition.

It was observed that the managing team missed out on some of the set IPC protocols. Therefore, the patient was reviewed, and the ICT made a presumptive diagnosis of SSS due to methicillin-resistant *Staphylococcus aureus* (MRSA). Specimens were taken for microscopy, culture and sensitivity, and the managing team was advised to adhere strictly to the IPC protocol. After 72 hours, MRSA was isolated and confirmed, the patient was placed on intravenous vancomycin, and there was a rapid resolution of the SSS.

From an IPC perspective, it was advised that the patient be isolated, and barrier nursed. The managing team obliged. Dedicated nurses, equipment, materials, and consumables were also recommended. Afterwards, decontamination was carried out, and the unit was certified MRSA free before being put back to use in the neonatal ICU.

A second scenario still being tackled was observed following a point prevalence survey on antimicrobial use in 2018. We observed that less than 20% of the antibiotic prescriptions in the hospital were based on clear cut reports of organism susceptibilities from the clinical laboratories. Our team sprang into action by revealing the outcome of our survey to the clinicians and the hospital management and conducting training and retraining on the need for good antibiotic stewardship in the hospital. Today, dependence on clinical laboratory susceptibility reports have greatly improved.

Conclusion

An optimal IPC practice is one where the core components of an IPC programme are fully implemented. Unfortunately, IPC in most developing countries' healthcare facilities is yet to achieve optimal status; hence these hospitals are at risk of having outbreak occurrences. Although the IPC practice in NAUTH is not optimal, it has helped ensure a slow but progressive decline in HAI.

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CASE REPORTS & MEDICAL IMAGES

A CASE OF CUTANEOUS HISTOPLASMOSIS IN A CHILD WITH HIV INFECTION

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Abstract

Histoplasmosis is an endemic fungal infection that can infect both immunocompetent and immunocompromised individuals. Due to the non-specific clinical symptoms, it can often be misdiagnosed as a more commonly occurring infection such as tuberculosis. In this case report we describe the presentation of a young girl, recently diagnosed with HIV infection, with extensive facial lesions that were found to be positive for histoplasmosis on molecular testing. She responded well to antifungal therapy.

Introduction

Histoplasmosis species that are pathogenic in humans are *H. capsulatum* var *capsulatum* and *H. capsulatum* var *duboisii*. Previously described as being mostly endemic to the United States of America (USA), the fungus now has a worldwide presence with *H. capsulatum* var *duboisii* endemic to western and central Africa¹. Both species do however occur on the African continent. This dimorphic fungus exists as a mold with hyphae that produce spores or microconidia in the environment. Once a host inhales the microconidia, they transform into budding yeasts in the warmer conditions of the body. The yeasts can then spread through the body resulting in a progressive, disseminated form of the infection¹.

Opportunistic fungal infections can cause significant morbidity and mortality in patients with a compromised immune system such as in human immunodeficiency virus (HIV infection), post solid organ transplant, haematological malignancies, treatment with immunosuppressive agents as well as in individuals with T-lymphocyte and B-lymphocyte deficiencies^{2,3}.

In immunocompetent children, the disease can, however, be asymptomatic, self-limiting and may not require treatment⁴. Recent studies have shown that it is at times difficult to distinguish *H. capsulatum* from other dimorphic fungi namely *Emergomycosis* species and there is considerable clinical overlap between the two infections⁵. We describe the case of a child with an immunocompromised immune system who presented with non-resolving skin lesions.

Case presentation:

A 9-year-old girl was referred from a regional hospital to our tertiary level dermatology unit with a one month history of non-healing facial nodules and ulcers that were unresponsive to treatment with broad spectrum intravenous and oral antibiotic therapy.

Three months prior, the patient was admitted to the regional hospital with pneumonia and seizures. A diagnosis of infection with the human immunodeficiency virus (HIV) was confirmed with a positive HIV-1/2 ELISA. The cluster of differentiation (CD4) T cell count at presentation was 3 cells/uL. Investigations for pulmonary tuberculosis were negative (GeneXpert, auramine and culture); serum cryptococcal latex agglutination test (CLAT) was also negative. She had an elevated cytomegalovirus viral load (CMV VL) of 10 583 IU/ml (log 4). Intravenous gancyclovir was administered for the treatment of CMV-associated

pneumonitis and antiretroviral therapy (ART) was commenced (abacavir, lamivudine and efavirenz). Efavirenz was subsequently changed to dolutegravir in accordance with the South African National Department of Health treatment of HIV guidelines⁶.

She was referred to the dermatology clinic at our tertiary level hospital for facial skin lesions that had appeared approximately three months after ART initiation. At initial presentation, the skin lesions were assessed to be erythematous papules with central umbilication; nodules with central necrosis; and crusted pus-filled plaques on the face located centrally over nose and the nasal bridge predominantly. The papules with central umbilication resembled large molluscum contagiosum. Similar lesions were also seen on the scalp, neck and arms, **Figure 1a**. The patient at this time was virologically suppressed with an HIV viral load (VL) of 40 copies/mL and an improved CD4 T-cell count of 276 cells/uL. Previous use of broad-spectrum antibiotics resulted in no improvement of the lesions. Deep fungal infection or cutaneous tuberculosis was considered in the differential diagnoses. A biopsy of the facial lesions was taken.



Figure 1: a – Pre-treatment, b – after 1 week of Amphotericin B, c - 6 months on itraconazole (photographs used with consent of the child's parent)

Histology of the biopsied facial lesions showed ulceration and non-necrotizing granulomatous inflammation involving the superficial and deep dermis. The periodic acid-schiff (PAS) stain was negative for fungal elements and on the Grocott stain, a single yeast was seen. Culture of the biopsy was negative for a fungus. The biopsy sample was referred to the National Institute of Communicable diseases (NICD), a reference laboratory in Johannesburg, South Africa where a polymerase chain reaction (PCR) assay test was positive for *Histoplasmosis* / *Emergomycosis* species. This investigational assay targets the mitochondrial small-subunit gene in the fungal DNA. A normal chest x-ray and abdominal ultrasound excluded internal organ involvement.

A presumptive diagnosis of cutaneous histoplasmosis was therefore made.

Intravenous (IV) amphotericin B was commenced while awaiting the biopsy results and **Figure 1b** shows improvement after seven days on treatment. The facial lesions became less pustular and nodular. As a result of the rapid improvement of the skin lesions, oral itraconazole was commenced after one week of IV therapy. This will be continued to complete a minimum of 12 months of therapy and allow for further immune reconstitution. **Figure 1c** shows the patient having completed 6 months on itraconazole and continuation of ART. There is unfortunately considerable scarring of the face from the healing lesions.

Discussion

The World Health Organization (WHO) has included the deep mycoses in its list of neglected tropical diseases of which histoplasmosis is an example. In a recent review of childhood histoplasmosis in Africa, only 44 cases, with a median age of 9 years (range: 1-17 years), were described from across the continent over a 70-year period⁷. Similarly, low numbers were described in a global review of paediatric histoplasmosis (83 cases from 2000 to 2019) with most cases reported from the USA³. Co-infection with HIV was found in 6.8% (3/44) of cases in Africa.

The clinical manifestations of *H.capsulatum*, namely pulmonary disease, disseminated disease, extrapulmonary manifestations involving the skin, abscesses, bone and joint as well as generalised lymphadenopathy are not dissimilar to other more commonly diagnosed disease processes like tuberculosis and malignancies. Symptoms can be non-specific. It is therefore not uncommon for the diagnosis of histoplasmosis to be delayed or misdiagnosed leading to increased mortality^{3,7}. Co-infection with tuberculosis also occurs although not as commonly in children⁷. Skin manifestations have been described in infection with *H.capsulatum* var *duboisii*. Localised lesions include swellings, papules, superficial abscesses and ulcers like in our patient. The cutaneous lesions can progress to involve bony structures⁷.

The gold standard for the diagnosis of histoplasmosis is microbiological evidence of the yeast form of the organism from blood, bone marrow aspirate, sputum or tissue biopsy samples. The WHO recommends the use of antigen tests (sensitivity 95%, specificity 97%) for the diagnosis of disseminated histoplasmosis in adults infected with HIV⁸. Other clinical entities of histoplasmosis require additional investigations such as culture, histopathological analysis or antibody testing. Molecular testing is available but there is a lack of consensus on the technique and availability of services^{3,8}.

Liposomal amphotericin B for two weeks is recommended for the first one to two weeks of the therapy depending on clinical response. If not available, deoxycholate amphotericin B is an alternative. Side effects of the drug include infusion-related toxicity, nephrotoxicity (less so with liposomal amphotericin B), electrolyte abnormalities and anaemia. The induction phase is followed by a maintenance phase using itraconazole to complete at least 12 weeks⁹. In patients with disseminated histoplasmosis and those who are immunocompromised particularly with HIV infection, the maintenance phase is prolonged to 12 months^{8,9}. Where possible, blood levels of itraconazole should be obtained to ensure adequate drug exposure.

Our patient presented three months after commencing ART and there was virological suppression with some recovery of the CD4 count at the time. This patient may possibly have had a case of unmasking immune reconstitution

inflammatory syndrome (IRIS) associated with histoplasmosis. In a French Guiana study among adults living with HIV, the rate of IRIS associated with histoplasmosis was shown to be low at 0.74 cases per 1000 HIV-infected person years. The median time to IRIS symptoms following ART initiation was 11 days (range 7-40) although the literature review revealed a median time of 51 days (range 21-69)¹⁰.

In conclusion, histoplasmosis may be underdiagnosed in children and should be considered if there is not the expected response to therapy for the more commonly diagnosed conditions like tuberculosis.

Ethical considerations

Informed written consent was obtained from the parent of the child for the use of photographs. Ethics approval was obtained from the Frere and Cecelia Makiwane Hospitals Research Ethics Committee (FCMHREC/A0101/2021).

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AIDS CHOLANGIOPATHY: A CASE REPORT AND REVIEW OF RELEVANT LITERATURE

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Abstract

AIDS cholangiopathy is a syndrome that occurs in HIV/AIDS with advanced immunosuppression. It is characterized by obstruction of the biliary tree by opportunistic infection and may have complications including hepatic failure. Patients with this condition may have increased risk of poor outcome from opportunistic infection. Antiretroviral therapy is key to preventing this condition. Due to the paucity of literature on childhood AIDS cholangiopathy with the advent of antiretroviral therapy, a case of AIDS cholangiopathy is described and relevant literature is reviewed.

Background

Hepatobiliary disease in HIV infection is common, occurring in more than half of patients with HIV infection.^{1,2} This may occur due to direct effects of HIV itself, opportunistic infection in immunosuppressed persons, co-infection with hepatitis B or C, HIV-related malignancies, antiretroviral medications or medications used to treat associated opportunistic infection. One pathology observed in patients with advanced immunosuppression is AIDS cholangiopathy. This is a syndrome characterized by biliary tree obstruction and associated liver injury. In the pre-antiretroviral therapy era, this was present in about 26-46% of patients with AIDS.¹ Many cases have been reported in adults since the first published case in 1983,³ but remarkably less literature exists for paediatric cases. This condition follows biliary tree infection and inflammation from opportunistic infection, mostly *Cryptosporidium parvum*, *Cytomegalovirus* (CMV), *Histoplasma capsulatum*, *Microsporidia* and in some cases *Mycobacterium avium complex*.^{1,4} Chronic inflammation from these agents may lead to biliary tract strictures followed by cholestasis. CMV may also lead to vascular injury causing ischaemia of the biliary tree.

Typical symptoms on presentation are right upper quadrant pain, fever and diarrhoea. Less common signs and symptoms include jaundice and vomiting. This typically presents in patients with an absolute CD4 count <100 cells/uL.^{5,6} The signs and symptoms may overlap with those of multiple pathologies in advanced HIV/AIDS.

With the advent of antiretroviral therapy, the occurrence of AIDS cholangiopathy has decreased.^{5,7} Most of the literature on this pathology is in adults, hence there is a dearth in knowledge of this syndrome for children with HIV infection. In this report a paediatric case is described and relevant literature reviewed.

Case report

An eight-year-old boy was hospitalized at a tertiary hospital in Malawi with a five-day history of right upper quadrant abdominal pain, vomiting, diarrhoea and fever. There was no haematemesis. A fortnight prior to this he had been discharged from hospital where he was hospitalized with diagnoses of severe malaria and presumed sepsis. On this prior hospitalization he was identified as a patient with HIV infection who had defaulted antiretroviral therapy (ART) and

treatment for possible tuberculosis (TB) two years prior. On discharge from hospital, TB treatment and ART were recommenced.

Physical examination on rehospitalization revealed jaundice, fever, right upper quadrant abdominal tenderness and hepatosplenomegaly. There were no signs of increased effort of breathing or any features of respiratory failure. Due to concerns of drug induced hepatitis from ART and TB treatment, these medications were halted. Abdominal ultrasound revealed hepatosplenomegaly, mild ascites and thickened common bile duct and gall bladder wall with gall sludge but no dilatation of extrahepatic or intrahepatic ducts. Broad spectrum antibiotics were administered due to differential diagnosis of sepsis and possible cholangitis.

The full blood count showed a haemoglobin of 4.4g/dL, MCV 77.9 fL (71-95), a white cell count of 14,300 cells/uL and a platelet count of 95,000 cells/uL. A blood transfusion was administered for the anaemia. Hepatitis B and Hepatitis C serological tests were negative. The liver function chemistry tests are reported in Table 1. The trend of initial and follow up liver function tests is shown in table 1, with a trend reflecting cholestatic liver disease. Serum renal function chemistry tests were normal on hospitalization.

Table 1: Liver function tests results

Date (DD/MM)	15/09	20/09	26/09
ALP (42-98 u/L)	215.7	460	495
GGT (8-78 u/L)	41.7	233	291.5
TB (<2.0 mg/dL)	4.8	22.5	25.7
DB (0.2-0.5 mg/dL)	3.7	-	16.3
AST (≤ 35 u/L)	122.4	-	24.1
ALT (≤ 45 u/L)	23	-	7.8
Albumin (3.9-5.0mg/dL)	1.9	1.6	1.8

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; DB, direct bilirubin; GGT, gamma-glutamyl transferase; TB, total bilirubin

With an assessment of obstructed jaundice, a repeat abdominal ultrasound was performed with reported findings similar to the initial scan. In the second week of hospitalization, he developed increased effort of breathing requiring administration of oxygen via nasal prongs to maintain optimal peripheral oxyhaemoglobin saturation. The patient had a clinical course of progressive signs and symptoms of jaundice, right upper quadrant pain, fever and development of oedema. In week two of hospitalization, with increasing features of cholestatic liver disease and having previously defaulted ART, AIDS cholangiopathy was suggested as a diagnosis.

Due to the worsening abdominal pain, non-steroidal anti-inflammatory medications were commenced. Clinically the jaundice abdominal pain and oedema continued to worsen accompanied by the development of acute renal failure (Urea 234 mg/dL (20-40)). A clinical diagnosis of hepatorenal syndrome was made. The patient eventually died following the development of respiratory failure, confusion and progressive depression in level of consciousness. At the time of death neither TB treatment nor ART had been recommenced. The patient died within week two of hospital stay prior to performing microbiological tests for common causes of AIDS cholangiopathy. An autopsy was not performed, and the patient died within two days of the clinical diagnosis of AIDS cholangiopathy.

Discussion

Hepatobiliary disease is common in HIV/AIDS.² One such disease is AIDS cholangiopathy. This occurs in cases of advanced HIV/AIDS immunosuppression and is associated with opportunistic infections of the gastrointestinal tract,¹ most notably *Cryptosporidium parvum* and CMV.^{5,7} Chronic inflammation, epithelial apoptosis, opportunistic infection related dysfunction of the sphincter of oddi and ischaemic injury results in biliary tree strictures in turn leading to biliary obstruction and cholestatic liver damage and failure.^{1,5} Long-term biliary epithelial inflammation may lead to dysplastic changes. AIDS cholangiopathy patients have increased risk of morbidity and mortality due to associated opportunistic infections and liver failure.

A diagnostic approach towards AIDS cholangiopathy is based on clinical suspicion, deranged serum liver function tests reflecting cholestatic liver disease chemistry tests and imaging.^{1,5} Imaging modalities to reflect features of this pathology include ultrasonography, computerized tomography (CT), endoscopic retrograde cholangiopancreatography (ERCP) and magnetic resonance cholangiopancreatography (MRCP). These imaging investigations may reveal patterns of multifocal strictures and segmental dilatation of the biliary tree with patterns that may further be categorized into papillary stenosis, intrahepatic and/or extrahepatic sclerosing cholangitis or common bile duct stricture.⁵ The spectrum of AIDS cholangiopathy ranges from asymptomatic to symptomatic cases. The symptoms of severe abdominal pain are typically associated with papillary necrosis whilst mild to moderate abdominal pain occurs with sclerosing cholangitis.^{5,8}

Our case patient had clinical features of right upper quadrant abdominal pains, fever and vomiting in the context of advanced HIV/AIDS secondary to defaulting ART. In the advent of ART, cases of AIDS cholangiopathy are seen in cases of poor ART adherence, ART resistance or ART naïve patients.¹ Laboratory investigations reflected cholestatic disease, whilst abdominal ultrasound imaging did not reveal the typical features of this pathology. Ultrasound is typically recommended as the first line imaging modality to identify any abnormalities. CT abdomen was not possible for this patient due to CT equipment failure at that time. MRCP and ERCP imaging of the biliary tree is not available at the facility where the patient was hospitalized hence this was a limitation in the assessment of this patient. However the clinical and laboratory test results were suggestive of AIDS cholangiopathy.

AIDS cholangiopathy has limited therapeutic success with medical therapy. Treatment for *Cryptosporidium parvum*, CMV or other opportunistic aetiological agents has limited to no effect on this condition.⁵ Surgical interventions such as endoscopic sphincterotomy have been reported to decrease pain and reduce biliary dilatation. Unfortunately, such surgical interventions are seldomly available in low income and medium income countries which simultaneously have high HIV infection rates. Ursodeoxycholic acid is recommended for improving symptoms and liver function test derangements in cases with intrahepatic cholestasis.¹ The key medications demonstrated to prevent and reduce the clinical picture of AIDS cholangiopathy is ART. Despite reducing clinical and laboratory features of disease, ART does not reverse sclerosing cholangitis that has already developed.

AIDS cholangiopathy is associated with high mortality.¹ This may be due to cholestatic liver failure or the co-existence of opportunistic infections in advanced HIV/AIDS. With biliary obstruction superimposed bacterial cholangitis may develop.⁹ In this patient, sepsis or other opportunistic

infections possibly led to the decompensation and demise. Possible sepsis and/or the administration non-steroidal anti-inflammatory medications may have contributed to the in hospital development of hepatorenal syndrome, a challenging complication with high morbidity and mortality rates which may be triggered by intravascular volume contraction, sepsis and nephrotoxic medications.¹⁰

AIDS cholangiopathy is challenging pathology developing in advanced HIV/AIDS immunosuppression secondary to opportunistic infection in the hepatobiliary tree. Recognition of this condition in ART naïve or poorly ART adherent HIV infected patients is prudent. With limited chance of improving outcome of this by treating associated opportunistic infections, early ART commencement and adherence remain key in preventing morbidity and mortality in patients with AIDS cholangiopathy and other hepatobiliary diseases in HIV/AIDS.

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PUBLICATION WATCH

THE DURATION OF TREATMENT FOR DRUG-SUSCEPTIBLE TUBERCULOSIS: RECENT RESEARCH FINDINGS AND THEIR IMPLICATIONS FOR PAEDIATRIC PRACTICE

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The aims of this mini-review were to summarise the findings of clinical trials that have explored shortening the duration of treatment of drug-susceptible tuberculosis (TB), and the implications of this body of research for paediatric clinical practice.

Adult studies

Three pivotal randomised clinical trials published in 2014 tested whether the existing 6-month regimen for treating drug-susceptible pulmonary tuberculosis (PTB) in adult patients aged 18 years and older can be replaced with a shorter regimen. Four 4-month, fluoroquinolone containing regimens were evaluated in these trials. Unfortunately, these 4-month regimens were shown to be inferior to the existing 6-month regimen.¹⁻³

A patient-level pooled re-analysis of data from the three trials showed that despite not achieving non-inferiority, approximately 80% of patients treated with any of the 4-month fluoroquinolone-containing regimens were cured. In participants assigned to the 4-month experimental regimens, baseline smear grade of 3+ relative to negative and HIV infection were the two most important baseline risk factors for unfavourable outcome. However, when on-treatment variables were added to the risk factor analysis, non-adherence emerged as the most significant risk factor for unfavourable outcome. Similarly, in participants who received the 6-month control regimen, HIV infection was the most significant baseline risk factor for unfavourable outcome and non-adherence was the most significant on-treatment risk factor for unfavourable outcome.

Furthermore, in participants with a minimal disease phenotype, defined as a sputum smear positivity grade of <2+ or non-cavitary disease (47% of the study population), the 4-month regimens were shown to be non-inferior to the standard 6-month control regimen, suggesting that patients presenting with this phenotype can be cured with a four-month regimen. Conversely, in those with a hard-to-treat phenotype defined as 3+ smear and cavitary disease (34% of the study population) the 4-month regimens were inferior. Taken together, these results suggested that a stratified approach to the treatment of drug-susceptible PTB in adult patients should be explored as a 4-month treatment regimen could be effective for a sizeable proportion of adults with PTB.⁴

A more recent open-label, phase 3, non-inferiority trial conducted in adolescents and adults with drug-susceptible PTB, 12 years of age and older, compared two, 4-month treatment regimens with the standard 6-month regimen for adolescents and adults. The two experimental regimens were (1) a rifapentine regimen in which rifapentine replaced rifampicin, the intensive phase comprised four drugs administered over a 2-month period, and the continuation phase comprised 2 drugs administered for a further 2 months, and (2) a rifapentine-moxifloxacin regimen in which rifapentine replaced rifampicin, moxifloxacin replaced ethambutol, the intensive phase comprised four drugs (rifapentine, isoniazid, pyrazinamide and moxifloxacin) administered for two months, and the continuation phase comprised three drugs (isoniazid, rifapentine and moxifloxacin) administered for an additional two months. Non-inferiority was confirmed in the comparison of the rifapentine-moxifloxacin and control regimens. However, the rifapentine regimen was shown to be inferior to the control regimen. Of interest is that 73% of the more than 2300 participants had cavities on chest radiograph. These results showed that the 4-month rifapentine-moxifloxacin regimen is as effective as the standard 6-month regimen and suggest that this four-month rifapentine-moxifloxacin regimen can be used in the treatment of both non-severe and severe PTB in adolescents and adults.⁵

Findings of a recently published paediatric trial

An open-label, non-inferiority trial that was conducted in three African countries randomly assigned more than 1200 children less than 16 years of age with symptomatic non-severe tuberculosis, to 4 months or 6 months of standard first-line antituberculosis treatment. Non-severe or minimal TB included (1) extra-thoracic lymph node TB, (2) intra-thoracic uncomplicated (hilar) lymph node TB, (3) minimal or no parenchymal abnormality on chest radiograph and (4) smear-negative on gastric aspirate or other respiratory sample. Patients with cavitary TB, miliary TB, significant airway obstruction, complex pleural effusion, and other forms of extra-pulmonary TB were excluded. The primary outcome was unfavourable status by 72 weeks, defined as a composite of TB events (treatment failure, anti-tuberculosis treatment drug change or restart and TB recurrence), loss-to-follow-up during treatment, or death from any cause. For more information on the methodology of the trial, consult the protocol and trial publications.^{6,7}

In the primary analysis, the 4-month treatment regimen was shown to be non-inferior to the standard 6-month regimen. All secondary analyses were consistent with the primary analysis. Furthermore, the primary safety outcome (adverse events of grade 3 or higher during treatment up to 30 days after treatment) yielded similar incidences in the two treatment groups.⁷

In conclusion, this pivotal trial demonstrated that the duration of treatment of the majority of children with smear-negative, drug-susceptible TB can be shortened to 4 months using existing first-line anti-tuberculosis drug formulations.

Implications for paediatric practice

The World Health Organization (WHO) management guidelines published on 21 March 2022 now recommends that **children and adolescents between 3 months and 16 years of age with non-severe TB and without suspicion of multi-drug resistant / rifampicin-resistant TB should be treated with a 4-month treatment regimen comprising isoniazid, rifampicin, pyrazinamide ± ethambutol for 2 months followed by isoniazid and rifampicin for 2 months.**

Non-severe TB includes

- Peripheral lymph node TB
- Intrathoracic lymph node TB without airway compression
- Uncomplicated TB pleural effusion
- Paucibacillary, non-cavitary disease confined to one lobe of the lungs and without a military pattern

There are important considerations / precautions linked to this WHO recommendation, including:

- For **children and adolescents living with HIV infection (CALHIV)** and with non-severe TB, the sub-group analysis of data from the SHINE trial showed that the 4-month regimen was non-inferior to the 6-month regimen. However, only a small proportion of children with severe immunosuppression were included in this sub-group analysis. Thus because of the limited efficacy data, CALHIV with non-severe TB should be carefully monitored, particularly at 4 months of TB treatment, and if there is evidence of residual TB disease, the duration of TB treatment should be extended to at least 6 months.
- There were too few **children with severe acute malnutrition (SAM)** in the SHINE trial to conduct a sub-group analysis. Thus it is recommended that children with SAM and non-severe TB should receive 6 months of TB treatment.

- **Infants <3 months and/or bodyweight <3 kg** were not included in the SHINE trial. Therefore infants 0-3 months with non-severe TB should receive 6 months of TB treatment.
- **Children treated for TB in the past two years** were not eligible for inclusion in the SHINE trial. If they develop further episodes of TB, these additional episodes should be treated with a 6-month TB regimen.
- Chest radiography is required to evaluate the severity of intra-thoracic TB. In **settings without access to chest radiography**, WHO suggests that may be possible to use clinical criteria to assess eligibility for the shorter regimen, refer to the Operational Handbook on the Management of Tuberculosis in Children and Adolescents.⁹
- In children and adolescents with non-severe TB and living in **settings with high HIV prevalence and/or high prevalence of isoniazid resistance**, the intensive phase of TB treatment should include ethambutol.
- Another consideration for adolescents 12 years and older which is now conditionally recommended by WHO is the **4-month treatment regimen that consists of isoniazid, rifapentine, pyrazinamide and moxifloxacin for 2 months followed by isoniazid, rifapentine and moxifloxacin for a further 2 months**. As previously discussed, this regimen was shown to be non-inferior to the standard 6-month regimen in a recently published clinical trial.⁵

Conclusion

These developments herald the start of an interesting period for the treatment of childhood TB. National TB programmes need to decide the extent to which short-course TB treatment is implemented. Furthermore, the recently published trials on which the new WHO recommendations are based should stimulate further

research towards refining short-course TB treatment and even shorter TB treatment regimens for adults and children with drug-susceptible TB.

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