INDIAN JOURNAL OF PRACTICAL PEDIATRICS

IJPP

• **IJPP is a quarterly subscription journal of the Indian Academy of Pediatrics committed to presenting practical pediatric issues and management updates in a simple and clear manner**

• **Indexed in Excerpta Medica, CABI Publishing.**

Vol.16 No.4	**OCT.- DEC. 2014**
Dr.P.Ramachandran Editor-in-Chief	**Dr.S.Thangavelu** Executive Editor

CONTENTS

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

FOR YOUR KIND ATTENTION

* The views expressed by the authors do not necessarily reflect those of the sponsor or publisher. Although every care has been taken to ensure technical accuracy, no responsibility is accepted for errors or omissions.
* The claims of the manufacturers and efficacy of the products advertised in the journal are the responsibility of the advertiser. The journal does not own any responsibility for the guarantee of the products advertised.
* Part or whole of the material published in this issue may be reproduced with the note "Acknowledgement" to "Indian Journal of Practical Pediatrics" without prior permission.

- Editorial Board

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

INSTRUCTIONS TO AUTHORS

General

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

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

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

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

Manuscript

1st Page –

Title

Name of the author and affiliation

Institution

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

Word count

No. of figures (colour / black and white)

No. of references

Authors contribution

2nd Page –

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

3rd Page -

Acknowledgement

Points to remember (not more than 5 points)

Text

References

Tables

Legends

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

(4 x 6 inches – Maxi size) Glossy print

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

Text

Only generic names should be used

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

References

Recent and relevant references only

Strictly adhere to Vancouver style

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

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

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

Tables

Numbered with Roman numerals and typed on separate sheets.

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

Figures and legends

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

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

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

Article Categories

Review article

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

Case report (covering practical importance)

250 – 600 words, 8 – 10 recent references

Clinical spotters section

150 – 200 words write up

With 1 or 2 images of clinically recognizable condition

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

Letters to the Editor

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

Check List

Covering letter by corresponding author

Declaration (as enclosed) signed by all authors **

Manuscript (4 copies)

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

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

Author's contribution / Authorship Criteria

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

Declaration by authors

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

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

Selection procedures

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

TUBERCULOSIS

LABORATORY INVESTIGATIONS FOR THE DETECTION OF TUBERCULOSIS FROM CLINICAL SPECIMENS

***Balaji Subramanyam S**
****Uma Devi KR***

Abstract: *The occurrence and transmission of tuberculosis is a major concern worldwide. Early and accurate diagnosis followed by appropriate therapy without delay is absolutely essential to cut down the transmission and spread of the disease. This review briefly summarizes the various laboratory techniques that are available for identification and diagnosis of tuberculosis during the past and the present.*

Keywords: *M tuberculosis, Rapid diagnosis, Smear microscopy, Culture methods, Genotypic methods.*

Tuberculosis (TB) caused by Mycobacterium tuberculosis remains a major infectious disease in the world. Control of tuberculosis has become a global challenge due to the emergence of multi drug resistant (MDR) and extensively drug resistant (XDR) tuberculosis. Timely detection and identification of M. tuberculosis from the specimen forms the basis for initiation of anti-tuberculous drug therapy and thereby control the spread of TB in the community. Though the bedside decision on the initiation of anti-tuberculous drug therapy is based on epidemiologic, clinical, radiographic, and/or histological findings, it should be further supported by at least a rapid microbiological test or positive acid-fast bacilli (AFB) smear result.

Tuberculosis is diagnosed by the demonstration of M. tuberculosis in suitable clinical samples collected from patients. While other clinical investigations may suggest the diagnosis of tuberculosis they cannot be used to confirm the same. A complete evaluation for TB must include a carefully elicited medical history, physical examination, chest X-ray and microbiological examination of sputum or other appropriate samples. It always includes a tuberculin skin test and wherever indicated, surgical biopsy. Conventional smear by Ziehl-Neelsen (ZN) staining and culture on Lowenstein-Jensen medium are accepted as the gold standard for the diagnosis of tuberculosis and are still in use.

Spread of TB can be controlled by prompt and accurate diagnosis followed by proper medical intervention. When these aspects are not well supported it leads to spread of the epidemic. On the other hand, delay in the diagnosis and treatment increases the severity of the disease and is associated with higher risk of mortality and morbidity more so in HIV infected patients. This delay is also an important contributor for increased nosocomial outbreaks among patients and health care workers.

The Center for Disease Control and Prevention (CDC), USA has recommended that effort should be made by every laboratory to use the most efficient and rapid methods available for diagnosis of TB.[1] These recommendations include the use of at least one liquid medium along with a conventional solid medium for primary isolation of mycobacteria.

The current review provides insights into the mycobacteriological diagnostic methodologies available from the past to the present and also summarizes the future diagnostics in the pipeline.

Medical history and clinical examination

The medical history for the diagnosis of TB includes past history [TB, TB contact, bacillus Calmette-Guerin (BCG) immunization, HIV infection, social factors (homelessness, immigrant status)] and symptoms fever and/or cough of two or more weeks, chest pain, and hemoptysis. Systemic symptoms in children include chills, loss of appetite, loss of weight, easy fatigability and rarely night sweats and production of sputum. A physical examination is done to assess the patient's general health and to identify other factors which may affect the TB treatment plan. Medical history cannot be used independently to confirm or rule out TB.

Chest X-ray

Chest X-ray is the most common diagnostic test that leads to the suspicion of infection. In primary TB, an X-ray

* Technical Officer - A
** Scientist "D" Bacteriology Department,
National Institute of Research in Tuberculosis,
Chennai.

may show an abnormality in the mid and lower lung fields and hilar lymph nodes may be enlarged. Reactivated TB bacteria usually infiltrate the upper lobes of the lungs. Miliary tuberculosis exhibits diffuse nodules at different locations in the body. However, chest X-ray alone should neither be used to confirm TB nor to distinguish active and old disease. Studies on the usefulness of chest X-ray for early diagnosis of recurrent pulmonary TB had low sensitivity especially in non-symptomatic recurrent cases.[2]

Skin test

The Mantoux test [also known as the Tuberculin skin test (TST), Pirquet test, or purified protein derivative (PPD) test] is a diagnostic tool for TB. The Mantoux test is endorsed by the American Thoracic Society (ATS) and CDC. TST has been used for years as an aid in diagnosing latent tuberculosis infection (LTBI) and includes measurement of the delayed type hypersensitivity response, 48 to 72 hours after intradermal injection of PPD. TST is a simple and inexpensive test with medium to high sensitivity, which depends on population screening, but its specificity is low. Many studies indicate a positive relationship between positive PPD test and the risk of prospective active TB. Several studies have shown that treatment of latent tuberculosis diagnosed by PPD test reduces active TB risk by 60%-90%. BCG vaccination and infection by non-tuberculous mycobacteria (NTM) interfere with PPD test resulting in false positivity.[3]

American academy of pediatrics, CDC and ATS have stated unequivocally that "mandatory school-based tuberculin skin testing of all children is undesirable" and as it is an "ineffective method of detecting or preventing cases of childhood TB, it should be discontinued".[4]

Smear microscopy

Smear microcopy for testing the presence of tubercle bacilli in sputum samples is the only simple and rapid test available for the diagnosis of TB. Direct sputum smear microscopy is the most widely used test for the diagnosis of pulmonary TB, available in most primary health care laboratories at the health center level. The Ziehl-Neelsen (ZN) method is commonly used for staining sputum smears because of its simplicity and low cost. The majority of laboratories in low-income and middle-income countries use conventional light microscopy to examine Ziehl-Neelsen stained direct smears. ZN method is documented to be highly specific in areas with a high prevalence of TB but with varying degrees of sensitivity between 22% and 78%. In high-income countries, fluorescence microscopy using auramine phenol staining is used as the standard diagnostic method. Fluorescence microscopy (FM) is credited with increased sensitivity and lower work effort. Search of several databases and analyses of 45 relevant studies suggest that FM is more sensitive than conventional microscopy and has similar specificity.[5] A systematic review of 18 studies have suggested that the sensitivity of conventional and FM ranged from 32% to 94% and 52% to 97% respectively, in comparison with culture as reference standard.[5]

In 2009, the World Health Organization (WHO) recommended the replacement of LED microscopy in place of conventional FM, as an alternative for conventional ZN microscopy in a phased manner in both high and low volume laboratories.[6] The diagnostic performance, time and costs of LED-FM were evaluated in comparison with conventional ZN microscopy for diagnosis of pulmonary and HIV-associated tuberculosis. The study concluded that the high sensitivity of LED-FM combined with shorter reading time of sputum smear slides make this method a potential alternative to ZN microscopy.[7] In India, the services of LED-FM on sputum smear positive case detection under program conditions was assessed and found that LED-FM can significantly increase the proportion of smear positive cases among presumptive TB patients under routine program conditions in high workload laboratories.[8]

Culture on solid medium

Culturing of M. tuberculosis on media is more sensitive than sputum smear microscopy. Sputum smear microscopy requires approximately 5000 to 10000 acid fast bacilli (AFB) per ml of sputum while culture system can detect as few as 10 to 100 viable AFB per ml of sputum.[6] Lowenstein Jensen (LJ), an egg-based medium, is a special growth medium used for the culture of mycobacteria especially M. tuberculosis. It can be prepared locally and has long shelf life if stored appropriately. Middlebrook 7H10 medium is an agar-based medium also in use for the cultivation of M. tuberculosis. The organism grows as small and buff-colored colonies in both media. It takes 4-8 weeks to get visual colonies on either type of media due to slow doubling time of M. tuberculosis. Both these media can be used for the primary isolation, antibiotic susceptibility studies and differentiation of mycobacterial species.

The LJ medium is supplemented with egg albumin to enhance the growth of M. tuberculosis and malachite green to suppress the growth of non-mycobacterial contaminants while the Middlebrook medium is supplemented with bovine serum albumin for the former and antibiotic combination polymyxin B, amphotericin B, nalidixic acid, trimethoprim and azlocillin (PANTA) or PACT (Polymixin B, amphotericin B, carbenicilin, trimethoprim) for the latter.

Kirchner's medium

The selective Kirchner's liquid medium is recommended for the culture of specimens other than sputum for mycobacteria. The medium is formulated with basic nutrients and 10% calf serum. The medium is made selective for mycobacteria by the addition of PACT to control the overgrowth of normal flora in the specimens. Vancomycin was used in Kirchner's medium to control contaminants for culturing tubercle bacilli from gastric lavage. The use of the selective Kirchner's media along with LJ slopes increased the yield of specimens with cultures of tubercle bacilli and decreased the rate of contamination.[9] This medium can be used along with conventional solid medium where the number of viable mycobacteria present in the original specimen is very low. It cannot be used to replace any other existing methods. Kirchner's medium is also used as the transport medium to transport specimens to a central laboratory at ambient temperature without any loss of viability.

BACTEC 460 system

The first liquid-based method introduced for the detection and drug susceptibility testing of mycobacteria is BACTEC 460 system (Becton Dickinson). The system is specific for mycobacterial growth, wherein 14C labeled palmitic acid in 7H12 media is used. When the 14C labeled substrate present in the medium is metabolized by mycobacteria, 14CO2 is released and accumulated in the BACTEC vials. The presence of free 14CO2 in the vial is measured by BACTEC system and reported in terms of growth index (GI). Mycobacteria in clinical specimens can be detected in half the time compared to conventional culture methods.[10] The system was evaluated at different settings and its effectiveness in detecting tubercle bacilli over conventional methodologies was proved.[11] Use of radio labeled carbon in the medium and its further issues with proper waste management necessitated the withdrawal of the methodology by the manufacturers.

BACTEC MGIT 960 system

BACTEC MGIT 960 (Becton Dickinson) is now widely accepted as the gold standard for the primary isolation as well as for the drug susceptibility testing of M. tuberculosis. It is a fully automated, non-radiometric and non-invasive system. The system includes a modified 7H9 broth, a growth supplement [(Middlebrook Oleic Albumin Dextrose Catalase (OADC)] and antibiotic mixture (PANTA). PANTA is used to suppress the growth of contaminating bacteria. A fluorescent compound embedded in silicon is at the bottom of each MGIT tube, which is sensitive to the presence of oxygen dissolved in the broth. Initially the large amount of dissolved oxygen quenches the compound and only little fluorescence can be detected. Later, actively growing cells consuming the oxygen allow the compound to fluoresce. The changes in the fluorescence is detected by the system and reported in terms of growth unit (GU).[17]

Decreased time to detection, greater sensitivity than LJ media, comparable sensitivity to the radiometric BACTEC 460 system in detecting mycobacteria in clinical specimens, and good concordance with both LJ and Bactec 460 drug susceptibility testing (DST) for first-line drugs (FLD) have been demonstrated in several studies to support BACTEC MGIT 960 system.[18]

Higher rate of contamination is reported in MGIT 960 system than BACTEC 460 as observed in most of the studies.[11] The reason for higher contamination rate is attributed to the presence of rich protein in MGIT 960 medium, the percentage of NaOH used to decontaminate sputum specimens and climate condition and delay in transport of specimens to the laboratory. The high contamination rate for MGIT 960 system resulting in lower recovery rate of M. tuberculosis is also reported.[19] Whyte et al. reported that the performance of MGIT 960 system in terms of isolation of mycobacteria is not superior to the BACTEC 460 system and that the high contamination of MGIT 960 remains a significant problem. Other culture systems available are summarized in Table I.

Microscopic observation drug susceptibility (MODS) assay

MODS is a manual liquid culture method that uses as inverted light microscope for the detection of characteristic M. tuberculosis morphology in medium in sealed, multiwell plates.[20] The characteristic cord formation by M. tuberculosis complex is used for the detection and the approach can be used for the direct susceptibility testing of isoniazid and rifampicin to M. tuberculosis.

Thin layer agar (TLA) method

TLA is a solid agar based method which microscopically detects the growth of mycobacteria in clinical specimens. Enriched Middlebrook 7H11 medium is employed for the growth of mycobacteria. The method allows the detection of mycobacteria within 9-14 days and also allows the initial identification of M. tuberculosis on the basis of its colony morphology. Incorporation of para-nitrobenzoic acid with media helps the identification of M. tuberculosis complex whereas incorporation of isoniazid and rifampicin helps the detection of MDR-TB directly from the specimens.[21]

Table I. Other culture systems

Name	Principle	Advantage
MB/BacT (BacT/Alert)[12]	Carbon dioxide released into the medium by actively growing mycobacteria is detected through a gas-permeable sensor containing a colorimetric indicator embedded at the bottom of culture vials.	Non-radiometric, fully automated, continuous monitoring, walk away system
VersaTREK[13]	Detects mycobacterial growth by monitoring the rate of oxygen consumption within the head space of the culture container	Significantly reduces the time to detection of mycobacteria compared to LJ medium
ESP culture system II[14]	Based on detection of pressure changes within the headspace above the broth culture medium in a sealed bottle, i.e., either gas production or gas consumption due to microbial growth	Fully automated, continuously monitoring system
MB Redox system[15]	Has invisible tetrazolium salt which appears as red-to-violet particles when reduced by the growth of mycobacteria	Combining a liquid medium and a redox indicator which enables an easy macroscopic vision of growth
BACTEC 9000 MB[16]	Uses an oxygen-quenched fluorescence indicator for the rapid detection of mycobacteria. The fluorescence of the sensor is a function of the oxygen depletion that results during microbial metabolism.	Fully automated, non-radiometric, fluorescent based method

Table II. Genotypic Methods - nucleic acid amplification (NAA) tests

Name	Principle	Advantage
Amplicor PCR[25]	Amplifies a portion of the 16S rRNA gene that contains a sequence that hybridizes with an oligonucleotide probe specific for M. Tb	More sensitive than smears and radiometric culture for rapid and highly specific detection of TBM
Amplified MTD[26]	Combines isothermal transcription-mediated amplification of a portion of the 16S rRNA with a detection method that uses a hybridization probe specific for M. Tb	Speeding up of TB diagnostic as results can be obtained within six hours
BD ProbeTec[27]	Strand-displacement amplification technique	Positive predictive value (PPV), negative predictive value (NPV), sensitivity and specificity were 97%, 90%, 92.7% and 96.0% respectively.
Genotype[28] Mycobacteria Direct	23S rRNA amplification-based detection of MTB	Detects Mycobacterium tuberculosis and four atypical mycobacterium species in one assay and from same clinical sample
Loop-mediated isothermal amplification[29]	Detection of trace amounts of DNA under specific isothermal conditions	More sensitive than culture for detection of M. Tb. Sophisticated instrumentation is not required.

Nitrate reductase assay (NRA)

The nitrate reductase assay is also known as the Griess method in which M. tuberculosis can be detected based on the capacity of M. tuberculosis to reduce nitrate to nitrite. NRA can be done either on solid or liquid media. By incorporating potassium or sodium nitrate in to the medium which will be reduced to nitrite by actively growing M. tuberculosis; the reaction can be further visualized upon addition of the Griess reagent which produced a pink-purple color during the assay.[22] The assay can also be used for direct detection of drug susceptibility testing of M. tuberculosis to isoniazid and rifampicin and for second line anti-TB drugs.

Mycobacteriophage-based methods

Phage-based methods have been developed for the detection and drug susceptibility testing of M. tuberculosis.[23] Mycobacteriophages are used in two different diagnostic methods, the luciferase reporter phage (LRP) assay and the FAST Plaque TB assay. LRPs are genetically engineered phages harboring the fflux reporter gene, which codes for firefly luciferase, which in turn catalyses a reaction that releases light in the presence of luciferin and ATP. LRPs are able to infect, replicate, and express the fflux gene only within viable mycobacterial cells. Luciferase activity can then be detected only if cellular ATP is present with the help of substrate luciferin (added externally), allowing the detection of M. tuberculosis in clinical samples. The FAST Plaque TB test employs the capability of the phages to infect, replicate and release progeny virions which are picked up by secondary host viz. M. smegmatis. Plaque formation on the lawn of secondary hosts reflects the presence of viable cells in the original sample.[24]

Genotypic Methods

Line probe assay (LPA)

The assay allows the molecular identification of the M. tuberculosis complex and its associated genotypic susceptibilities to rifampicin and isoniazid. This assay can be applied for smear-positive patient specimens, primary culture isolates either on solid or liquid media and NaOH-NALC decontaminated specimens. The use of LPA may eliminate the diagnostic delay associated with phenotypic conventional drug susceptibility of M. tuberculosis complex. The performance of the assay was evaluated with smear-positive specimens and found to have 98.9% and 94.7% sensitivity to rifampicin and isoniazid respectively, and 98.8% of sensitivity for the detection of MDR-TB.[30] A meta analysis of the assay has identified a pooled sensitivity of 98.1% and specificity of 98.7% for rifampicin resistance and 84.3% of sensitivity and 99.5 of specificity for isoniazid.

Gene Xpert

It is a single-tube, molecular beacon--based, real-time PCR Xpert MTB assay (Xpert® MTB/RIF) for the detection of rifampicin-resistant M. tuberculosis.[6] The system allows simultaneous detection of both M. tuberculosis and rifampicin resistance. The system is exceptionally sensitive for the detection of M. tuberculosis even in smear negative specimens. The result is made available in two hours and requires no instrumentation other than the GeneXpert® System. In 2010, WHO endorsed the use of this assay as an initial diagnostic test for suspected cases of MDR-TB or HIV-TB and as a follow-up test for microscopy on AFB smear-negative suspects in settings where MDR-TB or HIV is a lesser concern.[6] Other genotypic methods are given in Table II.

Interferon-gamma release assay (IGRA)

The development of IGRAs is an important advance in the diagnosis of latent tuberculosis infection (LTBI). IGRAs are in vitro blood tests of cell-mediated immune response; they measure T cell release of interferon (IFN)-gamma following stimulation by antigens unique to M. tuberculosis. IGRA can be a surrogate marker of M. tuberculosis infection and indicate a cellular immune response to M. tuberculosis. IGRAs cannot distinguish between latent infection and active tuberculosis (TB) disease and should not be used for diagnosis of active TB, which should be done by a microbiological diagnosis. A positive IGRA result may not necessarily indicate active TB, and a negative IGRA result may not rule out active TB.[31] As IGRAs are not affected by Bacille Calmette-Guérin (BCG) vaccination status, these assays are useful for evaluation of LTBI in BCG-vaccinated individuals, particularly in settings where BCG vaccination is administered after infancy or when multiple (booster) BCG vaccinations are given.

QuantiFERON®-TB test

In 2001, the QuantiFERON®-TB test (QFT) was approved by Food and Drug Administration (FDA) as an aid for detecting latent M. tuberculosis infection. This is an in vitro diagnostic aid that measures a component of cell-mediated immune reactivity to M. tuberculosis. It is based on the quantification of interferon-gamma released from sensitized lymphocytes in whole blood incubated overnight with purified protein derivative from M. tuberculosis and control antigens. In a CDC-sponsored multicenter trial, QFT and tuberculin skin test (TST) results are moderately

concordant (overall kappa (κ) value = 0.60). The level of concordance is adversely affected by prior BCG vaccination, immune reactivity to NTM and prior positive TST. Limitations of QFT include the need to draw blood and process it within 12 hours after collection. Further, the utility of QFT in predicting progression to active tuberculosis has not been evaluated. It has been suggested that the manufacturer-recommended incubation time of 16 to 24 h should be respected because prolonged incubation can cause indeterminate or false-positive results.

T SPOT TB Assay

T SPOT TB is a new commercial enzyme-linked immunospot (ELISPOT) assay used for tuberculosis diagnosis, which belongs to the group of IGRA assays. It counts number of anti-mycobacterial effector T cells, in a sample of blood. This gives an overall measurement of the host immune response against mycobacteria, which can reveal the presence of infection with M. tuberculosis. The assay was used in combination with tuberculin skin test for the diagnosis of latent TB in the presence of HIV co-infection. The sensitivity of the assay for diagnosis of tuberculosis in clinical practice and in diagnosis of pediatric tuberculosis was also assessed.[32]

Newer technologies

LAM ELISA is an immune-based assay which detects M. tuberculosis antigen, lipoarabinomannan (LAM), in urine specimens. The commercially available tests to detect LAM in urine by antigen capture ELISA were evaluated recently for the diagnosis of TB. The breath analysis using volatile markers for the diagnosis of TB is also in the process. The method seems to be non-invasive, totally painless and more agreeable to patients. The use of smell in clinical diagnosis has been rediscovered over the last few years due to major advances in odor-sensing technology and artificial intelligence. The use of immunomagnetic beads to capture bacteria in clinical specimens is in process. It requires extensive specimen processing procedures; however, the technology is more sensitive and faster for the detection of organisms. The simplified smart flow cytometry has also been demonstrated for rapid detection of active TB cases.

Advances in instrumentation and bioinformation have contributed to the successful applications of mass spectrometry (MS) for rapid and high-throughput identification and characterization of pathogens. Electrospray ionization-tandem mass spectrometry has also been successfully evaluated to detect the presence of mycolic acid specific to M. tuberculosis complex.[6]

Overall, it can be seen that the recent techniques for laboratory diagnosis of tuberculosis are improving with increased sensitivity and specificity. Newer diagnostic methods are coming up which are more rapid and highly specific for the detection of TB. However there is still room for further development of diagnostic methodologies for tuberculosis especially for extrapulmonary case detection and diagnosis of childhood tuberculosis.

Points to Remember

- ***Tuberculosis (TB) which is caused by Mycobacterium tuberculosis, still remains a major infectious disease in developing countries.***
- ***Drug resistant TB and HIV-TB co-infection are the major hurdles to control TB in the community.***
- ***Lab investigation for TB must include a microbiological examination of sputum or other appropriate samples.***
- ***Sputum smear by Ziehl-Neelson staining and culture on Lowenstein-Jensen medium are accepted as the gold standard for the diagnosis of TB and are still in use.***
- ***Growing M. tuberculosis in liquid medium is faster than on solid LJ medium.***
- ***Genotypic methods for detection of drug resistance in M. tuberculosis are recommended by World Health Organization for patient management.***
- ***Newer technologies for rapid detection of TB are in pipeline.***

References

1. Kent PT, Kubica GP. 1985. Public Health Mycobacteriology; A Guide for the Level III Laboratory, US Department of Health and Human Services, Public Health Service/Centers for Disease Control Atlanta, GA 30333.
2. Ito K. Limits of chest X-ray investigation in the diagnosis of recurrent pulmonary tuberculosis. Kekkaku (Japanese) 2005; 80(7): 521-526.
3. Poorhasan AM, Haghdoost, Mashrabi O. Comparison of tuberculin skin test and interferon gamma assay for the diagnosis latent tuberculosis. Am J Infect Dis 2010; 6: 50-53.
4. Starke JR. Tuberculosis skin testing: new schools of thought. Pediatrics. 1996; 98(1):123-125.
5. Steingart KR, Henry M, Ng V, Hopewell PC, Ramsay A, Cunningham J, et al. Fluorescence versus conventional sputum smear microscopy for tuberculosis: a systematic review. Lancet Infect Dis 2006; 6(9):570-581.

6. Parsons LM, Somoskovi A, Gutierrez C, Lee E, Paramasivan CN, Abimiku A, et al. Laboratory diagnosis of tuberculosis in resource-poor countries: challenges and opportunities. Clin Microbiol Rev 2011; 24(2):314-350.
7. Chaidir L, Parwati I, Annisa J, Muhsinin S, Meilana I, Alisjahbana B, et al. Implementation of LED fluorescence microscopy for diagnosis of pulmonary and HIV-associated tuberculosis in a hospital setting in Indonesia. PLoS One 2013; 8(4):e61727.
8. Reza LW, Satyanarayna S, Enarson DA, Kumar AM, Sagili K, Kumar S, et al. LED-fluorescence microscopy for diagnosis of pulmonary tuberculosis under programmatic conditions in India. PLoS One 2013; 8(10):e75566.
9. Mitchison DA, Allen BW, Manickavasagar D. Selective Kirchner medium in the culture of specimens other than sputum for mycobacteria. J Clin Pathol 1983; 36 (12): 1357-1361.
10. Siddiqi SH, Libonati JP, Middlebrook G. Evaluation of rapid radiometric method for drug susceptibility testing of Mycobacterium tuberculosis. J Clin Microbiol 1981; 13(5): 908-912.
11. Rodrigues CS, Shenai SV, Almeida D, Sadani MA, Goyal N, Vadher C, et al. Use of bactec 460 TB system in the diagnosis of tuberculosis. Indian J Med Microbiol. 2007; 25(1):32-36.
12. Scarparo C, Piccoli P, Rigon A, Ruggiero G, Nista D, Piersimoni C. Direct identification of mycobacteria from MB/BacT alert 3D bottles: comparative evaluation of two commercial probe assays. J Clin Microbiol 2001; 39(9): 3222-3227.
13. Falconi FQ, Suarez LI, Lopez Mde J, Sancho CG. Comparison of the VersaTREK system and Lowenstein-Jensen medium for the recovery of mycobacteria from clinical specimens. Scand J Infect Dis 2008;40(1):49-53.
14. Woods GL, Fish G, Plaunt M, Murphy T. Clinical evaluation of difco ESP culture system II for growth and detection of mycobacteria. J Clin Microbiol 1997; 35(1):121-124.
15. Cambau E, Wichlacz C, Truffot-Pernot C, Jarlier V. Evaluation of the new MB redox system for detection of growth of mycobacteria. J Clin Microbiol 1999; 37(6): 2013-2015.
16. Zanetti S, Ardito F, Sechi L, Sanguinetti M, Molicotti P, Delogu G, et al. Evaluation of a nonradiometric system (BACTEC 9000 MB) for detection of mycobacteria in human clinical samples. J Clin Microbiol 1997; 35(8): 2072 - 2075.
17. Heifets L, Linder T, Sanchez T, Spencer D, Brennan J. Two liquid medium systems, mycobacteria growth indicator tube and MB redox tube, for Mycobacterium tuberculosis isolation from sputum specimens. J Clin Microbiol 2000; 38(3):1227-1230.
18. Balabanova Y, Drobniewski F, Nikolayevskyy V, Kruuner A, Malomanova N, Simak T, et al. An integrated approach to rapid diagnosis of tuberculosis and multidrug resistance using liquid culture and molecular methods in Russia. PLoS One 2009; 4(9):e7129.
19. Huang TS, Chen CS, Lee SS, Huang WK, Liu YC. Comparison of the BACTEC MGIT 960 and BACTEC 460TB systems for detection of mycobacteria in clinical specimens. Ann Clin Lab Sci 2001; 31(3):279-283.
20. Moore DA, Evans CA, Gilman RH, Caviedes L, Coronel J, Vivar A, et al. Microscopic-observation drug-susceptibility assay for the diagnosis of TB. N Engl J Med 2006; 12;355(15):1539-1550.
21. Robledo J, Mejia GI, Paniagua L, Martin A, Guzman A. Rapid detection of rifampicin and isoniazid resistance in Mycobacterium tuberculosis by the direct thin-layer agar method. Int J Tuberc Lung Dis 2008; 12(12):1482-1484.
22. Angeby KA, Klintz L, Hoffner SE. Rapid and inexpensive drug susceptibility testing of Mycobacterium tuberculosis with a nitrate reductase assay. J Clin Microbiol 2002; 40(2):553-555.
23. Carriere C, Riska PF, Zimhony O, Kriakov J, Bardarov S, Burns J, et al. Conditionally replicating luciferase reporter phages: improved sensitivity for rapid detection and assessment of drug susceptibility of Mycobacterium tuberculosis. J Clin Microbiol 1997; 35(12):3232-3239.
24. Wilson SM, al-Suwaidi Z, McNerney R, Porter J, Drobniewski F. Evaluation of a new rapid bacteriophage-based method for the drug susceptibility testing of Mycobacterium tuberculosis. Nat Med 1997; 3(4): 465 - 468.
25. D'Amato RF, Wallman AA, Hochstein LH, Colaninno PM, Scardamaglia M, Ardila E, et al. Rapid diagnosis of pulmonary tuberculosis by using Roche AMPLICOR Mycobacterium tuberculosis PCR test. J Clin Microbiol 1995; 33(7):1832-1834.
26. Putova I, Havelkova M, Svandova E. Application of the Gen-Probe amplified MTD test (Mycobacterium tuberculosis Direct Test) in the diagnostics of tuberculosis. Cent Eur J Public Health 1996; 4(2):91-95.
27. Barrett A, Magee JG, Freeman R. An evaluation of the BD ProbeTec ET system for the direct detection of Mycobacterium tuberculosis in respiratory samples. J Med Microbiol 2002; 51(10):895-898.
28. Franco-Alvarez de Luna F, Ruiz P, Gutierrez J, Casal M. Evaluation of the GenoType Mycobacteria Direct assay for detection of Mycobacterium tuberculosis complex and four atypical mycobacterial species in clinical samples. J Clin Microbiol 2006; 44(8):3025-3027.
29. Boehme CC, Nabeta P, Henostroza G, Raqib R, Rahim Z, Gerhardt M, et al. Operational feasibility of using loop-mediated isothermal amplification for diagnosis of pulmonary tuberculosis in microscopy centers of developing countries. J Clin Microbiol 2007; 45(6): 1936 - 1940.
30. Barnard M, Albert H, Coetzee G, O'Brien R, Bosman ME. Rapid molecular screening for multidrug-resistant

tuberculosis in a high-volume public health laboratory in South Africa. Am J Respir Crit Care Med 2008; 177(7): 787-792.

31. Metcalfe JZ, Everett CK, Steingart KR, Cattamanchi A, Huang L, Hopewell PC, et al. Interferon-gamma release assays for active pulmonary tuberculosis diagnosis in adults in low and middle-income countries: systematic review and meta-analysis. J Infect Dis 2011; 204 Suppl 4:S1120-1129.
32. Wang X, Wu Y, Wang M, Wang Y. The Sensitivity of T-SPOT.TB assay in diagnosis of pediatric tuberculosis. Fetal Pediatr Pathol 2014; 33(2):123-125.

CLIPPINGS

Variation in Resource Utilization for the Management of Uncomplicated Community-Acquired Pneumonia across Community and Children's Hospitals.

Objective: To describe patterns of diagnostic testing and antibiotic management of uncomplicated pneumonia in general community hospitals and children's hospitals within hospitals and to determine the association between diagnostic testing and length of hospital stay.

Methods: A retrospective cohort study of children 1-17 years of age hospitalized with the diagnosis of pneumonia from 2007 to 2010 to hospitals contributing data to Perspective Database Warehouse, assessing patterns of diagnostic testing and antibiotic management. Construction of logistic regression models of log-transformed length of stay (LOS) and grouped treatment models was done to ascertain whether performance of blood cultures and viral respiratory testing is associated with LOS.

Results: A total of 17 299 pneumonia cases occurred at 125 hospitals, with considerable variability in pneumonia management. Only 40 (0.2%) received ampicillin/penicillin G alone or in combination with other antibiotics, and 1318 (7.4%) received macrolide monotherapy as initial antibiotic management. Performance of blood culture and testing for respiratory viruses was associated with a statistically significant longer LOS, but these differences did not persist in grouped treatment models.

Conclusions: Greater rates of diagnostic testing in this cohort of structurally diverse hospitals when compared to previously reported at freestanding children's hospitals, with extremely low rates of narrow-spectrum antibiotic use. Tailored antibiotic stewardship initiatives at these hospitals are needed to achieve adherence to national guideline recommendations.

JoAnna K. Leyenaar, Tara Lagu, Meng-Shiou Shieh, Penelope S. Pekow, Peter K. Lindenauer. Variation in Resource Utilization for the Management of Uncomplicated Community-Acquired Pneumonia across Community and Children's Hospitals. J Pediatr 2014;165 (3):585-591.

NEWS AND NOTES

7th National Assembly on Pediatric Emergency Medicine (NAPEM)

An International Conference

Date: 20th to 22nd February, 2015

Contact:

Dr.K.Rajendran

Organising Secretary, NAPEM 2015

HOD, Department of Pediatrics & Neonatology,

Kovai Medical Center and Hospital,

Coimbatore - 641014, Tamil Nadu, India.

TUBERCULOSIS

NEUROTUBERCULOSIS

Anoop Verma

Abstract: *The most devastating form of tuberculosis is involvement of the central nervous system in the form of meningitis. The infection reaches mostly by hematogenous route from primary focus elsewhere in the body. Small tubercles (Rich focus) in the covering of brain may remain dormant for years, wait for favorable stimulus to rupture for the clinical features to manifest ranging from focal deficits to cranial nerve involvement, hemiplegia, paraplegia and coma. CSF examination from routine microscopy to DNA PCR, along with neuro-imaging helps in diagnosis. HIV patients have 10%-20% more chances of infection. Four antitubercular drugs (HRZE) for 2 months followed by (HR) for 10 months is the standard treatment.*

Recent studies have shown that corticosteroids improved both survival rate and neurological outcome in patients with tuberculous meningitis. Neurosurgical options are open for developing hydrocephalus.

Keywords: *Neurotuberculosis, Tubercular meningitis, Tuberculoma, Children.*

Tuberculosis is one of the leading causes of death worldwide with one third of the world population believed to be infected with Mycobacterium tuberculosis.[1] Involvement of central nervous system is an important and serious type of extrapulmonary involvement. It has been seen that approximately 10% of all patients with tuberculosis have CNS involvement.[2] Neurotuberculosis, which affects mainly young patients, is considered the most dangerous complication as it often leads to severe neurological sequelae or death.

Epidemiology

The incidence of tuberculosis varies from 9 cases per 100,000 population per year in the US to 110-165 cases per 100, 000 population in the developing countries of Asia and Africa.[3] The incidence of CNS tuberculosis is directly proportional to the prevalence of tubercular infection in general. In developing countries CNS tuberculosis is a disease of childhood.[4] Tubercular meningitis (TBM) is the commonest form and makes up 70%-80% the cases of neurotuberculosis with a mortality of over 30%. The estimated mortality due to TBM in India is 1.5 per 100,000.[5]

Clinical spectrum of neurotuberculosis

The manifestation of neurotuberculosis is varied. The most accepted forms of the disease are shown in Table I.

Table I. Forms of neurotuberculosis[6]

Intracranial
• Tubercular meningitis (TBM)
• Tubercular encephalopathy
• Tubercular vasculopathy
• Space-occupying lesions: Tuberculoma (single or multiple), multiple small tuberculoma with miliary tuberculosis, tubercular abscess
Spinal
• Pott's spine and Pott's paraplegia
• Tubercular arachnoiditis (myeloradiculopathy)
• Non-osseous spinal tuberculoma
• Spinal meningitis

Pathogenesis

CNS tuberculosis is mainly caused by Mycobacterium tuberculosis. Less frequently, other mycobacteria such as M africanum and M bovis can contribute. Bacilli reach the brain via hematogenous route secondary to disease elsewere in the body.

The current understanding of three step process of pathogenesis is after the classic work of Rich and McCordock.[7]

1. The infection of meninges occurs by hematogenous route during the stage of bacteremia of primary tuberculous lesion or shortly afterwards. These initial

* Consultant Pediatrician,
Raipur, Chattisgarh.

lesions are called as 'Rich focus'. They are found in the meninges, subpial or subependymal surface of the brain or the spinal cord.

2. The bacteria then enter into quiescent phase, which may last from a week to many decades.
3. In the third step the mycobacteria in 'Rich focus' multiply and when a stimulus, either immune or traumatic, causes them to rupture or grow, the clinical manifestation of the disease becomes overt.

A study of immunological parameters showed a correlation between the development of tuberculous meningitis in children and significantly lower numbers of CD4 T-lymphocyte counts when compared with children who had primary pulmonary complex only.[8] The elevated level of tumour necrosis factor-alpha produced during mycobacterial infection is an important element in the immunopathogenesis which may result in impairment of the blood-brain barrier, development of cerebral edema and increased intracranial pressure.[9] The brain tissue underneath the tubercular exudate shows oedema, perivascular infiltration and a microglial reaction, a process known as 'border zone reaction'. The basal exudates around circle of Willis produce a vasculitis-like syndrome and can result in infarction in the distribution of medial striate and thalamo-perforating arteries. It has been suggested that with a sizeable inoculation or in the absence of an adequate cell-mediated immunity, the parenchymal cerebral tuberculous foci may develop into tuberculoma or tuberculous brain abscess.[10]

Tubercular meningitis

Tubercular meningitis is the most serious and commonest presentation of neurotuberculosis in developing countries. Incidence of tuberculosis in India is very high and the presentation of tubercular meningitis is variable with acute, sub-acute and chronic presentations. The British Medical Council divides the signs and symptoms into three stages (Table II).

Table II. British Medical Council staging of tubercular meningitis

Stage I - No definite neurological symptoms at admission or in the history before admission. Patient remains fully conscious and alert.
Stage II - Signs of meningitis, drowsiness or lethargy, cranial nerve palsies.
Stage III - Severe clouding of consciousness, stupor or coma, convulsions, gross paresis or paralysis.

Clinical features

Initially the presentation is vague and therefore a high index of suspicion for diagnosis is required. The disease takes its shape in three stages.

1. **Prodromal stage:** Symptoms are non-specific and start with apathy, irritability and not being interested in surroundings. Headache, vomiting and abdominal pain are common complaints in children above three years, while younger children can have altered behavior and fatigue which are subtle signs of TBM. Prodromal stage lasts for 2 to 3 weeks. Any illness which lowers the resistance can predispose the child to manifest tubercular infection of CNS, especially whooping cough, measles and occasionally head injury.
2. **Stage of meningeal irritation:** In this stage, child's irritability, headache and vomiting become more pronounced along with neck rigidity and positive Kernig's sign. An experienced eye can pick up papilledema and rarely choroid tubercle on fundus examination. The other presentations could be convulsions, paralysis, hydrocephalus and abdominal pain.
3. **Stage of local or diffuse cerebral involvement:** Signs of raised intracranial pressure, hydrocephalus and bulging fontanelle may be seen in this stage. Convulsions and features of cerebrovascular complications such as thrombosis and infarction can also be present. Cerebral edema can also occur due to syndrome of inappropriate ADH secretion (SIADH).

Generalized tonic and clonic seizures are the commonest type of seizures followed by focal seizures and tonic spasms.[11] At times, movement disorders may dominate the clinical picture like choreiform or hemiballistic movements, athetosis, generalised tremors, myoclonic jerks and ataxia.

Cranial nerve palsies occur in 20%–30% of patients. Sixth cranial nerve palsy is most commonly seen. Cranial nerves are affected either because of entrapment of nerve trunk in thick basilar exudates or because of increased intracranial pressure.[12,13]

Hemiplegia may occur at the onset of the disease or at a later stage. Quadriplegia secondary to bilateral infarction or severe cerebral oedema is less common. Terminal illness is characterized by deep coma, decerebrate or decorticate rigidity.

Modified clinical picture seen in BCG vaccinated children

BCG vaccination causes activation of 'T' lymphocyte which is responsible for localized lesions in meninges, brain, spinal cord and peripheral nervous system. The localized lesions are responsible for atypical presentation of neurotuberculosis. These presentations may have normal CSF but positive PCR for TB.

The various forms include serous tuberculous meningitis, isolated tubercular encephalopathy, a combination of several manifestations of multiple tuberculoma during or without treatment and development of infarction in the territory of large intracranial arteries and small arteries with lacunar infarcts with resultant syndromes.[14] The occurrence of TBM has been reported in the ratio of 1:3 among BCG-vaccinated and non-vaccinated children. It has been shown that single BCG immunization only postpones rather than prevents the occurrence of TBM to beyond 5 years of age.

Diagnosis

Today, tuberculous meningitis still poses a diagnostic problem. The reason is that it presents in a similar manner to other meningoencephalitides partially treated pyogenic meningitis in particular. Definitive diagnosis of tuberculous meningitis can be made by demonstration of mycobacteria in cerebrospinal fluid (CSF), by direct staining or culture. However, these tests are time consuming and seldom positive.

CSF examination: There is a predominant lymphocytic reaction (60-400 white cells per mL) with raised protein levels (0.8-4 g/L). In the early stages of infection, a signiûcant number of polymorphonuclear cells may be observed, but over the course of several days to weeks they are typically replaced by lymphocytes. CSF sugar is usually less than 50% of serum glucose concentration, the values may range between 18-45 mg/dL.

Because of difficulty in detecting tubercle bacilli in smears and culturing the bacilli from CSF, a number of tests have been developed to establish an early and deûnitive diagnosis.[15] The latex particle agglutination test, which allows the rapid detection of tubercle bacillus antigen in CSF, has been reported to be a simple and speciûc test.[16] The best method for diagnosing mycobacterial infection, however, is the polymerase chain reaction, in which cDNA probes are used to identify mycobacterial RNA or DNA sequences in CSF. This test is highly sensitive and speciûc in the diagnosis of tuberculous meningitis.[17]

Imaging

Basilar meningeal enhancement is seen in both CT scan and MR scan. Tubercular infarcts over thalamus, basal ganglia and internal capsule are picked up better in MRI than in CT scan. Ventricular enlargement is also seen depending on severity of the disease. Thick exudates in basal cisterns take shape of 'spider-leg appearance' and in the Sylvian fissure.[13] There is infrequent association of tuberculomas in patients with tubercular meningitis, about 16% in culture positive or presumptive tubercular meningitis.[18]

Tubercular encephalopathy

There is development of diffuse cerebral disorder leading to convulsions, stupor and coma in children suffering from pulmonary tuberculosis. The peculiar presentation is that neither the signs of meningeal irritation are present nor are features of focal deficit. This condition is specific for Indian children.[19] CSF examination is normal or there is minimal increase in cells and protein.

Intracranial tuberculoma

A tuberculoma or tuberculous granuloma is a well-defined focal mass that results from infection with Mycobacterium tuberculosis and is one of several morphological forms of tuberculous disease. Tuberculomas occur most commonly in the brain and lung. They usually result from hematogenous spread from a primary focus evident or dormant elsewhere in the body.

Tuberculomas may be solitary or multiple and may grow intraparenchymally or have a combined meningeal and parenchymal course.[20] The symptoms produced by tuberculomas are location related. Mild grade fever, headache, vomiting and focal seizures are features of supratentorial tuberculomas. In children, the infratentorial tuberculomas are common and present with brain stem syndromes, cerebellar manifestations and other cranial nerve palsy.

During the acute stage, non-contrast enhanced CT may show only a hypodense area caused by cerebritis or it may be normal. At the established inflammatory granulomatous stage, the lesion is either isodense or more commonly hypodense with a poorly defined outline on pre-contrast images and has marked enhancement following contrast. A target sign is seen that consists of ring enhancing lesions. CT is reported to have a sensitivity of 100% and specificity of 85.7%, with the negative predictive value of 35% thus indicating a need for further analysis with MR and or histological diagnosis.[21] Gupta et al[22] reported that

the MR features of brain tuberculomas are more specific than those of CT. With application of new MR techniques such as proton spectroscopy and diffusion weighted imaging the MR specificity can be significantly increased.[23]

A paradoxical appearance of tuberculoma or increase in size of existing tuberculoma can occur in patients of tubercular meningitis under treatment. Concomitant corticosteroids treatment have preventive role in these focal lesions.

HIV infection and CNS tuberculosis

Tuberculosis in HIV patient has chance of involvement of CNS to the extent of 10%-20%. It manifests in the form of meningitis, cerebral abscess and tuberculoma. Mycobacterium tuberculosis and atypical mycobacterium bacilli M avium intracellulare are associated with these patients. The latter organism is associated with single or multiple mass lesions more than twice as compared to non-HIV patient. The mortality in these patients is high. Early diagnosis shows good chance of recovery.[24]

Treatment

Concentration of antitubercular drugs in CSF

The effect of the drugs on the brain depends on their concentration in the CSF. The blood brain barrier in fact is responsible for achieving the therapeutic concentration of drug in the brain. Isonicotinic acid hydrazide (INH) diffuses readily in the CSF in presence or absence of meningeal inflammation. The concentration achieved in CSF is 20%-90% of serum level. Fast acetylators have low concentration. Rifampicin achieves 20% of serum concentration in the presence of meningeal inflammation. Ethambutol reaches up to 10%-50% of serum level in the presence of meningeal inflammation. Only 20% of serum level of streptomycin is detectable in CSF. Pyrazinamide penetrates well into the CSF in meningitis and with normal meninges.

WHO recommendation 2010: Children with suspected or confirmed tuberculous meningitis should be treated with a four-drug regimen (HRZE) for 2 months, followed by a two-drug regimen (HR) for 10 months; the total duration of treatment being 12 months. The doses recommended for the treatment of tuberculous meningitis are the same as those described for pulmonary tuberculosis.[25]

In RNTCP, CNS tuberculosis is included in category-l with intensive phase for 2 months. Continuation phase of treatment should be given for 6-9 months. Therapy should be extended to at least 12 months in those who fail to respond by 9 months. IAP also recommends a similar guideline for treating CNS tuberculosis as RNTCP.[26]

WHO currently recommends the following daily doses of antituberculosis medicines for the treatment of tuberculosis in children: Isoniazid-10 mg/kg (range 10-15 mg/kg); rifampicin-15 mg/kg (range 10–20 mg/kg), pyrazinamide-35 mg/kg (30-40mg/kg); ethambutol–20 mg/kg (15-25 mg/kg). It is important, as upper end of the recommended dose range should be considered in neurotuberculosis in view of uncertain penetration of antituberculosis medicines into the central nervous system.[27]

Corticosteroid

Prednisolone 2-4 mg/kg/d for 4 weeks followed by tapering over 1-2 weeks. The beneficial effects may be rapid clearing of sensorium, clearing of CSF abnormalities and improved intellectual outcome. There is no need for intrathecal corticosteroids.

Surgery

Neurosurgical corrections are often needed. The shunt surgery is needed in case of developing hydrocephalus. The shunts can safely be inserted even in the presence of active disease. Early shunting with drug therapy may offer the best therapeutic outcome.[28]

Points to Remember

- ***Tubercular involvement of brain and spinal cord is a very common neurological disorder seen in routine practice.***
- ***Fever, headache, vomiting, altered sensorium and focal deficits may come as the clinical presentation of the disease.***
- ***CNS involvement is 10%-20% more common in HIV patients with high mortality. There is high chance of infection with atypical mycobacteria.***
- ***In untreated cases, CSF picture contributes well in the form of pleocytosis, increased protein and low sugar (less than 60% of corresponding blood sugar). DNA-PCRs in CSF have high diagnostic yield, if facility exists.***
- ***Neuroimaging may reveal intense meningeal enhancement, hydrocephalus, infarction and basal exudates.***
- ***Antitubercular drugs are effective as discussed. Steroids and surgical intervention may be used as and when needed.***

References

1. Wetzel JG, Kollmann T. Neurotuberculosis. In: Inûammatory Diseases of the Brain. Medical Radiology, Stefan Hahnel (ed), Springer, US, 2009; pp75-83.
2. Chronic meningitis. In: Wood M, Anderson M, (eds). Neurological infections; major problems in neurology. Vol 16. Philadelphia, WB Saunders, 1998; pp169-248.
3. Raviglione MC, Snider DE, Kochi A. Global epidemiology of tuberculosis. Morbidity and mortality of a worldwide epidemic. JAMA1995; 273:220–226.
4. Molavi A, LeFrock JL. Tuberculous meningitis. Med Clin North Am1985; 69:315–331.
5. Chakraborty AK. Estimating mortality from tuberculosis meningitis in a community: Use of available epidemiological parameters in the Indian context. Indian J Tuberc 2000; 47:9-12.
6. Garg RK. Tuberculosis of the central nervous system. Postgrad Med J 1999; 75:133-140.
7. Rich MR, McCordock HA. The pathogenesis of tuberculous meningitis. Bull John Hopkins Hosp 1933; 52: 5-37.
8. Rajajee S, Narayanan PR. Immunological spectrum of childhood tuberculosis. J Trop Pediatr 1992; 2:490-496.
9. Tsenova L, Bergtold A, Freedman VH, Young RA, Kaplan G. Tumor necrosis factor alpha is a determinant of pathogenesis and disease progression in mycobacterial infection in the central nervous system. Proc Nat l Acad Sci USA 1999; 96:5657-5662.
10. Sheller JR, Des Prez RM. CNS tuberculosis. Neurol Clin1986; 4:143-158.
11. Patwari AK, Aneja S, Ravi RN, Singhal PK, Arora SK. Convulsions in tubercular meningitis. J Trop Pediatr1996; 42:91–97.
12. Hanna LS, Girgis NI, Abu el Ella AH, Farid Z. Ocular complications in meningitis: ''fifteen years study''. Metab Pediatr Syst Ophthalmol 1988; 11: 160–162.
13. Amitava AK, Alarm S, Hussain R. Neuro-ophthalmic features in pediatric tubercular meningoencephalitis. J Pediatr Ophthalmol Strabismus 2001; 38:229-234.
14. Mittal SK, Aggarwal V, Rastogi A, Saini N. Does BCG vaccination prevent or postpone the occurrence of tubercular meningitis? Indian J Pediatr1996; 63:659-664.
15. Daniel TM. New approaches to the rapid diagnosis of tuberculous meningitis. J Infect Dis 1987; 155: 599–602.
16. Krambovitis E, McIllmurray MB, Lock PE, Henfrickse W, olzel H. Rapid diagnosis of tubercular meningitis by latex particle agglutination. Lancet 1984; 2; 1229-231.
17. Harries A, Maher D. TB: a clinical manual for South East Asia. Geneva: World Health Organization, 1997.
18. Davis LE, Rastogi KR, Lambert LC, Skipper BJ. Tuberculous meningitis in the southwest United State: A community based study. Neurology 1993; 43:1775-1778.
19. Udani PM, Dastur DK. Tuberculous encephalopathy with and without meningitis: clinical features and pathological correlations. J Neurol Sci 1970; 10: 541-561.
20. Jinkins JR. Computed tomography of intracranial tuberculosis. Neuroradiology 1991; 33:126-135. [PubMed]
21. Selvapandian S, Rajshekhar V, Chandy MJ, Idikula J. Predictive value of computed tomography based diagnosis of intracranial tuberculomas. Neurosurgery. 1994; 35:845–850. [PubMed]
22. Gupta RK, Jena A, Sharma A, Guha DK, Khushu S, Gupta AK. MR imaging of Intracranial Tuberculomas. JCAT. 1988; 12:280–285. [PubMed]
23. Chang KH. Gd-DPTA enhanced MR imaging in intracranial tuberculosis. Neurology. 1990;32: 19–25.
24. Farrar DJ, Flanigan TP, Gordon NM, Gold RL, Rich JD. Tuberculous brain abscess in patient with HIV infection: case report and review. Am J Med 1997; 102:297–301.
25. Rapid advice: treatment of tuberculosis in children;World Health Organization 2010;WHO/HTM/TB/2010.13.
26. Working group on tuberculosis on Tuberculosis, Indian Academy of Pediatrics. Consensus statement of childhood tuberculosis. Indian Pediatr 2010; 47(1):41-55.
27. Sahu JK; Updated National guidelines for pediatric tuberculosis; concern regarding neurotuberculosis. Indian Pediatr 2013; 50: 800-801.
28. Leonard JM, Des Prez RM. Tuberculous meningitis. Infect Dis Clin North Am 1990; 4:769–787.

CONGRATULATIONS

Hearty congratulations to Dr.Abraham K Paul, Convenor, New Born Hearing Screening Programme, IAP Kerala & Lead Expert WHO New Born Hearing Screening, South East Asia Region, Kerala for being elected as Lead Expert from India for formulating the protocols for New Born Hearing Screening in South East Asian Countries by WHO collaborating centre, New Delhi.

TUBERCULOSIS

ABDOMINAL TUBERCULOSIS

***Bhaskar Raju B**
****** Sumathi Bavanandam**

Abstract: *Abdominal tuberculosis (TB) is not uncommon in children and is an important cause of morbidity and mortality. With the recent pandemic of HIV infection, the incidence of TB in general and abdominal TB are on the rise. Abdominal tuberculosis is the sixth most frequent type of extrapulmonary tuberculosis in all age groups. Its incidence however is significantly higher in children, relative to other forms of TB. Abdominal TB usually refers to the affliction of the gastrointestinal tract, peritoneum, and abdominal lymph nodes with TB. Nodal TB is the most common type of abdominal TB, followed by intestinal and peritoneal TB. Abdominal TB can present also as hepatic or splenic TB. Abdominal TB can be a part of disseminated TB especially in the background of immunodeficiency. Abdominal TB should be suspected in any child with prolonged abdominal symptoms, more so, if accompanied by systemic features like fever, weight loss, reduced appetite or chronic malaise. Often tests like endoscopy, contrast enhanced computerized tomography of abdomen, MR enterography and even diagnostic laparotomy may be needed to establish a diagnosis. High index of suspicion is necessary for early identification and initiation of appropriate therapy.*

Keywords: *Abdominal tuberculosis, GI tuberculosis, Tuberculous ascites, Children*

Tuberculosis (TB) is a disease, probably as old as mankind. Prehistoric human bone fossils have been identified showing evidence of TB infection. Ancient Indian (Sushruta) as well as Greek (Hippocrates) medical literature speak of disease resembling modern TB, including abdominal TB. In spite of BCG vaccine and international efforts to contain the disease through monitored chemotherapy, TB is still the second most common cause of mortality attributable to infections, next only to HIV. Abdominal TB is the most common extra pulmonary tuberculosis in children. Abdominal TB should always be considered in the differential diagnosis of any intestinal perforation, intestinal obstruction, ascites, organomegaly and any mass abdomen. Abdominal TB often occurs alone, though associated pulmonary involvement is much higher in the setting of HIV infections (up to 70%). TB often affects children with HIV even before CD4 cell count falls below 150 cells/mL.

The mode of presentation can vary from acute, acute on chronic or chronic. The clinical presentation depends upon the site of disease and the type of pathological involvement. Chronic diarrhea, malabsorption, weight loss and fever are seen in ulcerative type of intestinal tuberculosis whereas, the stricture type presents with colicky abdominal pain, vomiting, constipation or obstipation, suggestive of sub-acute or total intestinal obstruction. Children with peritoneal involvement present with abdominal distension or localized mass due to loculation of the ascitic fluid. Gastroduodenal tuberculosis may present as peptic ulcer with or without gastric outlet obstruction or perforation and this is rare in children. Esophageal TB too is rare and is usually an extension of mediastinal nodal TB. Prompt diagnosis of abdominal TB is crucial in preventing disease related morbidity and mortality.

Epidemiology

There is no data on exact prevalence of abdominal tuberculosis in Indian children. Gastrointestinal TB is reported in 10-20% of individuals with pulmonary TB, whereas associated pulmonary TB is seen in 20%-75% of patients with abdominal TB.[1] The WHO Core Clusters Committee for communicable diseases update in March 2009, has stated that 2 million people in India develop TB each year, of which 0.87 million are infectious.[2] A recent study in 2004 reported that, among all the patients suffering from abdominal tuberculosis, 21.4% belonged to the pediatric age group.[3]

Definition

Abdominal tuberculosis is defined as Mycobacterium tuberculosis infection of the abdomen involving

* Retired Professor and HOD,
** Assistant Professor
Dept. of Pediatric Gastroenterology,
Institute of Child Health and Hospital for Children,
Chennai.

gastrointestinal tract (GIT), peritoneum, omentum, mesentery, lymph nodes and/or other solid organs like liver, spleen and pancreas excluding genitourinary tract.[4]

Classification of abdominal TB

- Luminal TB
- Peritoneal TB
- Nodal TB
- Hepatosplenic TB

The clinical presentation of different types of abdominal tuberculosis is shown in Tables I, II, III and IV.

Pathogenesis

Mycobacterium tuberculosis, the human pathogen is now the principal organism causing abdominal TB. Mycobacterium bovis was the major pathogen of abdominal TB till a century ago. Pasteurization and boiling of milk has significantly reduced the spread of TB from cows to humans. M. bovis however is a common causal agent in abdominal TB in the setting of HIV infection. Mycobacterium avium and Mycobacterium intracellulare may also cause disease in HIV infected children.

The various ways by which TB bacilli get localized in GIT are the following.

- Hematogenous spread from the primary lung focus of childhood, with later reactivation
- Ingestion of bacilli through sputum from active pulmonary focus
- Direct spread from adjacent organs
- Through lymph channels from infected nodes
- Through infected bile from ruptured hepatic granuloma (very rare).

The capacity to invade the intestine and cause disease depends on the number of bacilli, virulence of the organism as well as nutritional and immunological status of the child. Stasis and sojourn of the organism for long periods is required for invasion and that explains the peculiar propensity of certain parts of GIT to TB infection. Further, besides prolonged contact, pH of the luminal fluid (low pH depresses the organism), abundance of lymphoid tissue which ingests the organism (but may not destroy it), absorptive capacity of the area, lack of active digestive processes (which could digest the fatty capsule), and the integrity of the mucosal layer, all affect the choice of site of infection. For all the above reasons, ileocaecal region is the preferred site of infection by TB bacilli. TB bacilli from lymphoid follicle in the submucosa spread via the lymphatics to the nodes in the mesentery, retroperitoneum and other areas. Various forms of peritoneal tuberculosis occur due to rupture of lymph nodes into the peritoneum. Sub-mucosal lesions can ulcerate to form ulcero- hypertrophic form of intestinal TB.

Abdominal TB may present as mesenteric or other intra abdominal lymphadenopathy, intestinal luminal disease, peritoneal disease with ascites, hepatosplenomegaly or as abdominal mass due to enlarged matted nodes or loculated ascites presenting as mass.

Pathology

Luminal TB is classified into three types: (a) Ulcerative (60%), (b) ulcerohypertrophic (10%) and (c) hypertrophic (30%).

Ulcerative luminal TB: This is an active form of the disease involving the small intestine, usually in children who are malnourished. It is characterized by inflammation and fibrosis of the bowel wall with regional adenopathy. Nodular masses of tubercles can be seen in the serosal surface. Pathologically, it is characterized by presence of inflammatory cells, epitheloid cells, granulomas and Langhans giant cells. Caeseation necrosis is commonly seen though not always. Ulcers are shallow with raised granulomatous edges and may be reversible if identified early and vigorously treated at this stage without fibrosis and scarring. Tuberculous ulcers are transverse ulcers following lymphatic flow, shallow, without skip lesions which help us to differentiate them from Crohns disease ulcers, though at times it can be very difficult to differentiate between them macroscopically. Endarteritis, which is common in intestinal TB, causes fibrosis, scarring, stricture formation and keeps bleed uncommon from the ulcers, which often contributes to late diagnosis. If the disease progresses ulcers become confluent leading to extensive fibrosis, bowel wall thickening, mass lesion, stricture and fistula formation.

Hypertrophic luminal TB: When the child's immune system fights the infection vigorously, hypertrophic form results and is usually seen in better nourished children. It is characterized by thickening of bowel wall with fibrosis and scarring. It may present as a rigid mass-like lesion mimicking carcinoma. The stricture can present later with obstructive symptoms.

Ulcero-hypertrophic TB: Some children have both ulcerative and hypertrophic types of TB in the intestines usually at the ileocecal site, presenting sometimes as right iliac fossa mass.

Diagnosis

Paustian's criteria

Paustian's criteria, postulated by Frederick F Paustian, the US gastroenterologist from Nebraska, in 1964, were extensively used to confirm diagnosis of TB in the pre-endoscopy/CT/MRI/PCR era. It depended on typical gross appearance, histologic evidence of caseation and identification of AFB and animal inoculation studies. It is no longer used, though finding AFB and caeseation are the commonest method of confirming TB even today.

Abdominal TB as a rule is paucibacillary and caseation, rather than identifying AFB, is the most useful marker for abdominal TB.

Base line investigations should include complete hemogram with ESR. Anemia, peripheral lymphocytosis and elevated ESR are common non-specific findings in abdominal TB.

Table I. Luminal abdominal TB [5,6]

Type	Clinical featutes	Associated features
Oral TB (very rare)	Small edematous red nodules often in tongue which can break down to painful shallow ulcers less than 2 cms in size with undermined edges	Seen in children with severe malnutrition
Esophageal TB (Very rare)	Due to spread from mediastinal nodes, lung or spine. Clinical presentation include dysphagia, retrosternal pain, hematemesis.	Least common site (0.2%)
Gastric and duodenal TB (Very rare)	Children can present with dyspeptic symptoms like upper abdominal pain, vomiting. Rare complications include perforation, fistula, ulcers extending into pancreas or even obstructive jaundice secondary to common bile duct compression. Barium contrast studies and upper GI endoscopy may show evidence of gastric outlet obstruction and duodenal strictures.	Rare (1%), due to sparse lymphoid tissue, high acidity and vigorous gastric peristalsis
Small bowel TB (common)	Prolonged pyrexia, recurrent abdominal pain, foul smelling offensive malabsorptive stools, steatorrhea, weight loss. Abdomen will feel doughy on palpation. Rare complications include perforation and obstruction.	Ileum is the common site (80%-90%). Malabsorption is due to stagnant blind loop with bacterial overgrowth, bile salt deconjugation, reduced absorptive area, and lymphatic obstruction.
Large bowel TB (common)	Segmental colonic TB refers to colonic involvement sparing ileocecal region. The common symptoms include irregular fever, chronic/recurrent diarrhea, weight loss, abdominal pain, RIF mass, bleeding PR. Rectal and anal TB are extremely rare in children. Constitutional symptoms, constipation and hematochezia can be the presenting feature. Fistula in ano rare in children but seen in adults with pulmonary TB	The common sites of colonic TB are sigmoid, ascending colon, transverse colon in that order. PR examination may show a tight annular stricture mimicking cancer requiring biopsy to exclude malignancy. Fistulas may follow an ischiorectal or perianal abscess. TB bacilli can be cultured from the fistulous tract. Fistulas should always raise suspicion of possible Crohns disease.

Table II. Peritoneal TB[5,6]

Acute/chronic - Four types Ascitic (Generalised or encysted)	Generalised type: More common in children. The common symptoms include fever, malaise, weight loss, abdominal distension. Clinical examination reveals shifting dullness, fluid thrill, umbilical hernia and abdominal mass at times, due to omental and nodal involvement.	Peritoneal surface will be studded with tubercles at laparoscopy and fluid is exudative, rich in proteins and lymphocytes.
Loculated (Encysted) type	Rare in children. Clinically, children present with distension limited to one quadrant of the abdomen due to fluid sealed off by matted bowel loops, surrounded by omentum, mimicking a cyst.	Differential diagnosis includes mesenteric cyst, pseudocyst of the pancreas, retroperitoneal cyst.
Fibrous (Plastic) type	Results, due to extensive fibrosis, forming dense adhesions of bowel loops with doughy feel. Abdominal distension occurs due to adhesions, bands, strictures. Pain is colicky with malabsorption, steatorrhea and resultant malnutrition.	Represents a delayed presentation of peritoneal TB.
Purulent type	Rare in children. More common in females as a complication of genitourinary TB especially, TB salphingitis.	Presents as acute peritonitis and peritoneal surface will be studded with tubercles, filled with cold abscess and pus. The prognosis is often poor due to toxemia and fistula formation

Table III. Tuberculous mesenteric lymphadenitis [5,6]

Acute mesenteric lymphadenitis	More common in children than adults May mimic acute appendicitis. Fever, vomiting, RIF pain with firm tender swelling in RIF.	DD- Acute appendicitis .
Chronic mesenteric lymphadenitis	Children present with PUO, weight loss, anemia, emaciation and probable mass abdomen.	DD-Lymphoma
Pseudo mesenteric cyst	This is due to caseation of mesenteric lymph nodes confined to the mesentery. Adhesions result in intestinal obstruction.	Often presents as mass abdomen
Calcified nodes	Incidentally identified radiologically as a calcified lesion along the line of mesentery extending from L2 vertebra to right sacroiliac joint. In about 50% of cases there is no active infection.	

Table IV. Miscellaneous form of abdominal TB[5,6]

Abdominal cocoon (Sclerosing peritonitis/sclerosing encapsulating peritonitis)	May be seen in adolescent females. Very rare in children. Presents as mass diagnosed at laparotomy, clinical features are colicky abdominal pain, bilious vomiting due to partial bowel obstruction.	
Hepatic TB	Congenital liver involvement may occur rarely, due to placental spread, or by aspiration of contaminated amniotic fluid, where the mother has TB. Neonate may present with failure to thrive, jaundice and hepatosplenomegaly. In older children liver may be co-involved in abdominal TB. Usually presents as hepatomegaly and biopsy might reveal granulomas in liver. Primary isolated liver TB presenting with PUO, jaundice, liver abscess or chronic hepatitis is extremely rare.	
Pancreatic TB	Very rare. Presents with abdominal pain suggestive of pancreatitis.	
Splenic TB	Presents as PUO and splenomegaly. Isolated involvement is extremely rare.	

Mantoux test is positive in approximately 50% of cases with abdominal TB in children. A study by Ira shah showed 47% of children with abdominal TB were negative for the Mantoux test[7]

Skiagram chest should be done to identify pulmonary TB which could coexist in 20% to 75% of abdominal TB in children. Plain X-ray of abdomen may show enteroliths, features of obstruction, ground glass appearance due to ascites, signs of perforation or intussusception if any. Calcified nodes and granulomas can be appreciated in some cases in plain skiagrams of abdomen. HIV screening is a must in all cases of abdominal TB. Baseline LFT should be done to identify hepatic involvement and to monitor therapy later.

Barium contrast study of small bowel (Barium meal follow through): Features of malabsorption include rapid intestinal transit, hyper-segmentation of barium, precipitation, flocculation of barium and bowel wall thickening with loss of symmetry in fold pattern. Rare findings include deep fissures, sinus tracts, enterocutaneous fistulae, perforation, etc. Luminal stenosis with smooth but stiff contours (Hour glass stenosis), multiple strictures with segmental dilatation of bowel loops can be appreciated in contrast studies, if present.

Barium enema: Thickened ileocecal valve with or without wide gaping of valve with narrowing of terminal ileum, the characteristic feature of ileocecal TB, is described as 'Fleischner's' sign or 'inverted umbrella sign'. Ulcers can be picked up by double contrast study as shallow ulcers with characteristic elevated margins, which may result in deformities like symmetric, annular or napkin ring stenosis, obstruction, shortening, retraction and pouch formation, as disease advances. Localized stenosis opposite the ileocecal valve with a rounded off smooth cecum and dilated terminal ileum is called as 'Purse string stenosis'. Caecum appears conical and shrunken in size, and is pulled up, out of the right iliac fossa due to contraction and fibrosis of the mesocolon**.** The hepatic flexure may also be pulled down by the contracting mesocolon. Fluroscopy can identify rapid emptying of inflamed terminal ileum. With the advent of colonoscopy, the many old colourful descriptions of contrast findings are no longer relied upon for diagnosis of colonic TB. Many contrast findings are common to Crohn's disease as well and should be carefully interpreted.

USG abdomen: There are no set criteria to diagnose abdominal TB on ultrasonography. However, corroborative evidence includes echogenic thickened mesentery with lymph nodes >15mm in size, dilated, thickened and matted bowel loops, thickened omentum and ascites.[8]

USG abdomen is more useful for diagnosing peritoneal TB. There may be free or loculated fluid in the abdomen. Presence of nodes like upper para aortic, paracaval, mesenteric, periportal, peripancreatic group of nodes with mixed and heterogenous echogenicity is highly suggestive of TB. The distribution of enlarged nodes reflect the draining nodes of commonly affected parts of intestine.[9] Calcified and caseating nodes on USG are highly suggestive of TB.

CECT abdomen is helpful to pick up nodal mass, bowel wall thickening, free fluid, nodular terminal ileum, ileocecal thickening/narrowing (Fig.1a), intestinal obstruction and complications like perforation, abscess formation and obstruction. Caeseating lymph nodes have hypodense centers and peripheral rim enhancement (Fig.1b). In TB peritonitis CT shows fluid with high attenuation due to high protein and cellular content.

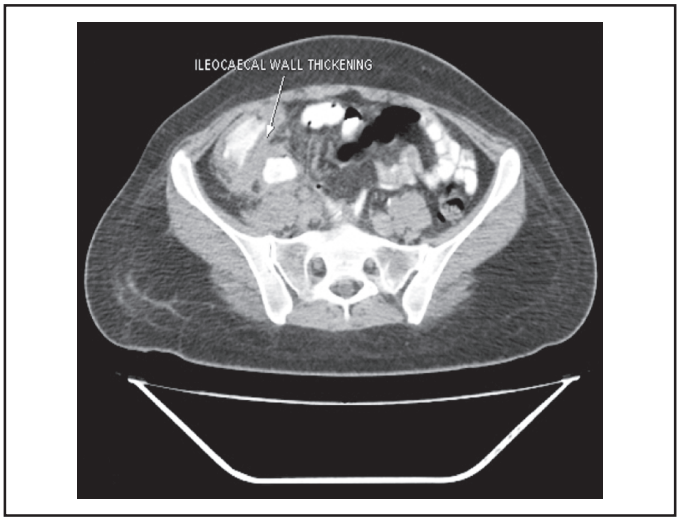


Fig.1a CECT abdomen showing thickening of ileocecal wall

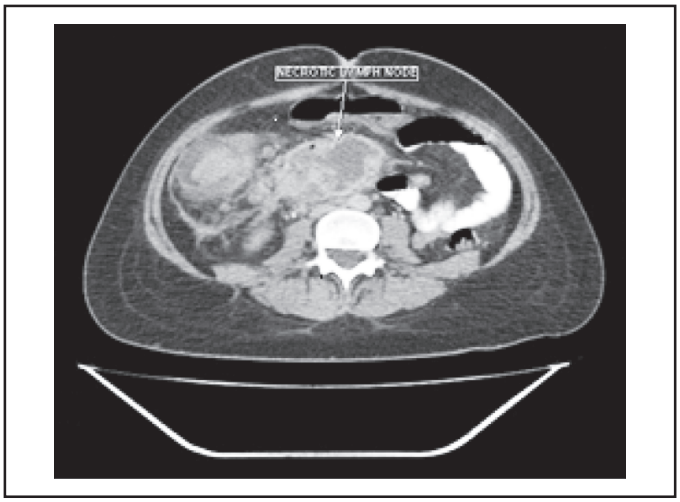


Fig.1b CECT abdomen showing necrotic node

MR enterography can be performed in older children where mucosal enhancement, stricture, abscess, evidence of intestinal obstruction can be easily picked up. While CT may pick up most of it, MR enterography is particularly useful for identifying isolated small bowel involvement.

Enteroscopy and wireless capsule endoscopy are useful for studying the small bowel. However, prior barium study is needed to rule out intestinal strictures before subjecting the child for capsule endoscopy. Capsule endoscopy visualizes small bowel, which is otherwise inaccessible. Its use is limited to older children. Availability of enteroscopy and capsule endoscopy are limited to very few specialized centers.

Colonoscopy with terminal ileal intubation with biopsy is an excellent diagnostic modality to confirm colonic and ileocecal TB. Typical tubercular mucosal ulcerations, nodular lesions, deformed ileocecal valve can be easily identified (Fig.2). Ulcers in tuberculosis are transverse ulcers unlike Crohn's disease where ulcers are longitudinal with classical skip lesions. Target biopsy is possible with colonoscopy and it can confirm TB (Fig.3).

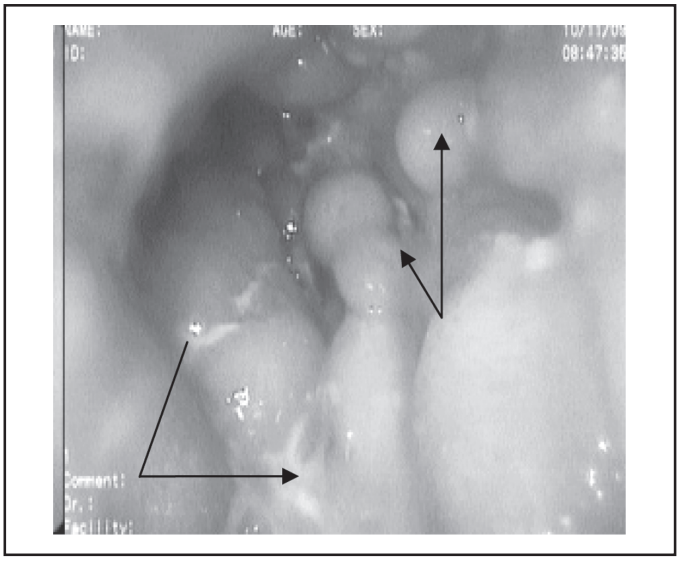


Fig.2. Nodularity, ileal narrowing and tubercular ulcers seen in colonoscopy

Ascitic fluid analysis: The fluid usually is straw coloured, but can be clear, opalescent, cloudy, chylous or even hemorrhagic. The cell count varies from 150-4000 / cmm with more than 70% lymphocytes. The ascitic fluid is exudative with protein content of more than 3 gm/dL. AFB may be positive by staining in a small percentage of cases (<4%). Mycobacterial cultures are positive in about 20% of cases, but may take up to 6 weeks for reporting. Adenosine deaminase (ADA) is increased in ascitic fluid.

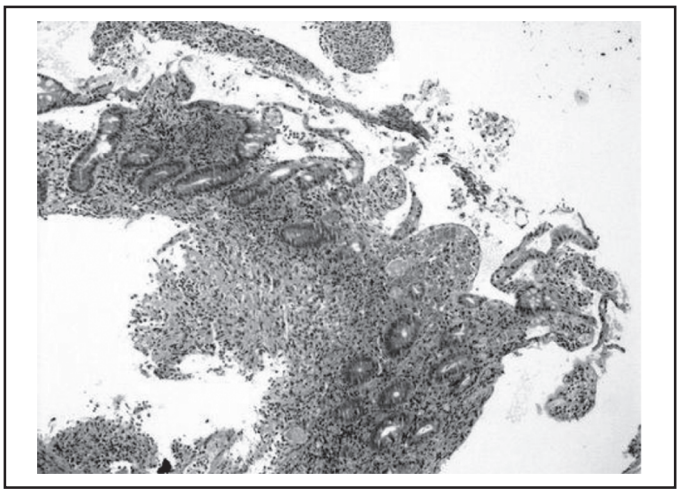


Fig.3. Photomicrograph of ileal biopsy showing granuloma and caseation necrosis

When coupled with identification of increased gamma interferon in the same fluid, the diagnosis becomes more dependable. ADA however may not be elevated in HIV infection since it requires functioning T cells for its production.

Molecular diagnosis: PCR is positive in 95% to 100 % of culture positive cases but only in 50% to 60% of culture negative cases. It may be false positive in 1% to 30% of cases and it cannot differentiate between live and dead bacilli. It remains positive even after successful therapy, making its utility limited in clinical practice to diagnosis, but not to assess the response to therapy.[10]

Fine needle aspiration cytology (FNAC): FNAC of intra-abdominal mass under USG guidance helps early diagnosis when other investigations are equivocal. Excision biopsy of peripheral nodes would be useful, if present.

Liver biopsy: Liver involvement is rare, but if significant hepatomegaly is seen, biopsy would give useful information. Presence of hepatic tuberculosis can be confirmed with findings like granuloma and tubercles with fatty liver. Many cases however may just show chronic hepatitis, which is a non-specific finding.

Laparoscopy and laparotomy: Diagnostic laparoscopy is an ideal modality for diagnosis of peritoneal TB and non-luminal TB. Tubercles can be seen on serosa, visceral peritoneum, liver and omentum, which can be biopsied for histopathological confirmation. Laparotomy is less useful in intestinal TB. However many luminal TB cases do show peritoneal involvement on laparoscopy and biopsy may be possible.

Interferon-gamma release assays (IGRA): Commercially available as Quantiferon Gold (QFT), it is an in vitro estimation of component of cell mediated immune reactivity to Mycobacterium tuberculosis and quantifies gamma interferon released from lymphocytes sensitized by incubation overnight to mycobacterial antigens (PPD). The estimation is usually done by ELISA, in the separated plasma from the affected child. It does not differentiate between active and latent disease and very expensive compared to tuberculin skin testing.

Xpert MTB/RIF[11]

The Xpert MTB/RIF detects DNA sequences specific for Mycobacterium tuberculosis and rifampicin resistance by polymerase chain reaction. It is based on the Cepheid GeneXpert system, a platform for rapid and simple-to-use nucleic acid amplification tests (NAAT). The Xpert MTB/RIF purifies and concentrates Mycobacterium tuberculosis bacilli from sputum samples, isolates genomic material from the captured bacteria by sonication and subsequently amplifies the genomic DNA by PCR. While its main use is for pulmonary TB, it can be modified for rapid diagnosis of abdominal TB as well. WHO has recommended its use in endemic countries especially those with high HIV infection rate. Besides confirming TB, it can also detect rifamycin resistance, the hallmark of MDR TB.

Treatment: Treatment of abdominal TB, is with traditional anti tuberculous drugs. The success of therapy depends upon choosing appropriate regimen, dosage and duration. The Revised National Tuberculosis Control Programme (RNTCP) defines abdominal TB treatment under Category 1, in which INH, rifampicin, pyrizinamide and ethambutol are given thrice weekly for 2 months and two drugs, INH and Rifampicin in continuation phase for four more months.[12] Anti-tuberculous treatment could result in healing with fibrosis leading to adhesions and strictures. The role of corticosteroids in prevention of strictures is not clearly defined, though widely used. Many studies have confirmed that radiological and clinical resolution can occur with ATT alone, without steroids, if started early, even in patients presenting with sub acute intestinal obstruction. Children should be closely monitored for hepatotoxicity, especially when on INH, rifampicin and pyrazinamide. Hepatotoxicity is higher in children with underlying liver disease, severe type of disease like miliary TB, TB meningitis and in those with significant malnutrition. Anorexia, nausea, vomiting and icterus herald the onset of hepatitis. In suspected drug induced liver injury INH, pyrazinamide and rifampicin should be stopped and alternate therapy with streptomycin, ethambutol may be given until resolution of symptoms. INH, rifampicin and pyrazinamide may be slowly reintroduced one by one after complete resolution of

hepatitis with close monitoring of LFT. Periodic LFT is a must while on ATT.

HIV and TB: All children with tuberculosis should be tested for HIV infection as co-infection is on the rise. Mantoux test of 5 mm is considered positive in children infected with HIV. PCR testing is not very useful, as negative PCR will not rule out tuberculosis and false positivity is frequent. All HIV children with TB should be treated with ATT and antiretroviral agents should be started after a period of 2-8 weeks in order to reduce the occurrence of 'inflammatory immune reconstitution syndrome (IRIS)'. The HIV infected child reacts violently to pre-existing infection when recovering and controlling infections prior to anti-retroviral therapy is a good way of preventing it.

Rifampicin is a cytochrome 450 enzyme inducer causing rapid clearance of drugs with resultant sub therapeutic level of other ATT drugs, when they are co-administered with rifampicin. Also, rapid metabolism of INH to toxic metabolite increases incidence of hepatic toxicity of INH when combined with rifampicin. Rifabutin, a derivative of rifampicin, is advocated instead of rifampicin to reduce INH induced hepatotoxicity and prevent too rapid a degradation of other ATT drugs. However it is very expensive compared to rifampicin and is not widely used in ATT regimens.

Surgical management

Stricturoplasty is ideal for long segment strictures, multiple strictures at long intervals and in children presenting with intestinal obstruction. Resection with anastomosis can be done. Terminal ileal stricture can be managed with limited resection of terminal ileum with ileocolic anastomosis. Otherwise, surgery has only a limited role in abdominal TB which is eminently responsive to ATT.

Points to Remember

- ***Abdominal TB is not uncommon in children and clinical presentation varies with the site and type of involvement.***
- ***Nodal form of abdominal TB is the commonest type followed by intestinal and peritoneal TB.***
- ***High index of suspicion is necessary to identify the disease and initiate therapy to prevent disease related morbidity and mortality, especially strictures and obstruction.***
- ***Though isolation of organism by culture or demonstrating the bacilli by AFB smear is ideal for diagnosis, histopathological evidence of caseating granuloma is sufficient for diagnosis of abdominal TB, since it is a paucibacillary disease with low yield on cultures.***
- ***Treatment with ATT is beneficial in most of the cases with good healing rates.***
- ***Surgery is reserved for obstructive stricture, multiple strictures and perforation.***
- ***Nutritional improvement is an integral part of management, since most cases are undernourished on presentation.***
- ***All children with TB should be screened for HIV.***

References

1. Pettengel KE, Larsen C, Garb M, Mayet FGH, Simjee AF, Pirie D. Gastrointestinal tuberculosis in patients with pulmonary tuberculosis. Q J Med 1990; 74:303-308.
2. World Health Organization (WHO). Core Programme Clusters. Communicable Diseases and Disease Surveillance. Tuberculosis, Geneva, WHO.2009.
3. Wadhwa N, Agarwal S, Mishra K. Reappraisal of Abdominal Tuberculosis. J Indian Med Assoc 2004; 102:31-32.
4. Udani PM. Tuberculous hepatic and splenic lesion and hepatosplenomegaly. Indian J Child Health 1962; 11: 372-387.
5. Riyaz A. Abdominal tuberculosis. In: Text book of Pediatric Gastroenterology and Hepatology, 3rd edn, 2013, Paras medical publisher, Hyderabad 2013; pp183-196.
6. Malathi Sathiyasekaran, Natwarlal Sharma. Abdominal tuberculosis in children, Indian J Pract Pediatr 2007; 9(3):173-181.
7. Ira Shah, Ramya, Uppuluri. Clinical profile of abdominal tuberculosis in children. Indian J Medi Sci 2010; 64(5): 204-209.
8. Jain R, Sawhney S, Bhargava DK, Berry M. Diagnosis of abdominal tuberculosis: sonographic findings in patients with early disease. Am J Roentgenol 1995; 165:1391-1395.
9. Sood R. Diagnosis of Abdominal Tuberculosis: Role of Imaging. J Indian Acad Clin Med 2001; 2(3):169-177.
10. Kabra SK, Lodha R, Seth V. Some current concepts on childhood tuberculosis. Indian J Med Res 2004; 120: 387-397.
11. (MDR-TB) WHO. Fact Sheet: Xpert MTB/RIF Test. Geneva: WHO, 2011. Available at http://www.who.int/tb/features_archive/factsheet_xpert_may2011update.pdf [accessed May 2011].
12. Working group on tuberculosis, Indian academy of Pediatrics (IAP). Consensus Statement on Childhood Tuberculosis. Indian Pediatrj 2010; l47:41-55.

TUBERCULOSIS

SKIN TUBERCULOSIS

***Jayakar Thomas**
****Kumar Parimalam**
*****Devaraj Kumar Dinesh**

Abstract: *Tuberculosis of the skin accounts for 1% to 2% of all extra-pulmonary cases of tuberculosis. Scrofuloderma and lupus vulgaris are the two most common clinical forms in children. In the last several years an increase in the number of tuberculids, especially lichen scrofulosorum, has been observed. Cutaneous tuberculosis in children can be severe and have a protracted course. Multiplicity of lesions and multifocal disseminated involvement in scrofuloderma and lupus vulgaris are common. One needs to remember that morbidities and deformities are more severe in children.*

Keywords: *Children, Cutaneous tuberculosis, Lupus vulgaris, Tuberculosis verrucosa cutis, Scrofuloderma, Tuberculids.*

Cutaneous tuberculosis is a rare form of extrapulmonary tuberculosis that accounts for 1% to 2% of cases. Childhood skin tuberculosis represents 18% to 82% of all cutaneous tuberculosis cases. Of these scrofuloderma and lupus vulgaris are the two most common clinical forms in children. An increase in the number of tuberculids, especially lichen scrofulosorum, has been observed in the last several years. Cutaneous tuberculosis in children can be severe and may have a protracted course. Multiplicity of lesions and multifocal disseminated involvement in scrofuloderma and lupus vulgaris is common. Scrofuloderma progressing to gummatous lesions (scrofulous gumma) is mostly described in children. Morbidities and deformities are severe in children. [1, 2, 3]

* Professor and Head,
Department of Dermatology,
Sree Balaji Medical College, Chennai.
** Professor and Head,
Department of Dermatology,
Thanjavur Medical College, Thanjavur.
*** Junior Consultant,
Department of Dermatology,
Kanchi Kamakoti CHILDS Trust Hospital, Chennai.

Definitions / Description

Cutaneous tuberculosis is highly variable in its clinical presentation, depending on the virulence and number of mycobacteria causing the infection, the immunological status of the host and the route of inoculation of the mycobacteria into the skin. Cutaneous tuberculosis may be classified as follows:

I. Inoculation tuberculosis (exogenous source)

1. Tuberculous chancre (primary tuberculosis of skin, primary inoculation complex, occurs in a non-immune host).
2. Warty tuberculosis (tuberculosis verrucosa cutis, a form of secondary tuberculosis, i.e., occurs in an immune person).
3. Lupus vulgaris, again a form of secondary tuberculosis, i.e., occurs in an immune person.

II. Secondary tuberculosis (endogenous source)

1. Contiguous spread (e.g., direct extension from lymph node, bone or joint) may result in scrofuloderma.
2. Orificial tuberculosis (TB ulcer) from autoinoculation.

III. Hematogenous tuberculosis

1. Acute miliary tuberculosis.
2. Some cases of lupus vulgaris.
3. Tuberculous gumma (metastatic tuberculous abscess).

IV. Eruptive tuberculosis (the tuberculides)

1. Micropapular variety: Lichen scrofulosorum.
2. Papular variety:Papular or papulonecrotic tuberculides.
3. Nodular varieties: there is no universal agreement on nodular tuberculides. These are erythema induratum of Bazin or nodular vasculitis, erythema nodosum (some cases). Erythema induratum is sometimes considered one form of the tuberculids, but the truth of its tuberculous etiological origin is still open to debate.

Cutaneous tuberculosis may follow BCG immunization.

Epidemiology/Etiology

Age: Acute miliary tuberculosis is more common in infants and in adults with advanced immunodeficiency. Primary inoculation tuberculosis is more common in infants. Scrofuloderma is more common in adolescents and elderly. Lupus vulgaris affects all ages.

Sex: Lupus vulgaris is more common in females, while tuberculosis verrucosa cutis is more common in males.

Etiology: Cutaneous tuberculosis is caused by the obligate human pathogenic mycobacteria; Mycobacterium tuberculosis, Mycobacterium bovis and occasionally Bacillus Calmette-Guerin (BCG).

Incidence: Cutaneous tuberculosis had steadily declined worldwide, paralleling the decline of pulmonary tuberculosis; lupus vulgaris and verrucous lesions are more common in the tropics; tuberculosis verrucosa cutis is a common type in third world countries. However, of late, the incidence of cutaneous tuberculosis has been increasing, often associated with AIDS.

Predisposing factors for tuberculosis include poverty, crowding and HIV infection. The type of clinical lesion depends on the route of cutaneous inoculation and the immunologic status of the host. Cutaneous inoculation results in a tuberculous chancre in the non-immune host and tuberculosis verrucosa cutis in the immune host. Route of cutaneous infection may be exogenous, by autoinoculation or endogenous.

The modes of endogenous spread to the skin include:

(a) Direct extension from an underlying tuberculous infection, e.g., lymphadenitis or tuberculosis of bones and joints (resulting in scrofuloderma)

(b) Lymphatic spread to skin resulting in lupus vulgaris

(c) Hematogenous dissemination resulting in acute miliary tuberculosis, lupus vulgaris or tuberculous gumma (metastatic tuberculosis abscess).

Clinical evaluation

Primary inoculation tuberculosis

Initially, a papule occurs at the inoculation site 2 to 4 weeks after the wound. The lesion enlarges to a painless ulcer, i.e., a tuberculous chancre (up to 5 cm), with shallow granular base and multiple tiny abscesses, or alternatively may be covered by thick crust. The ulcer margins are undermined and reddish blue in color. Older ulcers become indurated with thick crusts. Deeper inoculation results in subcutaneous abscess. Intraoral inoculation results in ulcers on gingiva or palate. Regional lymphadenopathy occurs within 3 to 8 weeks. Primary inoculation tuberculosis is most common on exposed skin at sites of minor injuries. Oral lesions occur following ingestion of bovine bacilli in non-pasteurized milk (in the past) and lesions in male babies have occurred on the penis after ritual circumcision.

Tuberculosis verrucosa cutis (Warty tuberculosis) (Fig.1)

Initially, there is a papule with a violaceous halo. It evolves to a hyperkeratotic, warty, firm, brownish-red to purplish plaque. Clefts and fissures occur from which pus and keratinous material can be expressed. The border is often irregular. Lesions are usually single but multiple lesions occur. There is no lymphadenopathy. Tuberculosis verrucosa cutis occurs most commonly on the dorsolateral hands and fingers. In children, the lower extremities and knees may be involved.

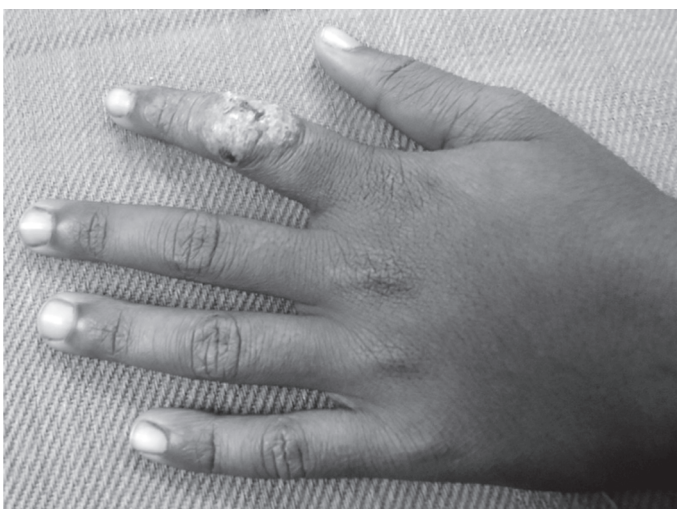


Fig.1. Warty tuberculosis with the rough and eroded surface

Lupus vulgaris (Figs. 2 & 3)

The initial flat papule is ill defined and soft. It evolves into a well-defined, irregular, reddish brown plaque. The consistency is characteristically soft; if the lesion is probed, the instrument breaks through the overlying epidermis. Surface is initially smooth or slightly scaly but may become hyperkeratotic. Hypertrophic forms result in soft tumorous nodules. Ulcerative forms present as punched-out, often serpiginous ulcers surrounded by soft, brownish infiltrate. Involvement of underlying cartilage but not bone results in its destruction (ears, nose). Scarring is prominent and characteristically, new brownish infiltrates occur within the atrophic scars. Diascopy (i.e., the use of a

glass slide pressed against the skin) reveals an 'apple-jelly' (i.e., yellowish-brown) color of the infiltrate.

The plaque of lupus vulgaris is usually solitary but several sites may be affected. Most lesions occur on the head and neck, most often on the nose and ears or the scalp. Lesions on the trunk and extremities are rare. Disseminated lesions may be seen after severe viral infection (measles).

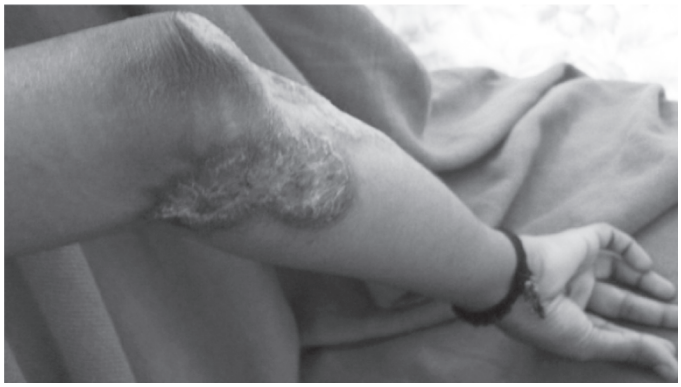


Fig.2. Lupus vulgaris: Note the healing at one end and extension at the other

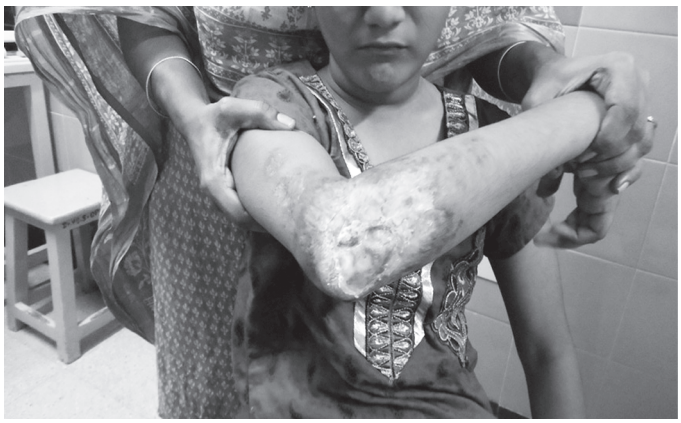


Fig.3. A case of ulcerating lupus vulgaris

Scrofuloderma (Fig. 4, 5 & 6)

The lesion consists of a firm subcutaneous nodule, which initially is freely moveable; the lesion then becomes doughy and evolves into an irregular, deep-seated plaque, which liquefies and perforates. Ulcers and irregular sinuses, usually of linear or serpiginous shape, discharge pus or caseous material. Edges are undermined, inverted and dissecting subcutaneous pockets alternate with soft, fluctuating infiltrates and bridging scars. The lesions are reddish blue or brownish in color. Scrofuloderma most often occurs in the parotid, submandibular, supraclavicular, or

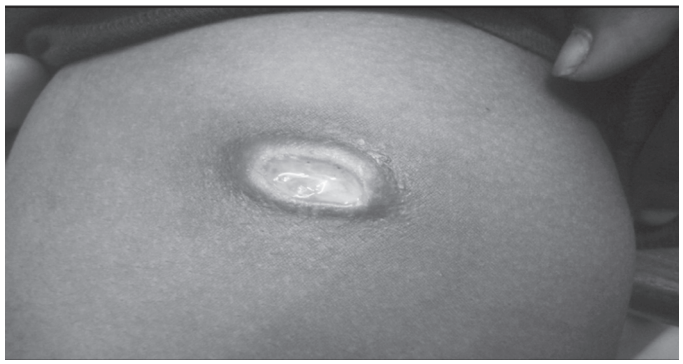


Fig.4. Scrofuloderma arising from an abscess on the thigh

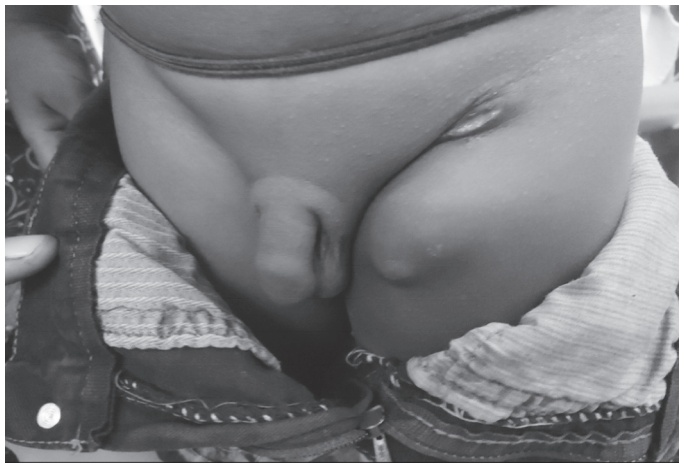


Fig.5. Scrofuloderma arising from inguinal node

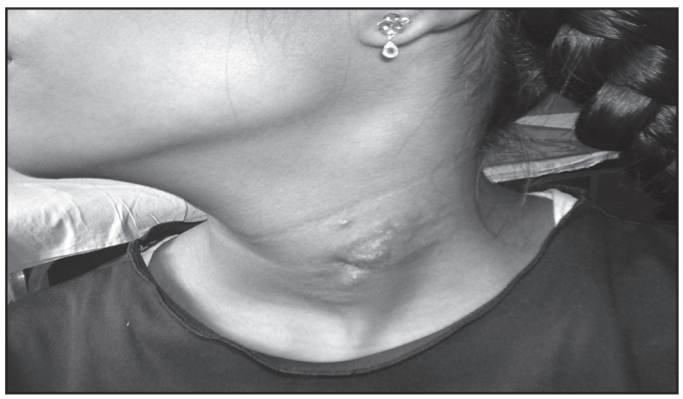


Fig.6. Scrofuloderma arising from a cervical node

axillary regions; the lateral neck maybe also involved. Scrofuloderma most often results from contiguous spread from affected lymph nodes or tuberculous bones (phalanges, sternum, and ribs) or joints.

The characteristics of tuberculosis verrucosa cutis, lupus vulgaris and scrofuloderma are given in Table I.

Metastatic tuberculosis abscess (tuberculous gumma)

This is a non-tender, 'cold' fluctuant subcutaneous abscess. The lesion coalesces with the overlying skin, breaks down and forms fistulas and ulcers. The color of the overlying skin is initially that of the normal skin; later it becomes reddish blue. Single or multiple lesions may occur, often at sites of previous trauma.

Acute miliary tuberculosis

Presents as an exanthem. Lesions are disseminated and consist of minute macules and papules or purpuric lesions. Sometimes vesicular and crusted lesions are observed. Removal of crust reveals umbilication. Lesions are red or purpuric in color. They are disseminated on all parts of the body, particularly the trunk.

Orificial tuberculosis

A small yellowish nodule on mucosa breaks down to form a painful circular or irregular ulcer with undermined borders and pseudomembranous material, yellowish tubercles and eroded vessels at its base. The ulcer is red, hemorrhagic, and purulent. The surrounding mucosa is swollen, edematous, and inflamed. Since orificial tuberculosis results from autoinoculation of mycobacteria from progressive tuberculosis of internal organs, orificial tuberculosis is usually found on the oral, pharyngeal (pulmonary tuberculosis), vulvar (genitourinary tuberculosis), and anal (intestinal tuberculosis) mucous membranes. Lesions may be single or multiple, and in the mouth most often occur on the tongue, soft and hard palates, or lips. Orificial tuberculosis may occur in a tooth socket following tooth extraction.

Erythema induratum (Bazin): this is a nodular tuberculid presenting with indolent inflamed deep-seated nodule and plaque, occurring bilaterally over the calves or feet. In severe cases there may be necrosis, ulceration, depressed scar and pigmentation. It is more common in females than in males. Usually there is no evidence of other distant tuberculous foci. The main differential diagnosis is erythema nodosum (front of legs, i.e., shins) and other forms of nodular vasculitis.

Investigations/Dermatopathology[4,5,6,7]

Primary inoculation tuberculosis: Initially non-specific inflammation; after 3 to 6 weeks: epitheloid cells, Langhans' giant cells, lymphocytes, caseation necrosis.

Acute miliary tuberculosis: Non-specific inflammation and vasculitis are observed.

All other forms of cutaneous tuberculosis show more or less typical tuberculous histopathology; tuberculosis verrucosa cutis is characterized by massive pseudoepitheliomatous hyperplasia of epidermis and abscesses.

Mycobacteria are found in primary inoculation tuberculosis, scrofuloderma, acute miliary tuberculosis, metastatic tuberculosis abscess and orificial tuberculosis, but only with difficulty or not at all in lupus vulgaris and tuberculosis verrucosa cutis.

Culture yields mycobacteria (also from lesions of lupus vulgaris and tuberculosis verrucosa cutis).

Table I. Essential differences between tuberculosis verrucosa cutis (TBVC), Lupus vulgaris (LV) and Scrofuloderma

	TBVC	LV	Scrofuloderma
Source	Exogenous	Exo- and endogenous	Endogenous
Immunity	Good	Good to poor	Poor
Site	Extremities	Head and neck	Neck, axilla, groin
Clinical feature	Hyperkeratotic, warty, firm, plaque	Reddish plaque.	Firm subcutaneous nodule
Important finding	Pus from crypts - on pressure	Diascopy Apple jelly nodule	Sinus tract on probing
Lymphadenopathy	Nil	Present	Underlying

Skin testing

Primary inoculation tuberculosis: Patient converts from (Mantoux test) negative to positive during the first weeks of the infection.

Acute miliary tuberculosis: Skin testing is usually negative.

Scrofuloderma and metastatic tuberculosis abscess: Skin testing may be negative or positive depending on state of immunity.

Lupus vulgaris and tuberculosis verrucosa cutis: Skin testing is positive.

Treatment [8,9,10]

The treatment of cutaneous tuberculosis is the same as that of tuberculosis elsewhere in the body. The regimen of two months of four drugs and four months of two drugs holds good and gives successful results.

Points to Remember

- ***Cutaneous tuberculosis is not as rare as reported.***
- ***Childhood skin tuberculosis represents 18% to 82% of all cutaneous tuberculosis cases.***
- ***Scrofuloderma and lupus vulgaris are the two most common clinical forms in children.***
- ***Clinical presentation depends on the virulence and number of mycobacteria causing the infection, the immunological status of the host and the route of inoculation of the mycobacteria into the skin.***
- ***Clinical diagnosis is confirmed, bacteriologically (smear for AFB), immunologically (tuberculin test), radiologically (X-ray of affected bone/joint) and histologically (skin biopsy).***
- ***At times, treatment may have to be commenced empirically when the clinical suspicion is compelling.***
- ***The treatment of cutaneous tuberculosis is the same as that of tuberculosis elsewhere in the body.***

References

1. Sethuraman G, Ramesh V. Cutaneous tuberculosis in children. Pediatr Dermatol 2013; 30(1):7-16.
2. Singal A, Sonthalia S. Cutaneous tuberculosis in children: The Indian perspective. Indian J Dermatol Venereol Leprol 2010; 76:494-503.
3. Kumar B, Rai R, Kaur I, Sahoo B, Muralidhar S, Radotra BD. Childhood cutaneous tuberculosis: A study over 25 years from northern India. Int J Dermatol 2001; 40:26-32.
4. Umapathy KC, Begum R, Ravichandran G, Rahman F, Paramasivan CN, Ramanathan VD. Comprehensive findings on clinical, bacteriological, histopathological and therapeutic aspects of cutaneous tuberculosis. Trop Med Int Health 2006; 11:1521-1528.
5. Ramesh V, Misra RS, Jain RK. Secondary tuberculosis of the skin. Clinical features and problems in laboratory diagnosis. Int J Dermatol 1987; 26:578-581.
6. Cutler RR, Baithun SI, Doran HM, Wilson P. Association between the histological diagnosis of tuberculosis and microbiological findings. Tuber Lung Dis 1994; 75: 75–79.
7. Dogra S, Narang P, Mendiratta DK, Chaturvedi P, Reingold AL, Colford JM Jr, et al. Comparison of a whole blood interferon gamma assay with tuberculin skin testing for the detection of tuberculosis infection in hospitalized children in rural India. J Infect 2007; 54:267-276.
8. Ramam M, Mittal R, Ramesh V. How soon does cutaneous tuberculosis respond to treatment? Implications for a therapeutic test of diagnosis. Int J Dermatol 2005; 44: 121-124.
9. Ramam M, Tejasvi T, Manchanda Y, Sharma S, Mittal R. What is the appropriate duration of a therapeutic trial in cutaneous tuberculosis? Further observations. Indian J Dermatol Venereol Leprol 2007; 73:243-246.
10. Treatment of tuberculosis: guidelines. 4th ed. Geneva: World Health Organization, 2009 (WHO/HTM/TB/2009.420).

NEWS AND NOTES

ISPID 2015
21st to 23rd February, 2015
Venue: Hotel Leela Palace, Chennai

For further details Contact
Dr. Meenakshi Krishnan
Mob: 9445110583

TUBERCULOSIS

IMMUNOLOGY OF TUBERCULOSIS

***Prawin Kumar**
****Rakesh Lodha**
*****Sushil Kumar Kabra**

Abstract: *The understanding of immunopathogenesis of tuberculosis is important to know why only a few individuals exposed to M. tuberculosis develop disease. Immune response begins with the entry of M. tuberculosis inside the host and first innate immunity comes into action followed by adaptive immunity which leads to development of effective immune response against tuberculosis (TB) in the majority. But these immune responses are not able to eliminate the bacilli completely, which remain in non-replicating state (Latent TB Infection- LTBI). M. tuberculosis has also evolved several mechanisms to combat with the human host defence system. How latent infection develops into active TB is not well understood; it has strong association with weakening of immune response. Over the last 20-30 years, only two new antitubercular drugs have been developed while drug resistant tuberculosis is spreading at a steady rate. Hence, immunotherapy might be of value in control of TB. Also, as no new vaccine against TB has been developed after 1902, the knowledge of immune pathways may give an opportunity to develop new vaccines.*

Keywords:*Immunology, IGRA, Mantoux test, Childhood tuberculosis.*

Tuberculosis (TB) is a major global health problem. As per WHO estimates, about one-third of the world population has latent TB infection.[1] Reactivation from latent infection occurs at the rate of 0.1%-0.5% per year and the lifetime risk of developing active infection is estimated to be 5%-10%. However, in HIV infected patients, the risk of development of active infection is 5-15% per year with estimated 50% life time risk.[2] Why all the individuals coming in contact with Mycobacterium tuberculosis do not develop infection and why some develop illness and remain in stage of latent TB is not clear. The complex process of 'infection-latency-illness' has been explained by various immune mechanisms. We have reviewed some of the important immune mechanisms in this article.

Immunopathogenesis

M.tuberculosis is an obligate aerobic intracellular pathogen. There are several components of mycobacteria which can stimulate and sustain host immune response.[3] The recent discovery of region of difference (RD) antigen by genomic study is considered to have a role in the virulence mechanism of M.tuberculosis. The most prominent RD antigens are ESAT-6 (EsxA) and CFP-10 (ExsB) which are secreted proteins and influence in vivo interaction between Mycobacterium and host response system.[3,4]

Infection with TB can be divided into 3 stages: primary, latent and secondary infection. Primary TB usually occurs during childhood after an initial contact with tubercle bacilli. After reaching terminal alveoli, mycobacteria are engulfed by phagocytic cells, get internalized and start replicating intracellularly. At this stage bacilli laden immune cells move to lymph nodes and to blood leading to systemic dissemination before development of adaptive immunity. Cell-mediated immune response develops in 2-8 weeks after initial infection and macrophages together with other immune cells form granuloma which walls off the necrotic tissue and this limits further multiplication and spread of the bacilli to other sites.[5]

Role of innate immunity in M.tuberculosis

Innate immunity plays a very important role in the prevention of M. tuberculosis infection.

The first step begins with phagocytosis of bacilli by antigen presenting cells (APC) which include alveolar macrophage and dendritic cells. How these innate immune cells recognize the bacilli is one of the areas of TB research. APC interacts with M. tuberculosis by specific pathogen recognition receptors (PRRs) which recognise'pathogen-associated molecular pattern (PAMP)' on the surface of bacilli which is essential for initiation and coordination of the host innate immune response.[5,6]

* Senior Research Medical Officer
** Additional Professor
*** Professor
Department of Pediatrics,
All India Institute of Medical Sciences,
New Delhi.

There are several groups of specific pathogen recognition receptors (Table I) identified on APC in which toll-like receptors (TLRs) are the most important. The fates of M. tuberculosis after internalization through different receptors are also different.[6,7]

The interaction of M. tuberculosis with specific receptors on APCs leads to intracellular signalling cascade that results in the production of proinflammatory cytokines such astumor necrosis factor (TNF-α), IL-1, IL-12, chemokines and nitric oxide.[5] TLRs also activate vitamin D receptors which leads to synthesis of antimicrobial peptides cathelicidin and beta-defensin to kill intracellular bacilli.[5,8]

M. tuberculosis has evolved to evade host innate immunity to survive and proliferate inside the phagocytes. When ManLAM (mycobacterium cell envelope components) binds with mannose receptor,it results in anti-inflammatory response as ManLAM inhibits mannose receptor-dependant IL-12 production. It also interferes with negative feedback mechanism on TLR for their benefits.[9]

Fate of M. tuberculosis inside the host cells

After entry of M. tuberculosis inside the cells as phagosomes, the phagocytes try to kill them by phagosomes-lysosome fusion, generation of reactive oxygen intermediates and generation of reactive nitrogen intermediates, particularly nitric oxide. M. tuberculosis also evolves to develop the mechanism to escape from this immune response.[4,5]

Death of bacilli-laden phagocytes by different mechanism is considered a part of innate host immune system. The binding of some specific M. tuberculosis ligands to macrophage can lead to autophagy, apoptosis and necrosis by which intracellular pathogens are eliminated along with dying host cells.[4,5] Natural killer (NK) cells, play an important role in the killing of M. tuberculosis either directly or by killing the infected phagocytes. In the early stage of infection, it activates the phagocytic cells at the site of infection. It produces IFN-γ which can lyse bacilli laden macrophage. Cytotoxicity of NK cell is most likely due to apoptosis. It can also modulate the adaptive immune

Table I. Specific pathogen recognition receptors on APCs and corresponding M.tuberculosis components[4,5,6&7]

Specific pathogen recognition receptors on antigen presenting cells (APCs)	M. tuberculosis components
Pattern recognition receptors as Toll like receptors (TLRs) lipoproteins, lipoarabinomannan and lipids	Recognize bacterial cell wall components, including
Cytosolic nucleotide-binding oligomerization domain (NOD) like receptors (NLRs)	Muramyl dipeptide
C type lectin: it includes - Mannose receptor (CD207) Dendritic cell-specific intercellular adhesion molecule grabbing non-integrin (DC-SIGN) Dectin-1	ManLAM (MannosylatedLipoarabinomannan)expansion on cell envelope Mannose type carbohydrate Interact with TLR2
Complement receptors (CR1, CR3, CR4)	Complement attached to mycobacterium
Scavenger receptors	Low density lipoprotein Polyribonucleotide Polysaccharides (Dextran sulphate)
Surfactant protein A receptors (Sp-A)	Surface lipoarabinomannan
Cholesterol receptors	Cholesterol-like molecule on cell surface Tryptophane-aspartate containing coat (TACO) protein

response against mycobacterium. The role of neutrophils in innate immunity against mycobacterial infection is less clear.[5]

Role of adaptive immunity in M. tuberculosis infection

There are two types of adaptive immunity i.e. cellular immunity mediated by T-cells, and humoral immunity mediated by soluble molecule antibodies that are produced by B-cells.[4]

Cell mediated immunity (CMI)

CMI develops 2-8 weeks after infection, along with tissue hypersensitivity reaction.[5] T lymphocytes work by either directly killing infected cells (accomplished by cytotoxic T lymphocytes) or by activating phagocytes to kill ingested microbes, via the production of soluble protein mediators called cytokines.

The activation of naive T cells requires presentation of processed antigen (M. tuberculosis) by antigen presenting cells (macrophages/dendritic cells) along with corresponding major histocompatibility complex (MHC) to naive T-cells. On the other hand antigens which have been processed in cytosol are recognized by CD8+ cells with MHC I molecule. After activation, CD4+ cells help to amplify the host immune response by activating effector cells and recruiting additional immune cells to the site of disease, whereas CD8+ cells are more likely to be directly cytotoxic to target cells.[4,5]

Some components of M.tuberculosis such as ManLAM, TDMand the 19 kDa lipoprotein can modulate antigen-processing pathways by MHC class I, MHC class II and CD1 molecules that results in persistence of bacilli inside the macrophages.[5]

CD4+ cells after activation secretes IL-2 which causes further proliferation and differentiation of CD4+ cells into effector and memory cells. Based on the pattern of cytokine secretion after antigen stimulation, effector cells can be classified as Th1, Th2, Th17 and Treg (regulatory) cells,of which Th1 cells play a prominent role in protection against TB.[4,5,11] Th0 or null cells under influence of IL-12 differentiate into Th1 cells which are characterized by secretion of cytokines IFN-γ and IL-2. The hallmark of Th1 cells is the production of IFN-γ which has been shown during the past several years to be a key effector cytokine in the host response against tuberculosis. This pro-inflammatory cytokine has multiple beneficial effects in tuberculosis and its action is mainly centered on the activation of macrophages at different levels including granuloma formation. Th2 cells secrete cytokine IL-4, IL-5 and IL-10 which involve in production of IgE and recruitment of eosinophils and do not play a major role in host defence against TB. In general, Th1 cells regulate the activity of macrophages and cytotoxic T-cells andhence provide protective immunity while Th2 cells regulate the activity of B-cell and often impaired immunity so a balance between Th1/Th2 will decide final outcome.[4,12]

Th 17, a relatively new subset of T-cells, is characterized by secretion of unique cytokines IL-17, IL-21 and IL-22 mediated by IL-6 and transforming growth factor-beta (TGF-β).These cytokines stimulate defensin production and neutrophil and monocyte recruitment at the site of immune response and involved in inflammatory response as early phase of hostdefence. During infection with M. tuberculosis, both Th1 and Th17 are induced, but Th1response is predominant and Th17 may play a minor role during primary infection.[5,11]

Regulatory T-cells (Treg) play an important role in negatively regulating the immune response, by suppressing the effector functions of various immune cells, including T lymphocytes. They minimize the collateral tissue damage on one side but on other side help the pathogen to persist. There are two types of Treg cells one which is naturally present and the other being adaptive or induced Treg cells. IL-6 inhibits the generation while TGF- β induce Treg cells differentiation. These cells may play a role in the prolonged suppression of IFN-γ production in response to M. tuberculosis infection.[4,11]

CD8+ cells (Cytotoxic cells) produce cytokines like IFN-ã and are also cytotoxic to M. tuberculosis-infected macrophage. Secretion of IFN-γ regulates the balance between Th1 and Th2 cells to the protective side. It is usually activated by cytosolic antigen and so the bacilli which escape from phagosome are presented to CD8+ cells and result in killing of bacilli-laden macrophage. They kill intracellular bacteria by way of granulysin and perforin. It has been found that abundant number of M. tuberculosis-specific CD8+ cells are present in individuals with latent infection and depletion of CD8+ due to any cause may cause reactivation.[5,11]

γ/δ T-cellsare T-cells which seem to play a role in early immune response against TB and also have an important part in the protective immunity in patients with latent infection and after vaccination.[11,12]

NKT cells have properties of both NK and T cells and are CD-1 restricted cells which have recently been shown to mediate protection against M. tuberculosis in the

mouse model. NK cells contribute to protective immunity through killing of regulatory T-cells (Treg cells).[12]

Memory T (T_M) cells are formed after exposure or M. Tuberculosis infection and they can develop into effector and central Tm cells. Tm cells proliferate promptly after encounter with antigens and produce multiple cytokines such as IFN-γ, IL-2, TNF-α, lymph toxin and/or GM-CSF.[11]

Role of cytokines in M. Tuberculosis

Cytokines are key mediators of both innate and acquired immunity. A brief description of cytokines, their main source of production and important role in context of tuberculosis is given in Table II.[4,12,13]

It has been observed that individuals with the mutations of IL-12p40 or the IL-12R genes are highly susceptible to disseminated BCG and M.Tuberculosis. Recently work is going on to add IL-12 in vaccine development to improve vaccine potency.[12]

IFN-γ production may vary among different individuals and some studies suggest that IFN-γ levels are depressed in patients with moderate to severe pulmonary disease and in malnourished patients. Individuals with defective genes for IFN-γ or the IFN-γ receptor are more prone to M. tuberculosis infection.[12,13]

Chemokines are molecules which attract other inflammatory cells at the site of infection. The important chemokines in context of M. tuberculosis are IL-8, monocyte chemo-attractant protein-1 (MCP-1) and regulated on activation normal T cell expressed and secreted (RANTES).[4,12]

Role of granuloma formation in M.tuberculosis

Granuloma formation is the hallmark of M. tuberculosis infection.

TNF-α has been historically considered instrumental to granuloma formation and to increase the ability of macrophage control of intracellular mycobacteria in granuloma formation. Recent evidence showed that host matrix-metallo proteinase-9 (MMP-9) production by

Table II. Different cytokines, their main source and role in tuberculosis pathogenesis.[4,12,13]

Cytokines	Main source	Important role in TB
Interleukin -12	Macrophage and dendritic cells	Differentiation of CD4+ cells into Th1 subset
Interferon-γ (IFN-γ)	Activated lymphocytes and NK cells	With TNF-α activates macrophages and promote:- Bacterial killing Granuloma formation Potentiates antigen presentation
Tumor necrosis factor (TNF-α)	Macrophages, dendritic cells and T cells	Responsible for protection as well as immunopathology which cause tissue damage. Granuloma formation Potentiates expression of other cytokines
Interleukin-2	Activated T cells	Further multiplication and differentiation of activated T-cell.
Interleukin-4	Activated T cells	Differentiates CD4+ cells into Th2 subset.
Interleukin-1	Monocytes	Acute phase response (fever and cachexia) Stimulates T lymphocyte expression of IL-2 receptors and IL-2 release
Interleukin-10	Activated macrophage, T cells	Suppresses proliferation of activated T cells and reverses the mycobactericidal effect of TNF-α
Transforming growth factor-beta (TGF-β)	Monocytes	Exhibits both pro-inflammatory and anti-inflammatory activities

macrophages and epithelial cells upon interaction with RD-1 locus-encoded, secreted.

ESAT-6 antigen of mycobacteria has important role in granuloma formation.[11,12] With development of adaptive immunity the active T- lymphocytes (CD 4+ and CD8+) and their product (IFN-γ) accumulated in early granuloma and formed the late phase granuloma.

In granuloma, cell death by necrosis causes cell lysis and viable mycobacteria spread locally and further increase the pathogen load while apoptosis maintains intact cellular membrane leading to containment of mycobacteria. Despite development of strong immune response, host immunity failsin complete elimination of the bacilli and they persist in granuloma in non-replicating stage as latent infection.[12]

Latent TB infection [LTBI]

Traditionally LTBI is considered as M. tuberculosis remaining in non-replicating state in granuloma. Whenever there is disruption of host immune responses (immune-compromised state) active TB infection results.[5] Recent experimental data showed a dynamic model of LTBI where both endogenous reactivation as well as damage response occurs constantly in immunocompetent individuals. According to this model during infection although M. tuberculosis grows inside phagosomes, some bacilli released from necrotic macrophages in extracellular milieu in developing granulomas stop replicating due to hypoxic and acidic environment and bactericidal enzyme released from dying neutrophils and macrophages. The actively growing bacilli are killed by effective immune response while non-replicating bacilli resist killing and survive.[5,11] According to WHO almost one third of world population has latent TB infection.[10]

Persons with LTBI actually represent a heterogeneous group of individuals which includes: 1) those who have subclinical disease, 2) those who will progress to primary active disease; 3) those who maintain persistent, lifelong infection; 4) those who temporarily suppress infection but later develop active TB, possibly as a result of immunosuppression or some other event (i.e., true latent infection); 5) those who are able, either through innate or adaptive immunity or the combination, to effectively clear the pathogen.[14]

Both TST and interferon gamma release assay (IGRA) are positive in LTBI so they are not able to differentiate between latent and active disease.

Reactivation of LTBI

Reactivation of LTBI means progression to symptomatic active disease which is different from re-infection from other strain of tuberculosis. Although disruption of host immunity is well known for reactivation of LTBI it can occur in several other common conditions such as diabetis mellitus, steroid therapy, hematological malignancy, malnutrition, cancer chemotherapy, uremia and advanced age. The exact mechanism of reactivation apart from impaired immunity is not well known and other possible mechanisms have been proposed on the basis of studies in animal model.[5,10,14]

Disruption of host immunity

In HIV positive individual, depletion (quantity and qualitative) of CD4+ cells results in more risk of progression to active TB from LTBI. The risk of development of active infection is 5%-15 % per year with estimated 50% lifetime risk in HIV positive patient.[1] There is also increased risk of reactivation in association with therapeutic neutralization of TNF-α with monoclonal antibodies.

T cell exhaustion

It is one of the possible mechanisms of reactivation in which bacilli-specific T cells are present but express inhibitory receptors that prevent their proliferation and their ability to mediate effector functions. T cell exhaustion is best described in chronic viral infections, such as lymphocytic choriomeningitis virus (LCMV) infection in mice, and hepatitis C virus and HIV infection in humans.[10,14]

Altered antigen expression

M. tuberculosis regulate their gene expression in response to signals from their environment that give an opportunity for alteration of antigen gene expression allowing the bacteria to evade recognition by T cells specific for certain antigens. There are at least two mycobacterial antigens ESAT6 and Ag85B that are down regulated after the appearance of activated T lymphocytes.[10,14]

Altered cell trafficking

For maintaining effective immunity for a long time (decades) against M. tuberculosis continuous recruitment of effector immune cells is essential and so any defect in cell trafficking could lead to reactivation of TB. In experimental model (mice) transgenic overexpression of chemokine ligand 2 (CCL2) also known as monocyte chemotactic protein 1 (MCP1) or the absence of chemokine (c-c motif) receptor 2 (CCR2) decreases the recruitment of monocytes and dendritic cells (DCs) to the site of M. tuberculosis infection and is associated with poorer immune control of infection.[10,14]

Immunodiagnosis

Some new biomarkers for diagnosis of TB have the potential of being used as point of care test. These biomarkers may be host-specific or mycobacterial-specific; out of these Interferon Gamma Release Assay (IGRA) has been studied extensively. The overview of biomarkers has been given in Table III.[4,11]

Table III. Various biomarkers of tuberculosis infection

Host-specific biomarkers	M. tuberculosis-specific biomarkers
Tuberculin skin test (TST)	Antigen 85 complex proteins
IGRAs -QuantiFERON -TB-T-SPOT.TB	38 kDa Antigen Lipoarabinomannan Transrenal Mycobacteria DNA
IL4/IL-4δ2 ratio	MPT64
Antigen/Antibody Based Test	Antigen 60 PE and PPE antigens HBHA DosRRegulon Regulated Protein Volatile Mycobacterial Markers in Breath

Interferon gamma release assays

It is a host-specific biomarker developed in 2001 by Lalvani, et al as an enzyme-linked immuno-spot test (ELISpot). It detects release of IFN-γ from T-cells in response to M. tuberculosis specific antigens ESAT-6 and CFP-10. These specific antigens are present only in M. tuberculosis not in BCG vaccine strain. Currently there are only two commercially available IGRAs test: QuantiFERON-TB® and T-SPOT.TB®. Although IGRAs are 94%-100% sensitive, these are unable to differentiate between active and latent TB. Studies have shown that with recovery from disease stage there is fall in specific IGF-ã production. IGRAs may be more beneficial in LTBI, in contact tracing and screening of high risk group in low endemic area.[4,11] However, these are not of much use in high endemic region.

Immunology of tuberculosis in children

Infants are also more prone for meningeal and disseminated TB (20%) than older children and adults (< 1%). This is due to the fact that they have immature immune system (both innate and adaptive) and also due to their prolonged contact with infected care givers. The incidence of disease after M. tuberculosis infection is much more common in children less than 2 years of age. The basic deficiency in innate immunity is impaired macrophage function. Both human and experimental studies have shown that infants and young children have deficiency of macrophage function (chemotaxis, phagocytosis) which is the first and most important part in host immunity against TB. Dendritic cells which have paramount importance in priming of adaptive immunity also have impaired function. The balance between Th1 andTh2 type of cell-mediated immunity is complex in infants and some studies have shown that it is towards Th2 type. The role of CD8+ cell in immunity against TB is possibly limited. Likewise cytokine production also seems to be depressed in younger children. Although the basic pathways of immune response are similar, due to immature immune system, younger children are more susceptible to M. tuberculosis than older children and adults.[15]

Role of immunotherapy in TB

As we have seen on one side, tuberculosis disease occurs with the failure or inappropriate immune regulation and on the other side most of the lung damage is due to excessive host response rather than mycobacterium virulence. Several attempts have been taken to modulate the immune response for therapy but most of them either are not effective or have not shown beneficial evidence till now in experimental model only. Single dose of M. vaccae was not effective in clinical trial although full results of multiple dose studies are awaited. Role of recombinant IFN-γ and IL-2 showed minimal or no effects, but rIL-12 which drives the immunity towards Th1 subset showed benefit in a murine model. Role of high dose prednisolone which acts by attenuating TNF production which is responsible for host damage in large controlled trial showed dramatic effect on enhanced sputum conversion.[5,11]

Role of immunology in development of vaccine

BCG (BacilleCalmette Guerin) was introduced in 1902 and is still the only approved anti-tuberculosis vaccine and widely used globally. It has very good safety profile in immunocompetent individual. Several attempts have been taken to develop a new vaccine with aim to prevent primary M. tuberculosis infection through preinfection vaccination or which prevents transition from latent to active disease. The basic methods in development of newer vaccines are incorporation of M. tuberculosis antigens (such as ESAT-6, CFP-10 and Ag85) either in BCG or through viral vectors

by genetic engineering (DNA vaccine). Attempts are also going on to develop aerosolized TB vaccine and preliminary studies have shown strongly induced local pulmonary antigen-specific T-cell responses that may have characteristics of protective immunity.[4,11] The summary of the candidate anti-tubercular vaccines being evaluated is given in Table IV.

Table IV. Summary of anti-tubercular vaccine candidate being evaluated[4, 11,&15]

Group	Vaccine
Recombinant BCG (rBCG)	rBCG 30rBCG-pfo rBCGΔUreC:Hly VPM-X rBCG (AERAS-407)
Attenuated M.tuberculosis	ΔlysA ΔpanCD mutant ΔRD1 ΔpanCD mutant
Subunit	Mtb72F Hybrid-1 GSK M72
Viral-vector	MVA expressing Ag85A

Conclusion

Tuberculosis remains a global health problem. The understanding of immunopathogenesis of tuberculosis is important so as to appreciate why only some individuals exposed to M. tuberculosis develop the disease as well as in the development of newer antitubercular therapy and new vaccines. After the entry of M. tuberculosis, first innate immunity comes into action followed by adaptive immunity which leads to development of effective immune response against tuberculosis. However, immune response is not able to eliminate the bacilli completely and they do remain in non-replicating state leading to LTBI in most while disease develops in few. M. tuberculosis has also evolved several mechanisms to combat human host defense system. For the last 20-30 years, only a few new antitubercular drugs have been developed while drug resistant tuberculosis is spreading; development of immunotherapy may be valuable in the control of TB. There is a great need for a new vaccine to reduce the burden of tuberculosis infection and disease.

Points to Remember

- ***A clear understanding of immune response against tuberculosis which is however a complex process, is important for development of new antitubercular therapy as well as vaccines.***
- ***Both innate and cell-mediated immunity play an important role but it is the latter which provides protective immunity against diseases as well as development of hypersensitivity skin reaction.***
- ***Mycobacterium tuberculosis has also evolved several mechanisms to evade the protective immune response and persist inside the host cells.***
- ***Reactivation from latent tuberculosis is not well understood but several studies point towards weakening host immune response.***
- ***Although the basic mechanism of immune responses is similar in young infants, they are more susceptible for development of disease after exposure to M. tuberculosis as they have an immature immune system.***
- ***The development of newer vaccines against M. tuberculosis is based upon incorporation of M. tuberculosis antigens (such as ESAT-6, CFP-10, and Ag85) either in BCG or viral vectors.***
- ***The role of immunodiagnosis and immunotherapy in tuberculosis are emerging.***

References

1. World Health Organization, "Global tuberculosis control: surveillance, planning and financing," WHO/HTM/TB/ 2009.411, WHO, Geneva, Switzerland, 2009.
2. Wells CD, Cegielski JP, Nelson LJ, Laserson KF, Holtzl TH, Finlay A, et al. HIV infection and multidrug-resistant tuberculosis-the perfect storm. J Infect Dis 2007; 196: S86 - S107.
3. Jo EK. Mycobacterial interaction with innate receptors: TLRs, C-type lectins, and NLRs. CurrOpin Infect Dis 2008; 21: 279–286.
4. Seth V, Kabra SK. Immunology of tuberculosis: basic aspect and relevance for immunodiagnostic test. In: Seth V, Kabra SK, Eds. Essential of Tuberculosis in Children. 4th edn, Jaypee Brothers Medical publishers, Delhi 2011;pp66-89.
5. Ahmad S. Pathogenesis, Immunology and diagnosis of latent mycobacterium tuberculosis infection. Clin Dev Immunol 2011;2011:814943.doi: 10.1155/2011/ 814943. Epub 2010 Dec 27. Review. PMID: 21234341.
6. Akira S, Uematsu S, Takeuchi O. Pathogen recognition and innate immunity. Cell 2006; 124: 783–801.
7. Harding CV, Boom WH. Regulation of antigen presentation by Mycobacterium tuberculosis: a role for Toll-like receptors. Nature Rev Microbiol 2010; 8: 296–307.

8. Liu PT, Stenger S, Tang DH, Modlin RL. Cutting edge: vitamin D-mediated human antimicrobial activity against Mycobacterium tuberculosis is dependent on the induction of cathelicidin. J Immunol 2007; 179: 2060-2063.
9. Nigou J, Zelle-Rieser C, Gilleron M, Thurnher M, Puzo G. Mannosylatedlipoarabinomannans inhibit IL-12 production by human dendritic cells: evidence for a negative signal delivered through the mannose receptor. J Immunol 2001; 166: 7477-7485.
10. Ernst JD. The immunological life cycle of tuberculosis. Nature Immunol 2012; 12: 581-591.
11. Dheda K, Schwander SK, Zhu B, Zyl-smit RN, Zhang Y. The immunology of tuberculosis: from bench to bedside. Respirology 2010; 15: 433-450.
12. Schluger NW, Rom WN. The host immune response to tuberculosis. Am J RespirCrit Care Med 1998; 157: 679-691.
13. Raja A. Immunology of tuberculosis. Indian J Med Res 2004; 120: 213-232.
14. Bozzano F, Marras F, Maria AD. Immunology of tuberculosis. Mediterr J Hematol Infect Dis 2014;6: e2014027.
15. Lewinsohn DA, Gennaro ML, Scholvinck L, Lewinshon DM. Tuberculosis immunology in children: diagnostic and therapeutic challenges and opportunities. Int J Tuberc Lung Dis 2004; 8: 658-674.

CLIPPINGS

Watching Sex on Television Predicts Adolescent Initiation of Sexual Behavior.

A national longitudinal survey of 1792 adolescents, 12 to 17 years of age was conducted in USA. In baseline and 1-year follow-up interviews, participants reported their TV viewing habits and sexual experience and responded to measures of more than a dozen factors known to be associated with adolescent sexual initiation. TV viewing data were combined with the results of a scientific analysis of TV sexual content to derive measures of exposure to sexual content, depictions of sexual risks or safety, and depictions of sexual behavior (versus talk about sex but no behavior).

Outcome Measures: Initiation of intercourse and advancement in non coital sexual activity level, during a 1-year period.

Results: Multivariate regression analysis indicated that adolescents who viewed more sexual content at baseline were more likely to initiate intercourse and progress to more advanced non coital sexual activities during the subsequent year, controlling for respondent characteristics that might otherwise explain these relationships. The size of the adjusted intercourse effect was such that youths in the 90th percentile of TV sex viewing had a predicted probability of intercourse initiation that was approximately double that of youths in the 10th percentile, for all ages studied. Exposure to TV that included only talk about sex was associated with the same risks as exposure to TV that depicted sexual behavior. African American youths who watched more depictions of sexual risks or safety were less likely to initiate intercourse in the subsequent year.

Conclusions: Watching sex on TV predicts and may hasten adolescent sexual initiation. Reducing the amount of sexual content in entertainment programming, reducing adolescent exposure to this content, or increasing references to and depictions of possible negative consequences of sexual activity could appreciably delay the initiation of coital and non coital activities. Alternatively parents may be able to reduce the effects of sexual content by watching TV with their teen aged children and discussing their own beliefs about sex and the behaviors portrayed. Pediatricians should encourage these family discussions.

Rebecca L. Collins, Marc N. Elliott, Sandra H. Berry, David E. Kanouse, Dale Kunkel, Sarah B. Hunter,et al . Watching Sex on Television Predicts Adolescent Initiation of Sexual Behavior. Pediatrics 2014; 114: e280-e289.

TUBERCULOSIS

SPECIAL SITUATIONS IN MANAGEMENT OF TUBERCULOSIS

**** Vijayasekaran D***
***** Shanthi Ramesh***

Abstract: *Pediatric tuberculosis accounts for 10%-15% of global TB. The current RNTCP guidelines emphasize that the treating physician should take responsibility for completion of treatment by the patient. Management issues in special situations like pregnant women with TB, perinatal TB, latent tuberculosis, children exposed to adults with TB, drug-induced hepatitis and TB in renal insufficiency are discussed. Ensuring patient adherence to the drug regimen and successful completion of directly observed therapy help both the individual and the society.*

Keywords: *Tuberculosis, Pregnancy, Perinatal TB,Latent TB, Chemoprophylaxis, Hepatitis, BCG.*

Tuberculosis (TB) affects people of all ages irrespective of the socioeconomic status. About one million cases of pediatric TB are estimated to occur every year accounting for 10%-15% of global TB.[1] Despite the availability of anti-tuberculosis drugs (ATT) and the Bacille Calmette-Guérin (BCG) vaccine, Mycobacterium tuberculosis continues to claim more lives than any other microbe. The complex features of the bacillus such as virulence factors, fatty envelope, intracellular pathogenesis, slow multiplication and dormancy help it to escape from containment in spite of effective chemotherapy.

Early diagnosis, combined with the knowledge of anti-tuberculosis drug therapy by the treating physician, efforts taken to maintain good compliance by the patient till the end of therapy and adequate nutrition for the patient are the key points that decide the successful outcome of anti-tuberculosis therapy.[2]

* Visiting Professor
Consultant Pediatric Pulmonologist,
** Associate Professor,
Sree Balaji Medical College,
Chennai.

The guidelines for management for tuberculosis are being constantly updated based on evidence from clinical trials. The current guidelines for tuberculosis management emphasize that the treating physician should take the responsibility of treatment completion by the patient which forms a fundamental principle in tuberculosis control.[3]

Special situations in tuberculosis

There are situations where special considerations need to be taken into account while treating TB like pregnant mother with tuberculosis, perinatal tuberculosis, management of neonate born to a mother with tuberculosis, management of latent TB, children with contact positivity, drug-induced hepatitis and TB in renal insufficiency. Considering the increasing trend of TB drug resistance and HIV, scientists who are closely associated with tuberculosis control have revised some of the past recommendations. The overall principles of tuberculosis management remain the same (Table I).

Table I. Principles in management of TB

a) For tuberculin skin test only 1 or 2 TU of purified protein derivative (PPD) should be used and definitely not >5 TU
b) A negative Mantoux test does not exclude the diagnosis of active tuberculosis.
c) Though bacteriological confirmation is difficult, it should be attempted in all cases.
d) Susceptibility testing for TB drugs should be performed on positive isolates in the context of increasing drug-resistant tuberculosis.
e) Directly observed therapy, short course (DOTS) should always be used in treating children.
f) Monthly clinical evaluation is mandatory to identify possible adverse effects and to ensure compliance.
g) Rifampicin must not be discontinued because of minor side effects.
h) Single drug should not be added in failing regimen or suspected drug resistance.

Anti-tuberculosis therapy (ATT)

Intermittent short course chemotherapy is preferable compared to daily treatment bearing in mind cost, patient compliance and drug toxicity. DOTS is the most effective way to monitor treatment adherence.

Isoniazid (INH), Rifampicin (RMP), Ethambutol (EMB) and Pyrazinamide (PZA) are considered as first-line antituberculosis agents and form the core of initial treatment regimens. Parents may be informed in advance about mild adverse effects associated with ATT (nausea, vomiting, poor appetite, abdominal pain) to avoid sudden cessation of therapy. The consequences of split dosing and selective omission of ATT (drug resistance) should be adequately explained during the initiation of therapy. Since complete adherence to therapy is the key to achieving cure and decreasing the chances of development of resistance, it is imperative that the treating pediatrician makes all efforts to ensure compliance.

Pregnancy and tuberculosis

In pregnant women the treatment of tuberculosis should be initiated immediately after the diagnosis, because of the risk of tuberculosis to the fetus. All the anti-tuberculosis drugs cross the placenta but they do not appear to have teratogenic effects. Streptomycin (SM) is the only anti-tuberculosis drug documented to have harmful effects on the human fetus (congenital deafness) and should not be used.

Perinatal tuberculosis

Perinatal tuberculosis may be missed unless there is a high index of suspicion.

Perinatal tuberculosis is the term preferred over congenital tuberculosis because in most of these situations, the transmission of infection happens postnatally. Perinatal tuberculosis may be caused by (a) transplacental spread through the umbilical vein to the fetal liver, (b) aspiration or ingestion of infected amniotic fluid, and (c) airborne inoculation from close contacts (mother, other family members or nursery personnel). Of all the above, airborne inoculation from close contacts especially from the mother is the most important mode of spread.

The neonate may look ill and the symptoms generally begin in the second or third week of life. The most common symptoms include fever, poor weight gain, irritability, respiratory distress, poor feeding and hepatosplenomegaly. Unless there is a high index of suspicion the affected infant may be treated for bacterial sepsis.

Though the yield is less, all the suspected neonates are subjected to microbiologic investigations. To diagnose TB, epidemiological data of the active tuberculosis in the mother or other members of the family are of utmost importance in the diagnosis.[4] Gastric lavage should be done in all such cases. It has been shown that sputum induction is safe and useful for microbiological confirmation of pulmonary tuberculosis in infants and young children and preferable to gastric lavage.[5]

Once diagnosis is confirmed, four drug therapy for the first two months (intensive phase) followed by two drug therapy for the next four months (continuation phase) should be given. While managing a neonate born to a mother with tuberculosis, breastfeeding should not be stopped. The treating doctor should be knowledgeable about the drug dosage for daily and intermittent therapy. Children receiving ATT should be monitored for drug adverse effects and response to treatment (Table II).

Table II. Drug dosage and adverse effects

Drug	Daily therapy Dose / Kg	Inter mittent therapy Dose/Kg	Adverse effects
Rifampicin	10 mg	15 mg	Hepatotoxicity, pruritis, rash, gastritis, flu-like illness
Isoniazid	10mg	15 mg	Hepatoxicity, peripheral neuropathy
Pyrazinamide	30mg	35 mg	Polyarthralgia, hepatoxicity
Ethambutol	20mg	30 mg	Retrobulbar neuritis, decreased red-green color discrimination
Streptomycin	15mg	20 mg	Ototoxicity (vestibular and hearing), parasthesias, nephrotoxicity

Neonate born to a mother with tuberculosis

An infant born to a mother diagnosed with TB in pregnancy should be thoroughly investigated to rule out

congenital TB. Particularly malnourished infants presenting with clinical and radiographic signs for more than two weeks should be evaluated for tuberculosis. If active tuberculosis is ruled out, prophylactic therapy with INH for 6 months is recommended for newborns born to a mother with active tuberculosis.[6]

Modern chemotherapy is so efficacious that separation of the mother and infant is no longer considered mandatory if maternal compliance is ensured. Through the act of coughing, sneezing, singing and other forceful expiratory efforts, droplet nuclei may spread the infection from mother to the baby. So appropriate cough hygiene (avoid directly coughing against the face of the baby / using hand kerchief to close the mouth) should be observed by the mother to prevent the spread of infection. The risk of spread is more in a small, poorly ventilated room and this point has to be highlighted. Breastfeeding should be encouraged as ATT concentration in breast milk is too small to produce any toxicity in the nursing newborn. BCG vaccination appears to decrease the risk of tuberculosis in exposed infants and should not be withheld.[7]

Latent tuberculosis infection (LTBI) and Chemoprophylaxis

After inhaling the tubercle bacilli, many children may not develop disease (clinical or radiographic evidence) but rather develop latent tuberculosis infection, as evidenced by a reactive tuberculin skin test. In a person with intact cell-mediated immunity, the response to infection with the tubercle bacillus provides protection against reinfection. It is presumed that these children are infected with a low number of viable tubercle bacilli that are dormant and do not cause clinical disease or pathologic changes.[8]

Tuberculin skin test (TST) conversion occurs within 8 weeks of exposure and infection. Infection may persist for lifetime as latent infection. The estimated lifetime risk of developing tuberculosis disease for a young child infected with Mycobacterium tuberculosis as indicated by positive TST is about 10%.[9]

TST is considered positive if the induration is 10 mm or more provided the recommended PPD strength is used. Ideally 1TU of PPD should be used, 2 or 5 TU may be acceptable and in no case strength higher than 5 TU is recommended.

Children with LTBI represent the future reservoir, from which adult cases may arise. Hence, treating LTBI in children will contribute to the long-term goal of TB elimination.[10]

Immunocompetent children with LTBI should be monitored periodically (by assessing their symptoms, weight, and wellbeing) as most of them may not develop any problem, due to their protective immunity. If there is a suspicion of disease, these children should be subjected to chest radiography and icrobiologic investigations to rule out active disease. The decision to treat LTBI should be individualized, with consideration of the risks of therapy from adverse events, such as hepatotoxicity, balanced against the risk of development of active disease.

After analyzing various issues pertinent to the Indian context, especially in the light of emerging INH resistance, chemoprophylaxis for LTBI (preventive therapy) is advised in the following situations.

(a) All TST positive children who are receiving immunosuppressive therapy (e.g. Children with nephritic syndrome, acute leukemia, etc.).

(b) All HIV infected children with either exposure to an infectious TB case or a Mantoux positive (>=5 mm induration) but no active TB disease.6

The currently recommended dose of INH for chemoprophylaxis is 10 mg/kg, to be administered daily for 6 months.

Management of contact positivity

The Updated National Guidelines for Pediatric Tuberculosis recommend TB preventive therapy to all asymptomatic children aged 6 years and below who are in contact with smear positive pulmonary tuberculosis case irrespective of their BCG, TST or nutritional status. The dose of INH for chemoprophylaxis is 10 mg/kg daily for 6 months.[6]

Before starting preventive therapy, active disease must be excluded carefully by means of history, physical examination and chest radiography. Induced sputum samples should be sent for smear and culture, or other appropriate investigations should be performed if active disease is considered.

Active TB in young children signals a recent infection and indicates the probability of an undiagnosed case amongst the child's close adult contacts. Therefore, when disease is diagnosed in children, a thorough contact investigation should be done to identify the source case.

Drug-induced hepatotoxicity

Hepatitis is the commonest serious drug toxicity seen with antituberculosis medications. INH, RMP and PZA are

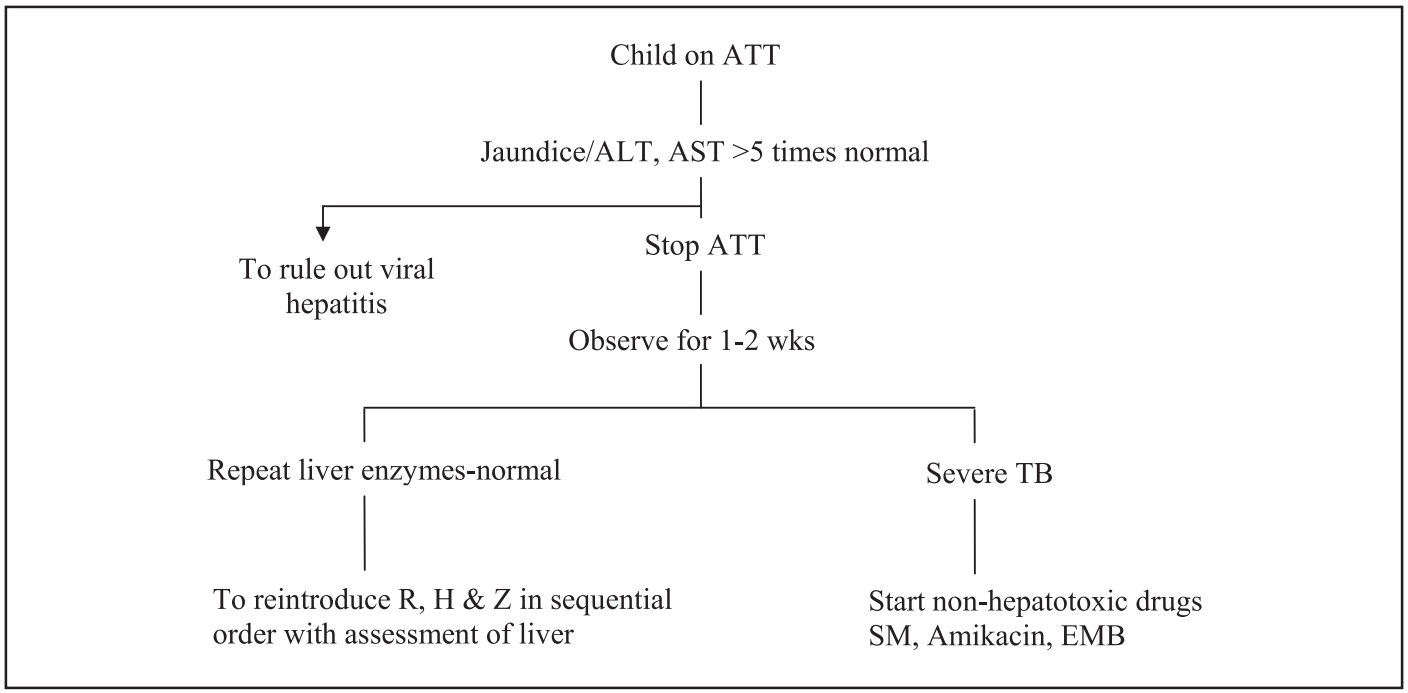


Fig.1. Drug-induced hepatotoxicity and its management

all hepatotoxic and may result in liver damage especially in patients with pre existing liver disease.

Drug-induced hepatitis is defined as a serum transaminase (AST) level more than five times the upper limit of normal in the absence of symptoms. As all anti-TB drugs are hepatic enzyme inducers, asymptomatic biochemical derangement without increase in bilirubin level maybe tolerated till the enzymes remain up to 5 times the normal range. If patient develops jaundice during therapy, all ATT should be stopped immediately. The drugs are withheld till the enzymes become normal (Fig.1).

Many patients with drug-induced hepatotoxicity can be successfully rechallenged with careful monitoring. Once the liver transaminases become near normal (decrease to less than two times the upper limit of normal) and/or symptoms of hepatitis have significantly improved, the first-line medications should be restarted. The drugs should be re-introduced in sequential order starting with RMP, followed by INH and then PZA. After adding the first drug, if the enzymes remain within the acceptable range, the second drug can be added (after 5-7 days). If the child with drug-induced hepatotoxicity is suffering with severe forms of tuberculosis like miliary-meningeal disease, considering the gravity of the situation, TB therapy with non-hepatotoxic drugs should be continued. Drugs like ethambutol, streptomycin, amikacin or a fluoroquinolone may be used in consultation with a specialist.

Tuberculosis with renal insufficiency

Patients with end-stage renal disease receiving hemodialysis are at substantially increased risk of active TB, due to impaired immunity in the context of chronic uremia. For tuberculosis patients with renal insufficiency undergoing hemodialysis, administration of all drugs after dialysis is preferred to avoid premature removal of drugs. To avoid toxicity it is important to monitor serum drug concentrations of these drugs.

BCG reactions

Normally BCG vaccination is given immediately after birth. The dose advised is 0.1 mL and should be given intradermally in the left deltoid region. Normal reaction involves the formation of papule, nodule, ulcer which is followed be scar formation and the reaction is usually completed by 8-12 weeks. BCG reactions depend upon a number of factors like the dosage, the strain of BCG vaccine, the age and the immunologic status of the recipient. The deviant BCG reactions include, nodule, recurrence of ulcer and abscess at the BCG injection site. Most of these reactions heal by themselves in 4-6 weeks' time. ometime BCG lymphadenopathy may appear at the left axillary or cervical area and regress spontaneously over a few months. Since these lesions are caused by bovine vaccine bacilli the current guidelines advise no ATT in these situations. Reassurance and a conservative therapeutic approach are usually adequate for their management.

Points to Remember

- ***Pregnant mothers can be safely administered anti tuberculous medications***
- ***Breast feeding should not be stopped while the mother is on ATT.***
- ***All efforts should be taken for bacteriological confirmation in perinatal TB and once confirmed 6 months of ATT recommended***
- ***If no evidence of TB is found in a neonate in contact with an infected mother, 6 months of INH prophylaxis is advised.***
- ***For Latent TB infection and asymptomatic children in contact with smear positive pulmonary TB, INH alone is to be given for 6 months.***
- ***If serum transaminase level rises more than 5 times upper limit of normal or jaundice develops while on ATT, medications are stopped and reintroduced when enzymes normalize. Viral Hepatitis needs to be excluded.***
- ***Patients with renal insufficiency undergoing hemodialysis needing ATT should be given all medications after dialysis.***
- ***Deviant BCG reactions need not be treated with ATT.***

References

1. World Health Organization. Guidance for National Tuberculosis Programmes on the Management of Tuberculosis in Children, Geneva: WHO, 2006.
2. Vijayasekaran D. Treatment of Childhood Tuberculosis. Symposium on Pediatric Tuberculosis. Indian J Pediatr 2011; 78 (4):443-448.
3. Treatment of Tuberculosis. Recommendations and Reports. American Thoracic Society, CDC and Infectious Diseases Society of America. 2003/ 52(RR11); 1-77.
4. Jacobs RF, Abernathy RS. Management of tuberculosis in pregnancy and the newborn. Clin Perinatol 1988; 15: 305-319.
5. Zar HJ, Hanslo D, Apolles P, Swingler G, Hussey G. Induced sputum versus gastric lavage for microbiological confirmation of pulmonary tuberculosis in infants and young children. Lancet 2005; 365(9454):130–134. Erratum in: Lancet. 2005 Jun 4-10; 365(9475):1926.
6. Kumar A, Gupta D, Nagaraja SB, Singh V, Sethi GR, Prasad J. Updated National Guidelines for Pediatric Tuberculosis in India, 2012. Indian Pediatr 2013; 50: 301-330.
7. Working Group on Tuberculosis, Indian Academy of Pediatrics. Consensus Statement on Childhood Tuberculosis. Indian Pediatr 2010; 47: 41-55.
8. Mandalakas AM, Strake JR. Tuberculosis and Nontuberculous Mycobacterial Disease. In: Chernick V, Boat TF, Wilmot RW, Bush A, eds. Kendig's disorders of the Respiratory Tract in Children, WB Saunders, 6th edn, Philadelphia, PA, USA 1998; pp507–529.
9. Enarson DA. The International Union Against Tuberculosis and Lung Disease. Model National. Tuberculosis Programmes. Tuber Lung Dis 1995; 76: 95-99.
10. Nelson LJ, Wells CD. Global epidemiology of childhood tuberculosis. Int J Tuberc Lung Dis 2004; 8(5):636-647.

CLIPPINGS

Comparative effectiveness of empiric antibiotics for community-acquired pneumonia.

In this study from USA, the objective was to compare the effectiveness of empiric treatment with narrow–spectrum therapy versus broad–spectrum therapy for children hospitalized with uncomplicated community-acquired pneumonia (CAP). This multicenter retrospective cohort study using medical records included children aged 2 months to 18 years at 4 children's hospitals in 2010 with a discharge diagnosis of CAP. Patients receiving either narrow-spectrum or broad-spectrum therapy in the first 2 days of hospitalization were eligible. A multivariate logistic regression analysis evaluated the relationship between antibiotic and hospital length of stay (LOS), 7-day readmission, standardized daily costs, duration of fever, and duration of supplemental oxygen. The adjusted analysis, the narrow-spectrum group had a 10-hour shorter LOS (P = .04). There was no significant difference in duration of oxygen, duration of fever, or readmission. Compared with broad–spectrum agents, narrow–spectrum antibiotic coverage is associated with similar outcomes. The findings support national consensus recommendations for the use of narrow–spectrum antibiotics in children hospitalized with CAP.

Queen MA, Myers AL, Hall M, Shah SS, Williams DJ, Auger KA, MD, Jerardi KE, Statile AM, Tieder JS. Comparative effectiveness of empiric antibiotics for community-acquired pneumonia. Pediatrics 2014; 133:1-7.

TUBERCULOSIS

HIV AND TUBERCULOSIS IN INDIAN CHILDREN

***Ira Shah**

Abstract: *Tuberculosis (TB) is one of the most common opportunistic infections affecting patients with HIV. HIV and TB co-infection have a synergistic effect on each other with one disease worsening the effects and treatment of the other. In the recent past, varying levels of drug resistance are also being found in HIV and TB co-infected patients. In this article, we discuss the issues of TB and HIV co-infection, particularly, the management of drug resistant TB in HIV infected children.*

Keywords: *HIV, TB, Co-infection, Children, Diagnosis.*

Epidemiology of tuberculosis

Tuberculosis (TB) is a major health concern and the main cause of death worldwide. In 2010, it was estimated that 8.8 million new TB cases occurred in the world. Out of the 12 million prevalent TB cases, around 650,000 were estimated to be multidrug-resistant (MDR) (resistant to at least isoniazid and rifampicin). India has the world's highest burden of tuberculosis (TB) overall with prevalence of multidrug-resistant TB (MDR-TB) among all patients with TB estimated to be 4.1%. A crude estimate derived from these data is that 4500–6000 HIV-infected persons develop MDR-TB annually in India.[1] Those at highest risk of drug resistant TB (DR-TB) are cases in whom treatment was a failure, in relapsers in defaulters and contacts of MDR-TB.[1] Drug resistance is rarely seen in the pediatric population due to the paucibacillary nature of the disease and originates mainly in adult contacts who are treatment failures or defaulters. Thus, the main method of resistance in children is primary transmission of the resistant bacilli.[2] Diagnosis of any form of TB, including DR-TB, is more challenging in the presence of HIV disease and together they result in higher case fatality rates.

* Incharge, Pediatric TB and HIV Clinic,
B.J.Wadia Hospital for Children,
Consultant in Pediatric Infectious Diseases and
Pediatric Hepatolgy, Nanavati Hospital,
Mumbai.

HIV and tuberculosis

Tuberculosis is one of the most common opportunistic infections in HIV.[3] The lifetime risk of TB in general public is found to be 5% to 10%, while in HIV-positive people it is estimated to be 5% to 15% every year.[4] HIV positive individuals are 20-40 times more likely to develop active TB as compared to those not infected with HIV.[5]

HIV and drug-resistant tuberculosis

Several factors contribute to increased preponderance of drug resistant TB in HIV positive patients. HIV co-infection is considered important in development of DR-TB by increasing rates of malabsorption of anti-TB drugs and inducing acquired rifamycin resistance.[5] and thus, causing treatment failures. Also, HIV increases the rate of TB transmission.[1] MDR-TB co-infection with HIV, poses multiple challenges for treatment, and has a high rate of mortality. MDR-TB co-infection with HIV has been reported in African children. HIV along with DR-TB has rarely been reported in Indian children[6,7] though it has been reported frequently in non-HIV infected children right from 2003 with increased incidence recently.[8-10]

Studies have also shown that another frequent cause for MDR-TB in HIV infected people is increased exogenous transmission. A systematic review published in 2009 showed a statistically significant association between HIV status and the direct transmission of an MDR strain of M. tuberculosis.[11] Rifampicin mono-resistance is often encountered. It may arise independently from mutations in drug susceptible strains.[12] Certain observational studies in adults have documented that the risk of acquired rifamycin resistance is higher if intermittent regimens are used in advanced HIV disease.[13] Similarly, rates of relapse and mortality have been attributed to severe immunosuppression, thrice weekly dose of rifampicin, lack of rifampicin in the treatment regimen and less than six months treatment duration in adults.[14-16]

Diagnosis of drug-resistant TB in HIV infected children

Conventional culture, the most common method to detect drug resistance in developing countries, has the inherent problem of a delay in diagnosis varying from

6 weeks to 3 months. A more rapid detection of drug-resistant TB is desirable in populations with a heavy burden of MDR-TB or coinfection with HIV, in order to reduce the time spent on ineffective treatment and to decrease mortality.[17] A history of previous treatment for tuberculosis is a useful predictive factor for MDR-TB in a cohort of HIV-infected patients with tuberculosis.

One must also keep in mind that immune reconstitution in the setting of recent initiation of anti-retroviral therapy may unmask drug-resistant tuberculosis and hence timely empiric MDR-TB treatment is important in suspected cases.[18]

Since many of the genes encoding resistance have been identified, nucleic acid amplification tests (NAATs) are being increasingly used for diagnosis of resistance to isoniazid (H) and rifampicin (R) and results are obtained in 24-48 hours directly from clinical specimens.

Treatment of TB in HIV infected individuals

Treatment of TB in HIV co-infected patients is the same as HIV negative individuals. First line drugs in the standard regimens are to be used unless drug resistance is proven. Daily dosing is recommended over thrice weekly therapy. However, due to the nature of the illness drug resistance is more common than in general population and should be actively investigated. A pilot study in adults by the Tuberculosis Research Centre found a favorable response in 72% of patients with advanced HIV with TB and an unfavorable response in 28% of these patients, when RNTCP Category I regimen was used.[12]

Literature is limited with regard to antiretroviral therapy (ART) and antituberculous therapy (ATT) drug interactions in children. Studies in adults published in the 1980s and 1990s showed interactions between ethionamide and ART.[19,20] Jenner, et al in 1981 showed that co-administration of ethionamide and protease inhibitors increases the serum concentration of ethionamide, thereby increasing its toxicity.[20] Another commonly observed side-effect of starting ART in patients being treated for TB is immune reconstitution inflammatory syndrome (IRIS). In a study by Narita, et al, the incidence of IRIS in TB alone was 2%; with HIV co-infection it was 7%; and in those started on HAART, it was 36%.[21]

Treatment of DR-TB in HIV/infected children

The outcome of treatment of MDR-TB with HIV co-infection is poor. In 2003, a study conducted in South Africa showed 41% mortality among HIV-positive patients with MDR-TB.[22] Earlier, a study in New York in 1996 showed 72% mortality among HIV-positive patients with MDR-TB.[23] Similar data in children is lacking though outcome has been good in a few case reports.[5,6]

Treatment of DR-TB should be tailored as per the drug susceptibility test (DST) results. Whenever DST of the child's strain is not available, treatment should be directed by the DST of the source case if available. In children with HIV infection, treatment of MDR-TB is extended to 24 months[24] and individualized treatment regimen is required. The principles of management of resistant disease include use of aggressive regimens for protracted periods, guided by DST to include at least five drugs likely to be effective.[25] Second line anti-tuberculosis drugs used in treatment of MDR-TB include aminoglycosides (streptomycin, kanamycin, amikacin and capreomycin), thioamides (ethionamide or prothionamide), fluoroquinolones (ofloxacin, ciprofloxacin, sparfloxacin, norfloxacin, levofloxacin, and gatifloxacin), cycloserine and PAS. Of these PAS and cycloserine are bacteriostatic. All others are weakly bactericidal. Fluoroquinolones play a key role in resistant tuberculosis and the later generation fluoroquinolones may be effective despite resistance to ciprofloxacin.

Use of an injectable agent such as capreomycin or aminoglycoside (e.g. kanamycin), has been shown to predict culture conversion and survival in studies, though resistance to more than one aminoglycoside is becoming increasingly common. The regimens may be reinforced by pyrazinamide and ethambutol, despite prior exposure to these drugs, as these contribute by increasing the regimen's activity or preventing resistance to more active agents.

Common adverse effects of second-line ATT include gastrointestinal effects, rash, ototoxicty, peripheral neuropathy, psychiatric symptoms and jaundice. The rate of thyroid toxicity is high, and may be due to ethionamide or PAS, requiring regular monitoring.[26] Besides, serial CD4 levels, monitoring of liver function tests, lipid profile and pancreatic enzymes is essential, for a child receiving ART.

Conclusion

A delay in laboratory diagnosis, limited choice of active drugs and increased toxicities and interactions when ATT along with ART is administered, all contribute in making the treatment of MDR-TB with HIV a challenging task, requiring individualization of treatment and adjustments in drug regimens from time to time.

Points to Remember

- ***HIV and TB co-infection have a synergistic effect on each other with one disease worsening the effects and treatment of the other.***

- ***HIV co-infection is considered important in development of drug resistant TB.***
- ***When using ART and ATT together, one must keep in mind possible drug interactions.***
- ***Treatment with ART need not be deferred if the child is on ATT.***

References

1. Wells CD, Cegielski JP, Nelson LJ, Laserson KF, Holtz TH, Finlay A, et al. HIV infection and multidrug-resistant tuberculosis: the perfect storm. J Infect Dis 2007; 196 Suppl 1:S86-107.
2. Newton SM, Brent AJ, Anderson S, Whittaker E, Kampmann B. Paediatric Tuberculosis. Lancet Infect Dis 2008; 8:498-510.
3. Lawn SD. Tuberculosis and HIV co-infection. Medicine 2005; 33:112–113.
4. Swaminathan S, Ramachandran R, Baskaran G, Paramasivan CN, Ramanathan U, Venkatesan P, et al. Risk of development of tuberculosis in HIV infected patients. Int J Tuberc Lung Dis 2000; 9: 839–844.
5. Wells CD, Cegielski JP, Nelson LJ, Laserson KF, Holtz TH, Finlay A, et al. HIV infection and multidrug-resistant tuberculosis: the perfect storm.J Infect Dis 2007; 196 Suppl 1:S86-107..
6. Shah I, Bansal N. Poly-resistant Tuberculosis in an HIV infected child. J Family Med Prim Care 2012; 1(2):153–154.
7. Shah I, Mohanty S. Multidrug resistant tuberculosis in an HIV infected girl and response to therapy. Natl Med J India 2012; 25(4):210-211.
8. Shah I. Multidrug-resistant Tuberculosis in Children. Pediatr Infect Dis J 2012; 31:970-972.
9. Shah I, Chilkar S. Clinical Profile of Drug Resistant Tuberculosis in Children Indian Pediatr. 2012; 49: 741-744.
10. Shah I. Multidrug Resistant Tuberculosis [MDR-TB] In Children from 2003-2005: A Brief Report. Indian J Med Microbiol 2012; 30:208-211.
11. Suchindran S, Brouwer ES, Van Rie A. Is HIV infection a risk factor for multi-drug resistant tuberculosis? A systematic review PLoS ONE 2009; 4:e5561.
12. Swaminathan S, Paramasivan C N, Ponnuraja C, Iliayas S, Rajasekaran S, Narayanan PR. Anti-tuberculosis drug resistance in patients with HIV and tuberculosis in South India. Int J Tuberc Lung Dis 2005; 9:896–900.
13. Nahid P, Gonzalez LC, Rudoy I, De long BC, Unger A, Kawamura LM. Treatment outcomes of patients with HIV and tuberculosis. Am J Respire Crit Care Med 2007;175: 1196–1206.
14. Lawn SD, Myer L, Bekker LG, Wood R. Tuberculosis associated immune reconstitution disease: incidence, risk factors and impact in an antiretroviral treatment service in South Africa. AIDS 2007; 21:335–341.
15. Lawn S, Myer L, Bekker LG, Wood R. Early mortality among patients with HIV associated TB in Africa: Implications for the time to initiate ART 2007 (Conference on Retroviruses and Opportunistic Infections: Abstract 81).
16. Jindani A, Nunn AJ, Enarson DA. Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomized trial. Lancet 2004; 364:1244–1251.
17. Rapid diagnosis and treatment of MDR TB. Available at URL: http://www.stoptb.org/assets/documents/resources/publications/technical/mdrtbinfo.pdf. Accessed on 5th August, 2011.
18. Rojas C, Solari L, Herrera C, Sanchez E, Young G, Bonilla C, et al. Challenges of Diagnosis and Management of Tuberculosis and HIV coinfection in Resource-limited settings: A case report from Lima, Peru. J Int Assoc Phys AIDS care 2008; 7:232-237.
19. Burman WJ, Gallicano K, Peloquin C. Therapeutic implications of drug interactions in the treatment of HIV-related tuberculosis. Clin Infect Dis 1999; 28:419-430.
20. Jenner PJ, Ellard GA. High performance liquid chromatographic determination of ethionamide and prothionamide in body fluids. J Chromatogr B Biomed Sci Appl 1981; 225:245–251.
21. Narita M, Ashkin D, Hollender ES, Pitchenik AE. Paradoxical worsening of tuberculosis following antiretroviral therapy in patients with AIDS. Am Crit Care 1998; 158:157–161.
22. Finlay AF, Walt MV, Holtz TH, Thorpe LE, Wells CD, Weyer K. Treatment outcome of patients with multidrug resistant tuberculosis in South Africa using a standardized regimen, 1999- 2000 (abstract 584); in Program and abstracts of the infectious diseases (Society of America 2004 Annual Meeting Alexandria, VA: infectious Disease society of America) 2004; p155.
23. Park MM, Davis AL, Schluger NW, Cohen H, Rom WN. Outcome of MDR–TB patients, 1983-1993: prolonged survival with appropriate therapy. Am J Respir Crit Care Med 1996; 153:317–324.
24. Seth V, Kabra SK, Lodha R. Multidrug Resistant Tuberculosis. In: Seth V, Kabra SK, editors. Essentials of tuberculosis in Children. 3rd ed. New Delhi: Jaypee, 2006; pp548-565.
25. Mitnick CD, Shin SS, Seung KJ, Rich ML, Atwood SS, Furin JJ, et al. Comprehensive treatment of Extensively drug resistant tuberculosis. N Engl J Med 2008; 359: 563-574.
26. Montaldo C, Dongre A, Varghese B, Rodrigues C, Sotgiu G, Centis R, et al. Diagnosis and treatment of MDR/XDR- tuberculosis in HIV-infected patients is feasible in a slum setting in Mumbai, India: experience of Medecins Sans Frontiere. 5th IAS Conference on HIV Pathogenesis and Treatment. Abstract no. TUPED089.

TUBERCULOSIS

CURRENT MANAGEMENT GUIDELINES IN CHILDHOOD TUBERCULOSIS

***Rakesh Kumar Pilania**
****Pankaj C Vaidya**
*****Meenu Singh**

Abstract: *Childhood tuberculosis (TB) has conventionally been a low priority issue for TB programs worldwide. The national guidelines for pediatric TB have been given by the Revised National Tuberculosis Control Program (RNTCP) 2012 for making the diagnosis of childhood TB based on clinical features, careful history (including TB contact and symptoms), clinical examination (including growth assessment), tuberculin skin testing (TST), chest X-ray, bacteriological confirmation wherever possible and HIV testing. All efforts should be made to demonstrate bacteriological evidence in the diagnosis of pediatric TB. Children with TB are classified, categorized, registered and treated, and should be given treatment under direct observation of treatment provider (DOT provider) and disease status is monitored during the course of treatment. Based on their pre-treatment weight, children are assigned to one of the pre-treatment weight bands and are treated with good quality anti-TB drugs which are available to every registered TB patient according to program guidelines.*

Keywords: *Tuberculosis, Children, DOTS, Patient-wise boxes (PWB)*

World health organization (WHO) has estimated that TB will continue to be the seventh most morbidity causing disease globally till 2020.[1] Most cases of TB in children occur in the TB-endemic countries but the actual burden of childhood TB is unknown. In 2012, WHO estimated that globally there were 530000 TB cases among children (<15 years of age) and 74 000 TB deaths (among HIV negative children), 6% and 8% of the global totals, respectively.[2]

* Senior Resident
** Assistant Professor
*** Professor
Department of Pediatrics,
Post Graduate Institute of Medical Education and Research,
Chandigarh.

Children can present with TB disease at any age but most commonly between 1 and 4 years in TB-endemic countries. Pulmonary TB is the commonest type. Extrapulmonary disease is also common (around 30% - 40% of cases) and can present in a wide variety of anatomical sites. Children who develop TB disease usually do so within 1 year following infection, which is why the presentation of TB in children is an indicator of recent and ongoing transmission of M. tuberculosis in the community.[3]

The technical strategy for directly observed therapy-short course strategy (DOTS) was developed by Karel Styblo in the 1970s and '80s and was refined as 'a treatment system of checks and balances that provided high cure rates at a cost affordable for most developing countries'.[4]

DOTS is a systematic strategy which has five components including political and administrative commitment, good quality diagnosis and drugs, an uninterrupted supply of good quality anti-TB drugs, supervised treatment to ensure the right treatment and systematic monitoring and accountability.[5]

Historically, childhood TB was neglected all over the world in view of difficult diagnosis, poor recording and reporting process, misperception of childhood TB such as occurrence of relatively few cases, that it is a non-infectious disease and that childhood TB would disappear simply by control of TB in adults. RNTCP has taken initiatives to focus on children and based on recent 'Rapid advice of WHO' and recommendations of IAP, has updated the national guidelines for pediatric TB in 2012.[6,7]

Diagnosis of pediatric tuberculosis

The diagnosis depends on thorough assessment derived from a careful history of contact, clinical examination and relevant investigations. The proposed approach to diagnosing TB in children is based on limited published evidence [3,8,9] and rests heavily on expert opinion. Approach to diagnosis of TB in children include:[8]

1. Careful history (including TB contact and symptoms consistent with TB)
2. Clinical examination (including growth assessment)

3. Tuberculin skin testing (TST)
4. Chest X-ray
5. Bacteriological confirmation whenever possible
6. Investigations relevant for suspected pulmonary TB and extrapulmonary TB
7. HIV testing

The salient recommendations are[7]

1. All efforts should be made to demonstrate bacteriological evidence. In cases where sputum is not available for examination or sputum microscopy fails to demonstrate AFB (acid fast bacilli), alternative specimens (gastric lavage, induced sputum, broncho-alveolar lavage) should be collected.
2. A positive Mantoux test is defined as ≥10 mm induration. The optimal strength of tuberculin 2 TU (RT 23 or equivalent) is to be used in children.
3. No role for inaccurate/inconsistent diagnostics like serology (IgM, IgG, IgA antibodies against MTB antigens), various in-house or non-validated commercial PCR tests and BCG test.
4. No role of interferon gamma release assay (IGRA) in clinical practice for the diagnosis of TB.
5. Weight loss defined as a loss of >5% of the highest weight recorded in past 3 months.

Treatment of pediatric tuberculosis[8]

All children treated for TB should be recorded and reported by RNTCP. The main objectives of treatment are to cure, prevent death from TB disease or its late effects, relapse, the development and transmission of drug-resistant TB, reduce transmission to others and achieve all this with minimal toxicity.[8]

To meet the concern of pediatric fraternity about under dosing, the drug dosages have been rationalized for childhood cases (Table I). In future, there will be six weight bands and three generic patient-wise boxes (PWB) which will be used in combination to treat patients in the six weight bands. Since, it would take time for supply of these products under RNTCP, the existing pediatric PWBs are to be used in different combinations, to meet these expectations till new PWBs are available.

(If body weight of child reaches 25 kg, adult dosing is recommended)

Table I. Recommended daily doses of first-line anti-TB drugs for children[8]

Anti-TB drug	Dose and range (mg/kg body weight)	Maximum dose (mg)
Isoniazid	10 (7-15)	300
Rifampicin	15 (10-20)	600
Pyrazinamide	35 (30-40)	2000
Ethambutol	20 (15–25)	1500

To ensure correct dosage for every child, weighing of the child in minimal clothing using accurate weighing scales is essential. All pediatric TB patients should be shifted to next weight band if a child gains a kilogram or more, above the upper limit of the existing weight band.[7]

Drug formulations

Younger patients have difficulty in swallowing tablets and the number of tablets is too many to consume. The DOT centers will be provided with pestle and mortars for crushing the drugs. It is the responsibility of the DOT provider to supervise drug consumption by the child and if child vomits within half an hour, fresh dosages for all the drugs vomited will be provided by the caregiver.[7]

Treatment regimens (Table II & III)[7,8]

Children with suspected or confirmed pulmonary TB or tuberculous peripheral lymphadenitis in settings with low HIV prevalence or low isoniazid resistance and HIV-negative children can be treated with a 3-drug regimen (HRZ) for 2 months followed by a 2 drug (HR) regimen for 4 months, while in settings with high HIV prevalence and/or high isoniazid resistance and/or extensive pulmonary disease should be treated with a 4-drug regimen (HRZE) for 2 months followed by a 2-drug regimen (HR) for 4 months. Infants aged 0-3 months with suspected or confirmed pulmonary TB or tuberculous peripheral lymphadenitis should be promptly treated with the standard treatment regimens.

TB meningitis and osteoarticular TB (suspected or confirmed) should be treated with a 4 drug regimen (HRZE) for 2 months, followed by a 2-drug regimen (HR) for 10 months, the total duration being 12 months.

During continuation phase, thrice-weekly regimens can be considered in HIV-uninfected children and in well-established DOT settings. While children with suspected or confirmed pulmonary or tuberculous

peripheral lymphadenitis in settings with a high HIV prevalence (or with confirmed HIV infection) should not be treated with intermittent regimens. Streptomycin should not be used as part of first-line treatment regimens for children with pulmonary TB or tuberculous peripheral lymphadenitis.

Corticosteroids

Steroids may be used for the management of some complicated forms, e.g. TB meningitis, airway obstruction by TB lymph glands, and pericardial TB. Corticosteroids have been shown to improve survival and reduce morbidity in advanced TB meningitis and so recommended in all cases of TB meningitis.[10] Prednisolone is used most frequently, in a dosage of 2 mg/kg daily, increased to 4 mg/kg daily in the case of the most seriously ill children, with a maximum dosage of 60 mg/day for 4 weeks. The dose should then be gradually reduced over 1–2 weeks before stopping.

Pyridoxine supplementation

Isoniazid may cause symptomatic pyridoxine deficiency, which presents as neuropathy, particularly in severely malnourished children and HIV-positive children on antiretroviral therapy (ART). Supplemental pyridoxine (5-10 mg/day) is recommended in HIV-positive or malnourished children being treated for TB.[11]

Nutritional support

Severe malnutrition is associated with increased mortality in TB patients, and a child's nutritional status should be assessed regularly during treatment. Additional energy is particularly important during the intensive phase of treatment and is best given through additional household foods, provided as part of a balanced varied diet.

Smear positive: Any sample (sputum, induced sputum, gastric lavage, broncho-alveolar lavage) positive for acid fast bacilli.

New case: A patient who has had no previous ATT or for less than 4 weeks.

Relapse: Patient declared cured/completed therapy in past and has evidence of recurrence.

Treatment after default: A patient who has taken treatment for at least 4 weeks and comes after interruption of treatment for 2 months and has active disease.

Failure to respond: A case of pediatric TB who fails to have bacteriological conversion to negative status or fails to respond clinically or deteriorates after 12 weeks of compliant intensive phase shall be deemed to have failed response, provided alternative diagnoses/reasons for non-response have been ruled out.

Table II. Recommended treatment regimens (WHO) for new cases of TB in children[8]

Diagnostic category		Intensive phase	Continuation phase
Low HIV prevalence (HIV negative) and low isoniazid resistance setting	• Smear-negative pulmonary TB • Intrathoracic lymph node TB • Tuberculous peripheral lymphadenitis	2HRZ	4HR
	• Extensive pulmonary disease • Smear-positive pulmonary TB • Severe forms of extrapulmonary TB (other than tuberculous meningitis / osteoarticular TB)	2HRZE	4HR
High HIV prevalence or high isoniazid resistance or both	• Smear-positive PTB • Smear-negative PTB with or without extensive parenchymal disease • All forms of EPTB except tuberculous meningitis and osteoarticular TB	2HRZE	4HR
Tuberculous meningitis and osteoarticular TB		2HRZE	10HR

Table III. Treatment regimens for childhood TB - National guidelines[7]

Category of treatment	Type of patients	TB treatment regimens	
		Intensive phase	Continuatio phase
New cases	• New smear-positive pulmonary Tuberculosis (PTB) • New smear-negative PTB • New extra-pulmonary TB	$2H_3R_3Z_3E_3$*	$4H_3R_3$
Previously treated cases	• Relapse, failure to respond or treatment after default • Re-treatment, Others	$2S_3H_3R_3Z_3E_3$ + $IH_3R_3Z_3E_3$	$5H_3R_3E_3$

Management of adverse events

Adverse events caused by anti-TB drugs are much less common in children than in adults.[12] The most important side effect is hepatotoxicity, which can be caused by isoniazid, rifampicin or pyrazinamide. Monitoring of serum liver enzyme levels is not done routinely, as asymptomatic mild transaminitis (<5 times the normal values) is not an indication to stop treatment. However, in the presence of liver tenderness, hepatomegaly or jaundice serum liver enzyme levels should be done immediately along with stopping of all potentially hepatotoxic drugs. Other causes of hepatitis should be ruled out and no attempt should be made to reintroduce these drugs until liver functions have normalized. Early signs of ethambutol toxicity can be tested in the older child through red-green color discrimination.

Follow up

1. Follow up visit should be: 1st visit 2 weeks after the start of treatment, then at the end of the intensive phase and every 2 months until completion of treatment.
2. Follow up assessment include: Symptom assessment, treatment adherence, enquiry about any adverse events, and weight measurement.
3. Most children with TB will start to show signs of improvement after 2-4 weeks of treatment
4. Dosages should be adjusted taking into account any weight gain.
5. A follow-up sputum sample for smear microscopy at 2 months after the start of treatment should be obtained from any child who was smear-positive at diagnosis.
6. Chest X-rays are not routinely required in children who are improving with treatment, particularly as many children will have a slow radiographic response to treatment.
7. Adherence should be assessed by reviewing the treatment card. For treatment adherence, children, their parents, other family members and other caregivers should be educated about TB and the importance of completing treatment.
8. Poor adherence is a common cause of 'treatment failure'. Treatment failure suggests the possibility of multidrug-resistant TB and needs careful assessment.

TB preventive therapy

Neonatal BCG vaccination provides substantial protection against the more severe types of disseminated TB, such as miliary TB and TB meningitis, to which infants and young children are particularly susceptible.[13] There is no evidence that revaccination with BCG affords any additional protection, and is therefore not recommended.[14] Preventive therapy for young children with TB infection who have not yet developed the disease will greatly reduce the likelihood of TB disease developing during childhood.[15] It should be given for 6 months as Isoniazid Prevention Therapy (IPT) (10 mg/kg per day, range 7-15mg/kg, maximum dose 300 mg/day).

Indications are

1. Children <5 years of age who are household or close contacts of people with TB and who, after an appropriate evaluation, are found not to have TB disease
2. All HIV infected children who either had known exposure to an infectious TB case or Mantoux test positive (≥5 mm in duration) but have no active disease
3. All Mantoux test positive children who are receiving immunosuppressive therapy
4. A child born to mother who was diagnosed to have TB in pregnancy, provided congenital TB has been ruled out.

Points to remember

- ***The diagnosis of childhood TB depends on thorough assessment.***
- ***All efforts should be made to demonstrate bacteriological evidence.***
- ***Six weight bands and three generic patient wise boxes (PWB) will be used in combination to treat children in the six weight bands.***
- ***Streptomycin should not be used as part of first-line treatment regimen for children with pulmonary TB or tuberculous peripheral lymphadenitis.***
- ***Steroids may be used in TB meningitis, airway obstruction complicated by TB lymph glands and pericardial TB.***

References

1. Murray Christopher JL, Lopez Alan D. The global burden of disease: A comprehensive assesment of mortality and disabilty from disease, injuries and risk factorsin 1990and projected to 2020: Summary- WHO Geneva, Switzerland, 1996;w7496GL-1/1996
2. Global Tuberculosis Report 2013. Geneva WHO, 2013.
3. Marais BJ, Gie RP, Hesseling AC, Schaaf HS, Lombard C, Enarson DA, et al. A refined symptom-based approach to diagnose pulmonary tuberculosis in children. Pediatrics. 2006 Nov; 118(5):e1350-9.
4. TB: Join the DOTS. "The Economist. May 20, 1995. P.89.
5. Pinet G. Good practice in legislation and regulations for TB control: an indicator of political will. Geneva WHO, 2001 WHO/CDS/TB/2001.290.
6. Rapid advice: treatment of tuberculosis in children. Geneva WHO, 2010, (WHO/HTM/TB/2010.13).
7. Kumar A, Gupta D, Nagaraja SB, Singh V, Sethi GR, Prasad J. Updated national guidelines for pediatric tuberculosis in India, 2012. Indian Pediatr 2013; 50(3): 301-6.
8. Guidance for National Tuberculosis Programmes on the Management of Tuberculosis in Children. 2nd edn, Geneva: World Health Organization; 2014.ISBN-13: 978-92-4-154874-8.
9. Perez-Velez CM, Marais BJ. Tuberculosis in children. N Engl J Med 26; 367(4):348-61.
10. Schoeman JF, Van Zyl LE, Laubscher JA, Donald PR. Effect of corticosteroids on intracranial pressure, computed tomographic findings, and clinical outcome in young children with tuberculous meningitis. Pediatrics 1997; 99(2):226-231.
11. Guidance for national tuberculosis programmes on the management of tuberculosis in children. Geneva, World Health Organization, 2006 (WHO/HTM/TB/2006.371).
12. Frydenberg AR, Graham SM. Toxicity of first-line drugs for treatment of tuberculosis in children: review. Trop Med Int Health 2009; 14(11):1329-37.
13. Trunz BB et al. Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta–analysis and assessment of cost-effectiveness. Lancet 2006; 367:1173-1180.
14. Global Tuberculosis Programme and Global Programme on Vaccines. Statement on BCG revaccination for the prevention of tuberculosis. Weekly Epidemiological Record, 1995, 32:229-31.Smieja MJ, Marchetti CA, Cook DJ, Smaill FM. Isoniazid for preventing tuberculosis in non-HIV infected persons. Cochrane Database Syst Rev 2000 (2): CD001363.

CLIPPINGS

Higher risk of neutropenia associated with piperacillin-tazobactam compared with ticarcillin-clavulanate in children.

Because neutropenia was seldom observed in children treated with ticarcillin–clavulanic acid (T/C), the authors conducted a study to determine if there is an increased risk of neutropenia in children exposed to piperacillin-tazobactam (P/T) in comparison with T/C. Medical records of subjects aged <18 years who received at least 1 dose of P/T or T/C between 1 January 2008 and 30 June 2011 were reviewed. Thirteen cases of neutropenia were observed during the study period. The average time to onset was 17.6 days and all patients were aged <13 years. Seven cases (10.8%) occurred in the P/T group and 6 (2.6%) in the T/C group (unadjusted odds ratio, 4.59; 95% confidence interval, 1.48-14.17). Also a statistically significant correlation was observed between age, treatment duration, and total dose and the development of neutropenia ($r = -0.121$, $P = .037$; $r = 0.267$, $P < .001$; $r = 0.260$, $P < .001$, respectively). The authors suggest that children receiving long courses of therapy (>2 weeks) with P/T may be at increased risk of neutropenia, compared with T/C.

Lemieux P, Grégoire JP, Thibeault R, Bergeron L. Higher risk of neutropenia associated with piperacillin-tazobactam compared with ticarcillin-clavulanate in children. Clin Infect Dis 2014 Oct 9.

TUBERCULOSIS

MULTIDRUG RESISTANT TUBERCULOSIS IN CHILDREN - WHEN TO SUSPECT AND HOW TO MANAGE

***Poorana Ganga Devi N**
****Soumya Swaminathan**

Abstract: *Resistance to anti-tuberculosis (anti-TB) drugs is an important challenge in global TB control. The knowledge on the magnitude of problem of drug-resistant (DR-TB) is limited in pediatric populations due to limited diagnostic capabilities and a higher proportion of paucibacillary nature of TB in young children. Children with MDR-TB are treated in a similar way to adults with (MDR-TB) one practical difference is that confirmation and drug susceptibility testing (DST) may not possible, so that empirical treatment is often required for children with suspected MDR-TB. WHO advocates that after screening for TB disease all infectious MDR-TB contacts should be followed up without medication, because the data supporting the use of drugs other than isoniazid and rifampicin are limited.*

Keywords: *Drug resistance, Tuberculosis, Children, Treatment.*

Resistance to anti-tuberculosis (anti-TB) drugs is an important challenge in global tuberculosis (TB) control. Globally, 3.6% (2.1%–5.1%) of new cases and 20.2% (13.3%–27.2%) of previously treated cases are estimated to have Multidrug Resistant (MDR)-TB.[1]

The knowledge on the magnitude of problem of drug resistant tuberculosis (DR-TB) is limited in pediatric populations due to limited diagnostic capabilities, (needing multiple specimens other than sputum and a laboratory capable of performing culture), a higher proportion of paucibacillary nature of TB in young children, and the low priority given to this group by public health programs particularly in low-resource, high-burden settings. A recent meta-analysis found only eight published studies on pediatric MDR-TB, accounting for 315 cases.[2] The World Health Organization (WHO) estimates there are 650,000 prevalent cases of multidrug-resistant (MDR)-TB globally[3] and as children (<15 years of age) comprise up to 20% of the TB caseload in high burden settings[4], the number of children with drug-resistant (DR)-TB is undoubtedly high.[5]

Drug resistance among children has been documented in both pulmonary and extra-pulmonary disease.[6] When children have MDR-TB, it is usually 'primary resistance', i.e., they are infected with strains transmitted from adults with MDR-TB rather than secondary resistance acquired as a result of suboptimal therapy or non-adherence.

Management of MDR TB in children

Diagnosis

Findings from several case series have shown that children are likely to develop MDR and XDR tuberculosis in settings where transmission is poorly controlled.[7] The diagnosis of pediatric MDRTB is often delayed due to reliance on the adult case definition and the need for bacteriologic confirmation.[8] Systematic approaches to the diagnosis of children with suspected drug resistance and consensus case definitions have been proposed recently.[9,10] Consideration of the clinical history, especially past treatment regimens and recent exposure history is essential. Expert consultation should always be sought when managing childhood DR-TB.

Drug-resistant TB should be suspected when:

- there is contact with known DR-TB,
- there is contact with suspected DR-TB, i.e. source case is a treatment failure or a retreatment case or recently died from TB,
- a child with TB is not responding to first-line therapy despite adherence,
- a child previously treated for TB presents with recurrence of disease.

When DR-TB is suspected, every effort should be made to confirm the diagnosis by obtaining specimens for culture and drug susceptibility testing (DST). Rapid DST of isoniazid and rifampicin or rifampicin alone is

* Scientist C
** Director,
National Institute for Resarch in Tuberculosis,
Chennai.

recommended over conventional testing or no testing at the time of diagnosis (Fig.1).

Depending on the age of the child, site of disease and available facilities, attempts can be made to obtain sputum, gastric aspirates, induced sputum, biologic fluid samples, nasopharyngeal aspirates, lymph node aspiration biopsy or tissue biopsy.[11-14] With extensive sampling, the proportion of children with a confirmed diagnosis can be >50%.[15] Invasive methods, such as bronchoalveolar lavage, bronchoscopic biopsy or open lung biopsy may sometimes be required.

Culture can be performed using solid media, such as the egg-based Lowenstein-Jensen or the agar-based Middlebrook medium, where the cultures are examined after 3–4 weeks instead of 4–6 weeks using the classic method. Automated liquid culture systems detect growth of

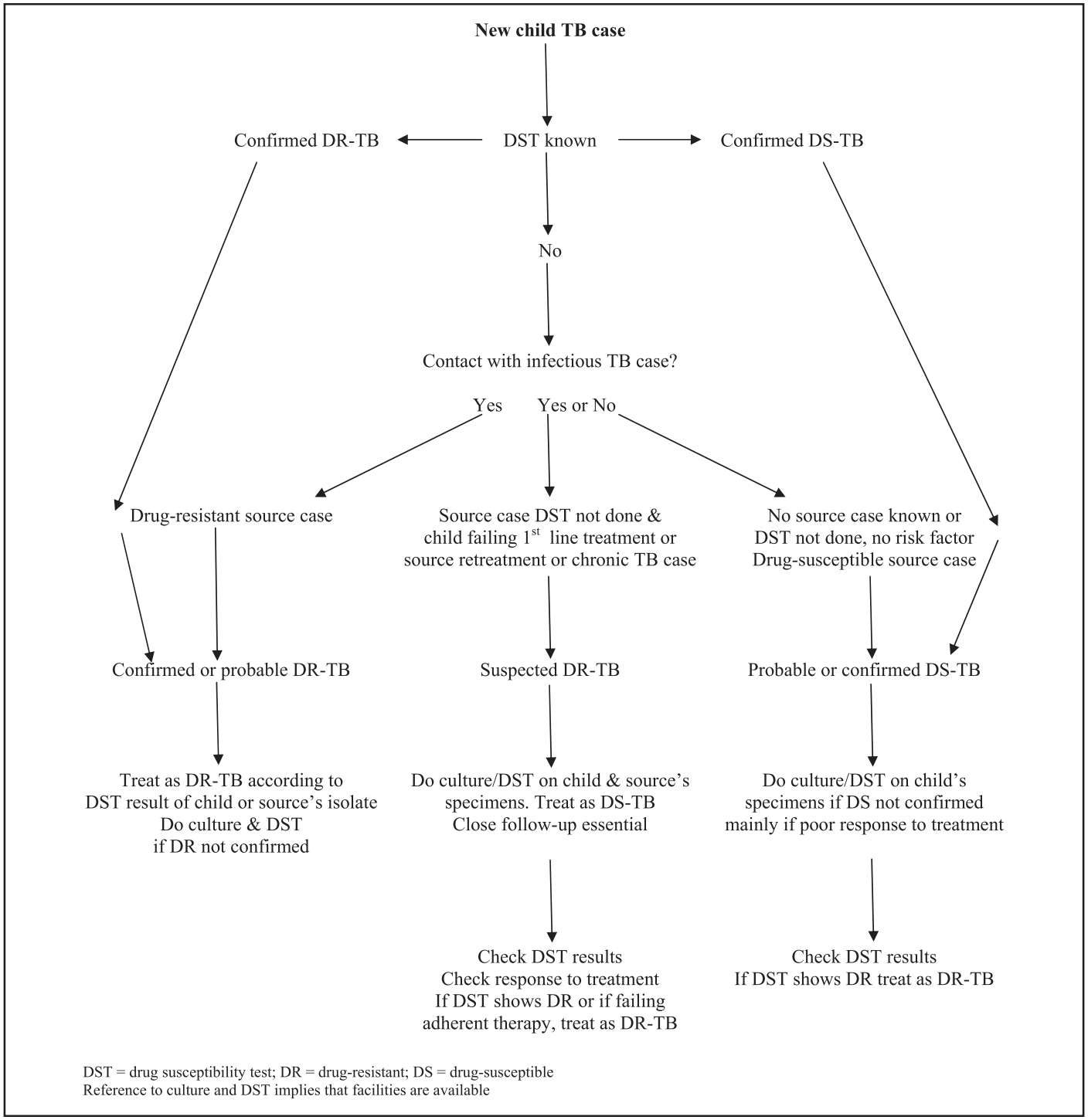


Fig 1. Diagnostic algorithm for DR-TB in children[7]

mycobacteria within 1-2 wk by fluorescent sensors [BACTEC Mycobacteria Growth Indicator Tube (MGIT) 960; Becton Dickinson Diagnostic Instruments Systems], colorimetric sensors (MB/ BacT system; OrganonTeknika), pressure sensors (ESP culture system II; Difco Laboratories, USA), or redox reagents such as Alamar blue.

Microscopic observation drug susceptibility (MODS) assay is a low cost non-commercial method that can be used for detection of microcolonies, cord formation and for early detection of drug resistance. It appears to have higher sensitivity, shorter time to culture positivity and is more cost effective than regular L-J medium.

The use of molecular tests [line probe assay (LPA) and Xpert MTB/RIF, both WHO endorsed] may provide evidence of resistance within hours to 1-2 days of specimen testing. However, current versions of the LPA work well only on smear positive specimens, and so may not be as useful in children. Early experience with Xpert MTB/RIF has shown that bacteriologic confirmation can be doubled.[16]

A major hindrance in the assay's application for diagnosis of childhood tuberculosis is the inability of a large proportion of children with pulmonary tuberculosis to expectorate sputum. In these children, the Xpert MTB/ RIF assay has proven useful with induced sputum.[14,17] A recent study showed that testing two nasopharyngeal aspirates in children with suspected pulmonary tuberculosis with the Xpert MTB/ RIF assay can be useful, especially in settings where facilities for inducing sputum and culture are not available.[14]

In all cases of confirmed MDR-TB, second-line DST should be performed to exclude XDR-TB and to help establish an effective treatment regimen. There must be recognition, however, that there will be a group of children who need treatment for MDR-TB in whom bacteriological confirmation is either pending or not possible.

Tuberculin skin testing using purified protein derivative and chest radiography are used as adjuncts to smear microscopy (and culture, if available); but do not differentiate between drug-sensitive and drug-resistant TB.

Treatment

Children with MDR-TB are treated in a similar way as adults with MDR-TB.[7] One practical difference is that confirmation and DST may not possible, so that empirical treatment is often required for children with suspected MDR-TB. Although outcome data in children are limited, the available evidence suggests that outcomes at least as good as those reported in adults can be achieved.

Formulating a treatment regimen for MDR-TB: Treatment regimens for children with MDR-TB follow the same principles as in adults. Depending on country guidelines, the regimen used is either individually constructed or a standardized one, such as the Category IV regimen recommended by WHO.[10]

The basic principles are

- Use any first-line medication to which susceptibility is documented or likely (high dose INH could be included routinely, unless high level INH resistance or Kat-G mutation is documented).
- Use of at least 4 second-line drugs to which the strain is likely to be sensitive; one of these agents should be an injectable aminoglycoside. A fluoroquinolone and PZA should be continued.
- Never add a single drug to a failing regimen; this may lead to amplification of resistance.
- All treatment should be given daily and under direct observation.
- Treat the child according to the DST results from the likely source case, unless M. tuberculosis culture and DST results are available from the child.
- Do second-line DST in all MDR-TB cases to exclude resistance to the fluoroquinolones and/or second-line injectables, as this may call for additional drugs early in therapy.
- Caregivers need counselling and support at every follow-up visit regarding adverse effects, treatment duration and importance of adherence.

In addition, the following assessment of the child should be undertaken as a minimum:

- Symptom assessment
- Assessment of treatment adherence
- Enquiry about any adverse events
- Weight measurement.Drug dosages should be adjusted to account for any weight gain.
- Clinical, radiographic and culture response to treatment should be monitored. Monthly smear microscopy and cultures should be done until they are confirmed negative on three consecutive occasions; thereafter, follow-up cultures can be done every 2-3 months.
- Special investigations as necessary for any adverse effects

Treatment duration should be for 18-24 months, at least

Table I. Drug groups used to treat drug-resistant TB[7, 22]

Group	Group Name	Drugs	Dosage(mg/kg/day)	Adverse events
1.	First-line oral agents	Isoniazid	10-15	Hepatitis, peripheral neuropathy
		Rifampin	10-20	Hepatitis, discoloration of secretions
		Ethambutol	15-25 (DR-TB: 20-25)	Optic neuritis
		Pyrazinamide	30-40	Hepatitis, arthritis
2	Injectable agents	Kanamycin	15-30	Ototoxicity, nephrotoxicity
		Amikacin	15-22.5	As above
		Capreomycin	15-30	As above
		Streptomycin	15-20	As above
3	Fluoroquinolones	Ofloxacin	15-20	Sleep disturbance, gastro-intestinal disturbance, arthritis, peripheral neuropathy
		Ciprofloxacin	20 twice daily	As above
		Levofloxacin	7.5-10^{+}	As above
		Moxifloxacin	7.5-10	As above but including prolonged QT syndrome
4	Oral bacteriostatic second-line agents	Ethionamide	15-20	Gastrointestinal disturbance, metallic taste, hypothyrodism
		Prothionamide	15-20	As above
		Cycloserine	15-20	Neurological and psychological effects
		Terizidone	15-20	As above
		Para-aminosalicylic acid	150	Gastrointestinal intolerance, hypothyrodism, hepatitis
5	Agents with unclear efficacy	Clofazamine	3-5	Skin discoloration, xerosis, abdominal pain
		Linezolid	10^{+}	Diarrhea, headache, nausea, myelosuppression, neurotoxicity, lactic acidosis, pancreatitis, and optic neuropathy
		Amoxicillin-clavulanic acid	10-15 (amoxicillin component) three times a day	Gastrointestinal intolerance, hypersensitivity reaction, seizures, liver and renal dysfunction

Group	Group Name	Drugs	Dosage(mg/kg/day)	Adverse events
		Imipenem/cilastin	20–40 mg/kg/dose IV every 8 hours up to 2 grams per dose	As above
		Thiacetazone	2.5	Stevens Johnson Syndrome in HIV-infected patients, gastrointestinal intolerance, hepatitits, skin reactions
		High dose isoniazid	15-20	Hepatitis, peripheral neuropathy, neurological and psychological effects
		Clarithromycin	7.5-15 twice daily	Gastrointestinal intolerance, rash hepatitis, prolonged QT syndrome, ventricular arrhythmias

12 months after the last positive culture/smear with minimal disease or 18 months with extensive (lung cavities or widespread parenchymal involvement) disease.

Drug groups used to treat drug-resistant TB are summarized in Table I. The second-line drugs are rarely produced in paediatric formulations or appropriate tablet sizes, necessitating breaking, splitting, crushing or grinding. Hence dosing may be inaccurate and sub-therapeutic or toxic levels are possible.

These medications are often unpalatable. Many of these drugs cause vomiting and diarrhoea which may affect the amount absorbed and causes further uncertainty about the dosing.

The pharmacokinetics and toxicity of drugs in children differ considerably from adults. Almost every aspect of pharmacokinetics (absorption, distribution, metabolism, excretion) is subject to age-related change. Current dosing recommendations for children are extrapolated from adult dosages and not based on pharmacokinetic or efficacy studies.

Adverse effects

Adverse effects occur less frequently in children than in adults. The risks and benefits of each drug should be carefully considered when designing a regimen. Second-line drugs should not be withheld from children unless hypersensitivity or an intractable adverse reaction has been documented. Baseline audiometry and monthly hearing tests are mandatory if the child is given injectable agents (Group 2 - Table I). In general, children tolerate drugs better than adults and most side effects are mild and manageable with counseling and symptomatic drugs. The published information on treatment outcomes on children with MDRTB suggests that when appropriately treated, outcomes are as good if not better than in adults.[2]

Additional management issues in the treatment of DR-TB include the following:

HIV-positive children with DR-TB should also receive treatment as follows:

- Pyridoxine (5-10 mg/kg per day); co-trimoxazole prophylactic therapy (CPT); ART, which markedly improves treatment outcome and should be initiated as early as possible.
- The use of corticosteroids as for drug-susceptible TB and for IRIS.
- Nutritional support measures are especially important for children with DR-TB.
- Infection control measures are crucial to prevent the spread of DR-TB.
- Adherence is critical to prevent further development of resistance.

Children should be monitored for three reasons: to determine response to therapy, to identify adverse events early and to promote adherence. Seddon et al have suggested a monitoring schedule which can be adapted to local conditions and resources.[18]

Most experts put all children being treated for DR-TB on multivitamin supplements. Nutritional and metabolic requirements should be assessed because these

children are commonly malnourished and supplements are provided when necessary.[18] Social workers should assess home circumstances and support the caregiver to look after a child who may have complex medical needs and must take multiple medications.

MDRTB and co-morbidities

HIV co-infection

Important practical considerations in the cotreatment of pediatric TB and HIV infection include the timing of initiation of ART, Immune Reconstitution Inflammatory Syndrome (IRIS), drug–drug interactions[19] and overlapping toxicities of ART and TB therapy.[20]

Generally, it is recommended that children with DR-TB and HIV infection be started on ART within 2 weeks of initiating TB therapy.[21,22] The MDR-TB regimens demonstrate their own distinct cumulative toxicities with concomitant antiretroviral (ARV) administration: the nephrotoxicity associated with tenofovir may be compounded by the antituberculous aminoglycosides and the peripheral neurotoxicity induced by stavudine and didanosine and psychiatric disturbances associated with efavirenz may be exacerbated by the antituberculous agent cycloserine.

Studies have demonstrated that, even in a setting of high HIV prevalence, it is possible to achieve favorable outcomes among children treated for MDR-TB using early empiric treatment delivered through a comprehensive community-based program.[2,8,23] Another study in South Africa examined outcomes in 111 children with MDR-TB, including 43 children with HIV co-infection, most of whom initiated ART prior to or during MDR-TB treatment. In that report, 82% of patients achieved favorable outcomes, and five of the 13 deaths occurred before confirmation of MDR-TB and initiation of appropriate treatment.[18]

Other co-morbidities

For children with DR-TB and diabetes, more frequent glucose monitoring is indicated because TB disease and some TB drugs (i.e., rifampin, ethionamide, PAS, and fluoroquinolones) can disrupt glycemic control. Chronic pulmonary disease may exist concurrent with pulmonary DR-TB or can occur later due to chronic lung inflammation and tissue damage. Breathing exercises and physiotherapy are advised to improve function, and, because there is frequently a reversible component, a trial of bronchodilators is often merited. The few case series of spinal DR-TB disease in children describe relatively good treatment outcomes.[24] These children should also be monitored by orthopedic surgeons because deformities can deteriorate with the growth of the child. TBM can cause devastating neurological damage, and affected children should have access to intensive physiotherapy and occupational therapy during and after their illness.

MDR TB child contacts

A 'DR-TB contact' should be defined as a child exposed to an infectious DR-TB source case who, in the last 12 months, had either slept in the same household or had daily interaction with the child. Few studies have assessed the management of MDR tuberculosis child contacts and none is a randomised controlled trial. Only three studies have investigated the role of preventive treatment in contacts[25] No definitive conclusions can be drawn from these studies but the findings suggest that preventive treatment of MDR tuberculosis child contacts is beneficial. WHO advocate that after screening for tuberculosis disease all contacts of patients with infectious MDR tuberculosis should be followed up without medication, because the data supporting the use of drugs other than isoniazid and rifampicin are limited.[26]

Infection control is of paramount importance in the management of MDR-TB in children. Children should be protected from becoming infected with MDR-TB in both the health facility and home setting.

Points to Remember

- ***The exact magnitude of drug resistant TB in children is not known.***
- ***When DR-TB is suspected it is necessary that culture and drug susceptibility testing should be done from any available body fluids.***
- ***Molecular tests (line probe assay and Xpert MTB/RIF) may be of use in smear positive than smear negative specimen.***
- ***MDR-TB in children is treated in the same way as in adults.***
- ***Child contacts of MDR-TB need to be followed up without medications, but after screening for tuberculosis disease.***

References

1. World Health Organisation. Global tuberculosis report 2013. WHO/HTM/TB/2013.11.
2. Ettehad D, Schaaf HS, Seddon JA, Cooke GS, Ford N. Treatment outcomes for children with multidrug-resistant tuberculosis: a systematic review and meta-analysis. Lancet Infect Dis 2012; 12: 449–456.

3. World Health Organization, Geneva, Switzerland. Global tuberculosiscontrol. WHO/HTM/TB/2011162011. Available at:http://www.who.int/tb/publications/global_report/2011/gtbr11_full.pdf.
4. Marais BJ, Hesseling AC, Gie RP, Schaaf HS, Beyers N. The burden of childhood tuberculosis and the accuracy of community-based surveillance data. Int J Tuberc Lung Dis 2006; 10:259–263.
5. Jenkins HE, Tolman AW, Yuen CM, Parr JB, Keshavjee S, Perez-Velez CM, et al. Incidence of multidrug-resistant tuberculosis disease in children: systematic review and global estimates The Lancet - 3 May 2014 (Vol. 383, Issue 9928, Pages 1572-1579 DOI: 10.1016 / S0140 - 6736 (14) 60195 - 1.
6. Banurekha, Swaminathan S. Childhood tuberculosis - Global epidemiology and the impact of HIV. Ped Respir Rev 2007; 8:99-106.
7. Schaaf HS, Marais BJ. Management of multidrug-resistant tuberculosis in children: a survival guide for paediatricians. Paediatr Respir Rev 2011; 12:31–38.
8. Mukherjee JS, Joseph JK, Rich ML, Shin SS, Furin JJ, Seung KJ, et al.Clinical and programmatic considerations in the treatment of MDR-TB in children: a series of 16 patients from Lima, Peru. Int J Tuberc Lung Dis 2003; 7:637-644.
9. Bayona J, Chavez-Pachas AM, Palacios E, Llaro K, Sapag R, Becerra M. Contact investigations as a means of detection and timely treatment of persons with infectious multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2003; 7(12):S501– 509.
10. Boston, USA: The Sentinel Project for Pediatric Drug-Resistant Tuberculosis. Management of Drug-Resistant Tuberculosis in Children: A Field Guide. November 2012.
11. Nicol MP, Zar HJ. New specimens and laboratory diagnostics forchildhood pulmonary TB: progress and prospects. Paediatr Respir Rev 2011; 12:16–21.
12. Wright CA, Hesseling AC, Bamford C, Burgess SM, Warren R, MaraisBJ. Fine-needle aspiration biopsy: a first-line diagnostic procedure in pediatric tuberculosis suspects with peripheral lymphadenopathy? Int J Tuberc Lung Dis 2009; 13:1373–1379.
13. Oberhelman RA, Soto-Castellares G, Gilman RH, Caviedes L, CastilloME, Kolevic Let al. Diagnostic approaches for paediatric tuberculosis by use of different specimen types, culture methods, and PCR: a prospective case-control study. Lancet Infect Dis 2010; 10:612–620.
14. Zar HJ, Workman L, Isaacs W, Munro J, Black F, Eley B, et al. Rapid molecular diagnosis of pulmonary tuberculosis in children using nasopharyngeal specimens. Clin Infect Dis 2012; 55:1088–1095.
15. Marais BJ, Hesseling AC, Gie RP, Schaaf HS, Enarson DA, Beyers N. The bacteriologic yield in children with intra thoracic tuberculosis. Clin Infect Dis 2006; 42:e69–e71.
16. Raizada N, Sachdeva KS, Sreenivas A, Vadera B, Gupta RS, Malik Parmar, et al. Feasibility of Decentralised Deployment of Xpert MTB/RIF Test at Lower Level of Health System in India. PLoS ONE 2014;9(2):e89301. doi:10.1371/journal.pone.0089301.
17. Rachow A, Clowes P, Saathoff E, Mtafya B, Michael E, Ntinginya EN, et al. Increased and expedited case detection by Xpert MTB/RIF assay in childhood tuberculosis: a prospective cohort study. Clin Infect Dis 2012; 54: 1388-1396.
18. Seddon J, Hesseling A, Willemse M, Donald P, Schaaf H. Culture-Confirmed Multidrug-Resistant Tuberculosis in Children: Clinical Features, Treatment, and Outcome. Clin Infect Dis. 2012; pp157–166.
19. Coyne KM, Pozniak AL, Lamorde M, Boffito M. Pharmacology of second-line antituberculosis drugs and potential for interactions with antiretroviral agents. AIDS 2009; 23:437–446.
20. Seddon JA, Hesseling AC, Marais BJ, McIlleron H, Peloquin CA, Donald PR, et al. Paediatric use of second-line anti-tuberculosis agents: a review. Tuberculosis (Edinb) 2012; 92:9–17.
21. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis: emergency update. WHO/HTM/ TB/2008.402. 2008 [accessed 2012 Aug 31]. Available from: http://hqlibdoc.who.int publications/2008/9789241547581_eng.pdf.
22. World Health Organization. Antiretroviral therapy for HIV infection in infants and children: towards universal access. Recommendations for a public health approach. Geneva, Switzerland: WHO; 2010.
23. Drobac PC, Mukherjee JS, Joseph JK, Mitnick C, Furin JJ, et al. Community-based therapy for children with multidrug-resistant tuberculosis. Pediatrics 2006; 117:2022–2029. doi:10.1542/peds. 2005-2235.
24. Seddon JA, Donald PR, Vlok GJ, Schaaf HS. Multidrug-resistant tuberculosis of the spine in children: characteristics from a high burden setting. J Trop Pediatr 2012; 58:341–347.
25. Fraser A, Paul M, Attamna A, Leibovici L. Drugs for preventing tuberculosis in people at risk of multiple-drug-resistant pulmonary tuberculosis. Cochrane Database Syst Rev 2006; 2:CD005435.
26. World Health Organization Stop TB Partnership Childhood TB Subgroup. Chapter 4: childhood contact screening and management. Int J Tuberc Lung Dis 2007; 11:12–15.

RATIONAL ANTIBIOTIC THERAPY

RATIONAL ANTIBIOTIC CHOICE IN AN INFANT WITH FEVER

Balasubramanian S

A 1 yr old male infant presents with fever for one day to a pediatrician. The infant has temperature of 102^0F and has no other symptoms. He is weighing 9 kg and his development has been essentially normal. Both the parents are employed and the infant goes to a day care centre. He had fever for 3 days a month ago and was treated by the family practitioner with cotrimoxazole for 4 days. For the current episode of fever, the practitioner has given a diagnosis of viral fever and prescribed amoxycillin to take care of secondary infections. The parents are worried that the infant has a serious bacterial infection and are also worried about their inability to go for work. Hence they want aggressive treatment to get the infant cured immediately. The pediatrician prescribes amoxyclav and tells the parents that he will get better in a day. The infant continues to have fever and develops vomiting and diarrhea next day. The pediatrician now stops amoxyclav and prescribes ofloxacin on day 3 of fever and asks for blood counts, widal and dengue NS1. He tells the parents that it could be dengue or typhoid and also administers one dose of ceftriaxone IM and advises them to take injection ceftriaxone daily along with oraofloxacin. The infant continues to have high grade fever and vomiting on day 4 and gets hospitalised in a tertiary care facility and undergoes blood and urine cultures along with complete blood count and urinalysis. Urinalysis shows plenty of pus cells and a diagnosis of urinary tract infection (probably acute pyelonephritis) is made and he is started on piperacillin tazobactam and gets better in 24 hrs. The urine culture report 2 days later confirms urinary tract infection with ESBL E.Coli with a colony count of 10^5/ml . The infant is discharged with amikacin as stepdown OP therapy and he recovers completely. Follow up investigations revealed Grade 3 reflux on one side and the infant is on nitrofurantoin prophylaxis and is doing fine.

* Head - Department of Pediatrics,
Kanchi Kamakoti CHILDS Trust Hospital and
CHILDS Trust Medical Research Foundation,
Chennai.

The following comments may be pertinent in the management of this infant :

1) This infant had fever without any localising sign.
2) There was no definite diagnosis made before prescribing antibiotics on 3 occasions.
3) Antibiotic was given for a very short period in the first illness without a diagnosis or evidence for bacterial infection.
4) In the second illness, antibiotic was changed rather than stopped after the infant developed diarrhea.
5) Two broad spectrum antibiotics were administered (ceftriaxone and ofloxacin) with an erroneous diagnosis of enteric fever.
6) Urinalysis perhaps is the most important and vital investigation for fever without focus in this age group was not asked for.
7) Widal test was done on day 4 of fever that too without doing blood cultures.
8) ESBL UTI occurred in this infant probably because of incomplete treatment for the earlier episode which could have led to drug resistance.??
9) Parental anxiety and pressure contributed to irrational antibiotic prescribing.
10) Irrational antibiotic prescribing led to hospitalisation and increased morbidity.

Prompt antimicrobial therapy for an infected patient can make the difference between cure and death or long-term disability. Unfortunately, the use and misuse of antimicrobials has driven the relentless expansion of resistant microbes leading to a loss of efficacy of these “miracle drugs”.

Increase appropriate use

Ensure that infected patients who need antimicrobial therapy have access to quality medicines which conform with policy recommendations and standard treatment guidelines.

Decrease inappropriate use

Discourage the indiscriminate use of antimicrobials in patients unlikely to derive any benefit.

The following are the most important reasons for practising doctors not adhering to rational practices with reference to antibiotic therapy

1) Lack of confidence in making diagnosis clinically without investigations.
2) Lack of concept that majority of febrile illnesses, respiratory illnesses and diarrhea do not require antibiotics.
3) Feeling of comfort that intervention with antibiotics is preferable even if there is no clear indication.
4) Fear of losing clientele – Many young doctors in the early stages of their career feel that parents might change the doctor if only symptomatic therapy is given.
5) Medical curriculum as it exists today does not lay much emphasis on Rational Antibiotic Therapy as much as it deserves. A lot of stress in medical examinations is on uncommon complicated problems not commonly encountered in day to day practice.
6) Not having a clear cut diagnosis or indication for antibiotics.
7) Lack of time - Busy practitioners find it easier to spend time in prescribing rather than counselling in situations where a straight forward diagnosis of viral illness is obvious.
8) Not keeping updated with fundamentals as well as recent developments in appropriate use of antibiotics.
9) Fever is always equated with bacterial infections that too serious infections.
10) Failure of the system wherein guidelines like the FMNCI have not reached most practitioners.
11) No monitoring of antibiotic prescribing practices and auditing at the community and tertiary care levels also.
12) Misleading commercial pressure from the pharma industry and unethical incentives.
13) Lack of awareness even amongst educated parents about appropriate use of antibiotics for their children.
14) Parental pressure to get the child well fast with strong medications and powerful antibiotics.

The WHO has recommended the following guidelines with regard to Rational Antibiotic Therapy.

The way forward

Pracising pediatricians should be conversant with the principles of Rational Antibiotic Therapy and should be periodically sensitised to practise the same in day to day practice. In office practice the following guidelines will help in this direction.

1) To write down the diagnosis routinely if an antibiotic is prescribed.
2) To remember that antibiotics are required only in the minority of children seen.
3) Antibiotics may be needed in office practice even without investigations only in the following situations such as a) dysentery b) bacterial pharyngitis c) sinusitis d) acute otitis media e) skin and soft tissue and wound infections f) pneumonia.
4) Antibiotics are needed in the following situations after cultures(without waiting for final reports) such as a) UTI b) enteric fever c) typhus d) leptospirosis.
5) Presumptive antibiotics may be considered in situations such as (these are infrequent)- a) diarrhoea in severe PEM b) cholera c) immunodeficiency d) bronchiectasis e) sepsis f) bacterial meningitis (Need inpatient care)
6) To remember that UTI is one of the most common causes of fever without focus particularly in young children below the age of 3 years.
7) To remember that antibiotics given to children will definitely not prevent secondary bacterial infections.
8) To promote awareness that exposure to antibiotics without indications not only promotes drug resistance; also it harms the individual with side effects and the community by triggering resistance.
9) To send appropriate cultures before starting antibiotics whenever indicated.
10) To be updated with established guidelines on Rational Antibiotic Therapy for diarrhoea, RTI etc.
11) To periodicllay update one's resources and knowledge by attending CME & refresher courses conducted by IMA, IAP such as RTI GEMS, Rational practice, FMNCI etc.
12) To promote antibiotic stewardship at various levels in medical profession.

GENERAL ARTICLES

PARASITIC INFESTATIONS - AN OVERVIEW

***Kalra A**
****Mazumdar P**

Abstract:*Parasitic infestations constitute a major disease burden worldwide especially in tropical areas. Human parasites are divided into endoparasites, which cause infection inside the body and ectoparasites, which cause infection superficially within the skin. Endoparasites include two main groups -protozoa and helminthic organisms. Malaria, a protozoan parasite, is a leading cause of mortality and morbidity worldwide. The effective control of this disease has been hampered by drug resistance underlining the need for rational drug therapy and diligent vector control. Helminthic infections are prevalent worldwide and are one of the commonest infections in children. Single drug therapy is available for most helminthic infections and this along with environmental sanitation can achieve effective control.*

Keywords:*Endoparasites, Protozoa, Helminths, Ectoparasites.*

Parasites are organisms that derive nutrition and shelter by living in or on another organism. Many devastating diseases in the world especially in tropical areas are the result of infection with parasites. In these regions, the combination of climate and poverty contribute to the transmission of parasitic infections. A recent World Health Organization (WHO) report on the leading causes of death worldwide shows that one-third of all deaths are due to infectious and parasitic diseases. It is estimated that about 1.5–2.7 million people die from malaria eachyear which is about the same as those who die from HIV/AIDS.[1] Human parasites are divided into endoparasites which cause infection inside the body and ectoparasites which cause infection superficially within the skin. Endoparasites include two main groups, the protozoa and the helminthic organisms. These parasites can infect just about any part of the body such as the lungs, liver, esophagus, brain, blood, muscles, joints, skin and even eyes. Some parasites like malaria, are a common cause of death, while others, like parasitic nematodes can lead to disfigurement, blindness and severe economic hardship. In many tropical and subtropical areas, the prevalence of parasitic infections is on the rise due to rapid and unplanned growth of cities, which creates additional breeding sites for the mosquitoes that transmit the parasites responsible for malaria and filariasis. Effective control of these diseases requires repeated administration of potent drugs and continuous efforts to reduce vector insect populations.[2]

Protozoa

Protozoa are microscopic, one-celled organisms that can be free-living or parasitic in nature. Their ability to multiply in humans contributes to their survival and also permits serious infections to develop from just a single organism. Transmission of protozoa that live in human intestine to another human typically occurs through a fecal-oral route (for example, contaminated food or water or person-to-person contact). Protozoa that live in the blood or tissue of humans are transmitted to other humans by an arthropod vector (for example, through the bite of a mosquito or sand fly). The protozoa that are infectious to humans can be classified into four groups based on their mode of movement[2]:

- Sarcodina – the amoebae, e.g., Entamoeba
- Mastigophora – the flagellates, e.g. Giardia, Leishmania
- Ciliophora – the ciliates, e.g., Balantidium

Sporozoa - organisms whose adult stage is not motile e.g., Plasmodium, Cryptosporidium

Table I provides the summary of protozoal infections seen in human beings and the drugs effective in their treatment.

* Former Professor, Pediatrics, S.N. Medical College, Agra
** Former Professor, Pediatrics, S.N. Medical College, Agra
Consultant Pediatrician and Neonatologist, Apollo Pankaj Hospital, Agra.

Table I. Common protozoal infections and their treatment

Common name	Latin name	Body part affected	Diagnostic specimen	Transmission	Treatment
Malaria	Pl falciparum, Pl vivax, Pl ovale, Pl malariae, Pl knowlesi	RBCs, liver	Blood film	Anopheles mosquito bite at night	Artemisinin derivatives, Quinine, Clindamycin, Chloroquine
Crypto-sporidiosis	Cryptosporidium	Intestines	Stool	Ingestion of Oocyst (sporulated), some species are zoonotic (e.g. bovine fecal contamination)	Nitazoxanide
Amoebiasis	Entamoeba-histolytica	Intestines (mainly large, can go to extraintestinal sites)	Stool (fresh diarrhoeal stools have amoeba, solid stool has cyst)	Fecal-oral transmission of cyst, not amoeba	Metronidazole, Tinidazole, Chloroquine in hepatic amoebiasis
Giardiasis	Giardia lamblia	Lumen of the small intestine	Stool microscopy	Cyst ingestion in fecalcontam -inated water or food, can be zoonotic (deer, beavers)	Metronidazole, Tinidazole, Nitazoxanide
Leishmaniasis	Leishmania	Visceral Cutaneous, mucocutaneous	Visual identifi-cation of lesion or microscopic stain with Leishman's or Giemsa's stain	Bite of several species of phlebotomines and flies	Sodium stibogluconate, Amphotericin B, Miltefosine, Pentamidine
Balantidiasis	Balantidium coli	Intestinal mucosa, may become invasive in some patients	Stool (diarrhoea: ciliated tropho-zoite; solid stool: large cyst with horseshoe-shaped nucleus)	Ingestion of cyst, zoonotic infection acquired from pigs (feces)	Metronidazole, Nitazoxanide

IAP guidelines for malaria treatment[3]

Uncomplicated P.vivax

Chloroquine combined with primaquine is the treatment of choice for chloroquine-sensitive P vivax infection. Chloroquine10 mg base/kg stat orally followed by 5 mg/kg at 6, 24 and 48 h (Total dose 25 mg/kg) or chloroquine 10 mg base/kg stat orally followed by 10 mg/kg at 24 h and 5 mg/kg at 48 h (total dose 25 mg base/kg) followed by primaquine given in a dose of 0.25 mg/kg once daily for 14 days to prevent relapse is the prescribed treatment.

Uncomplicated P.falciparum

Artemisinin-based combination therapies (ACTs) are the recommendedtreatmentof uncomplicated P falciparum malaria. Artemether plus lumefantrine, artesunate plus amodiaquine, artesunate plus mefloquine or artesunate plus sulfadoxine-pyrimethamine are recommended for treatment. The choice of ACT in a country or region will be based on the level of resistance of the partner medicine in the combination (Box 1 & 2).Artemisinin and its derivatives should not be used as monotherapy.

Box 1: Recommended treatment of uncomplicated P. falciparum malaria in all states other than North-Eastern states of India

Artesunate 4 mg/kg of body weight orally once daily for 3 days and a single administration of SP as 25 mg/kg of sulfadoxine and 1.25 mg/kg of pyrimethamine on day 1

OR

Artesunate as above and mefloquine 25 mg/kg of body weight in two divided doses (15 mg/kg and 10 mg/kg) on day 2 and day 3.

OR

Co-formulated tablets containing 20 mg of artemether and 120 mg of lumefantrine can be used as a six dose regimen orally twice a day for 3 days. For 5–14 kg body weight 1 tablet at diagnosis, again after 8–12 h and then twice daily on day 2 and day 3. For 15–24 kg body weight same schedule with 2 tablets. For 25–35 kg body weight and above same schedule with 3 and 4 tablets respectively.A single dose of primaquine (0.75 mg/kg) is given for gametocytocidal action.

Box 2: Recommended treatment of uncomplicated P. falciparum malaria in North-Eastern states of India

Co-formulated tablets containing 20 mg of artemether and 120 mg of lumefantrine can be used as a six dose regimen orally twice a day for 3 days. For 5–14 kg body weight 1 tablet at diagnosis, again after 8–12 h and then twice daily on day 2 and day 3. For 15–24 kg body weight same schedule with 2 tablets should be followed. For 25–35 kg body weight and above same schedule should be followed with 3 and 4 tablets respectively.

OR

Artesunate 4 mg/kg of body weight orally once daily for 3 days and mefloquine25 mg/kg of body weight in two divided doses (15 mg/kg and 10 mg/kg) on day 2 and day 3.A single dose of primaquine (0.75 mg/kg) is given for gametocytocidal action.

Severe malaria is a medical emergency. After rapid clinical assessment and confirmation of the diagnosis, full doses of parenteral antimalarial treatment should be started without delay with whichever effective antimalarial is available.For children, artesunate IV or IM is the drug of choice (Box 3).Artemether or quinine is an acceptable alternative if artesunate is not available.

Severe malaria

Severe malaria is a medical emergency. After rapid clinical assessment and confirmation of the diagnosis, full doses of parenteral antimalarial treatment should be started without delay with whichever effective antimalarial is available. For children, artesunate IV or IM is the drug of choice (Box 3). Artemether or quinine is an acceptable alternative if artesunate is not available.

Box 3: Recommended treatment of severe malaria

The schedule is artesunate 2.4 mg/kg IV stat then at 12 and 24 hand then once a day. Once the patient is able to swallow oral medication, complete thetreatment by giving a course of:artemether plus lumefantrine in North-Eastern States. Artesunate plus sulfadoxinepyrimeth-amineis to be given in all states other than North-Eastern states of India. Total duration of treatment is for 7 days.

OR

Artemether 3.2 mg/kg (loading dose) IM, followed by 1.6 mg/kg daily. Once the patient is able to swallow oral medication, completethe treatment by giving a course ofartemether plus lumefantrine in North-Eastern states.Artesunate plus sulfadoxinepyrimethamine in all states other than North-Eastern states of India.Total duration of treatment for 7 days.

OR

Quinine 20 mg/kg (loading dose) diluted in 10 ml/kg of isotonic fluid by infusion over 4 h. Then give a maintenance dose of10 mg salt/kg every 8 h, calculated from beginning of previous infusion, until the patient can swallow.Then quinine tablets,10 mg salt/kg 8 hourly to complete a 7-day course of treatment (including both parenteral and oral). Tetracycline ordoxycycline or clindamycin is to be added to quinine as soon as the patient is able to swallow and should be continued for 7 days.Tetracycline (above 8 years) or doxycycline (above 8 years) is to be given for 7 days in a 4 mg/kg/dose 4 times daily or 3.5 mg/kgonce a day respectively. Clindamycin is to be given 20 mg/kg/day in 2 divided doses for 7 days.If controlled IV infusion cannot be administered then quinine salt can be given in the same dosage by IM injection in the anterior thigh, half the dose in each thigh.

Ectoparasites[2,4-7]

This term is generally used to refer to organisms such as ticks, fleas, lice and mites that attach or burrow into the skin and remain there for relatively long periods of time

Table II. Common ectoparasites and their treatment

Name/ disease	Latin name	Body part affected	Diagnostic method	Transmission	Treatment
Bed bug	Cimexlectularis	Skin	Visual	Sharing of clothing, bedding, close contact	Pesticides, Mechanical cleaning, Calamine
Head louse-Pediculosis	Pediculashumanus	Hair follicles	Visual identification under magnification		Personal hygiene Topical 0.5% Malathion or 1% permethrin or oral Ivermectin, 200 mcg/kg x 3, d 1, 2 and 10
Body louse-Pediculosis	Pediculashuman-uscorporis	Hair follicles			
Crab louse-Pediculosis	Pthirus pubis	Pubic area Eyelashes			
Demodex - Demodicosis	Demodex folliculorum/ brevis/canis	Eye brow Eyelashes	Microscopy of hair follicle		Personal hygiene
Scabies	Sarcoptesscabiei	Skin	Microscopy of scraping of burrows / skin lesion		5% Permethrintopically, topically, Ivermectin 200mcg/kg once, 10% Crotamitontopically once/daily x 2
Flea	Pulexirritans	Skin	Visual identification under magnification	Environment	Topical steroid, calamine lotion

(e.g., weeks to months). Table II shows the common ectoparasiteswhich infest humans and their treatment.

Helminths

Helminthic infestations are the commonest form of parasitic infestations. It may start from the later half of infancy and may persist lifelong. The person gets infected and re-infected throughout life. It is estimated that 25% of the world's population is affected with helminthic infections. The highest disease burden is borne by children in the age group of 5-14 years.

Helminths are worms that are multicellular and have complex organ systems. They reside inside the human body being acquired usually in their egg form as a result of unhygienic living and eating habits. Some have adapted to living in the lumen of the intestine where conditions are anerobic; others reside in the blood or tissues. The helminths can be further divided into the roundworms (Nematodes) and the flatworms (Platyhelminthes), which include tapeworms (Cystodes) and flukes (Trematodes).[2] Tropical and subtropical conditions are active breeding grounds for all helminthic infestations. Helminths do not multiply in humans but can elicit eosinophilic responses when they migrate through tissue. Most helminths have complex life cycles that involve substantial time outside their human hosts. Exceptions are Strongyloides stercoralis, Capillaria philippinensis and Hymenolepis nana, which can increase in number due to autoinfection. Table IIIa, b & c summarise the various helminths, their mode of transmission, symptoms, diagnosis and treatment options.[4,6,7]

Drug of choice

The dosage schedule for intestinal and extraintestinal helminthic infestations is as in Table IV and V.

Table IIIa.Nematodes - Mode of transmission, symptoms, diagnosis and treatment

Organism	Transmission	Symptoms	Diagnosis	Treatment
Ascaris lumbricoides	Oro-fecal	Abdominal pain, weight loss, distended abdomen	Stool: corticoid oval egg	Mebendazole/ Albendazole, pyrantelpamoate, piperazine citrate
Trichinella spiralis	Poorly cooked pork	Depends on worm location and burden: gastroenteritis; edema, muscle pain, spasm; tachycardia, fever, chills, headache, vertigo, delirium, coma, etc	Medical history, eosinophilia, muscle biopsy, serology	Corticosteroid and Mebendazole/ Albendazole
Trichuris trichiura	Oro-fecal	Abdominal pain, bloody diarrhea, prolapsed rectum	Stool: lemon-shaped egg	Mebendazole / Albendazole/ Nitozoxanide
Enterobius vermicularis	Oro-fecal	Peri-anal pruritus, rare abdominal pain, nausea, vomiting	Stool: embryonated eggs, flat on one side	Pyrentalpamoate or Mebendazole / Albendazole
Strongyloides stercoralis	Soil-skin, autoinfection	Itching at infection site, rash due to larval migration, pneumonia, mid-epigastric pain, nausea, vomiting, dysentery, weight loss and anemia	Stool: rhabditiform larvae	Ivermectin or Thiabendazole / Albendazole
Necator-americanus; Ancylostoma duodenale (Hookworms)	Oro-fecal(egg); skin penetration (larvae)	Maculopapular erythema (ground itch), broncho-pneumonia, epigastric pain, GI hemorrhage, anemia, edema	Stool: oval segmented eggs (60× 20-25 µm)	Albendazole/ Mebendazole, Pyrantel pamoate
Dracunculus-medinensis	Oral: cyclops in water	Blistering skin, irritation, inflammation	Physical examination	Slow extraction of worm combined with wound care, Mebendazole
Wuchereria bancrofti; W brugiamalayi (Elephantiasis)	Mosquito bite	Recurrent fever, lymph-adenitis, splenomegaly, lymphedema, elephantiasis	Medical history, physical examination, microfilaria in blood (night sample)	Mebendazole; Diethyl carbamazine
Onchocerca volvulus	Black fly bite	Nodular and erythematous dermal lesions, eosinophilia, urticaria, blindness	Medical history, physical examination, microfilaria in nodular aspirate	Ivermectin/ Mebendazole; Diethyl carbamazine
Loa loa	Deer fly	As in onchocerciasis	As in onchocerciasis	As in onchocerciasis

Table IIIb.Trematodes - Mode of transmission, symptoms, diagnosis and treatment

Organism	Transmission	Symptoms	Diagnosis	Treatment
S mansoni, S japonicum	Skin penetration by cercaria	Dermatitis, abdominal pain, bloody stool, peri-portal fibrosis, hepato-splenomegaly, ascites, CNS	Eggs in stool	Praziquantel
S hematobium	Skin penetration by cercaria	Dermatitis, urogenital cystitis, urethritis and bladder carcinoma	Eggs in urine	Praziquantel
Fasciolopsisbuski	Metacercaria on water chestnut	Epigastricpain, nausea, diarrhea, edema, ascites	Eggs in stool	Praziquantel
Chonorchois sinensis (Chinese liver fluke) Opisthorchis felines (Cat liver fluke) or Opisthorchis viverini (South east Asian liver fluke)	Cysts in fish	Inflammation and deformation of bile duct, hepatitis, anemia and edema	Eggs in stool	Praziquantel
Paragonimus westermani	Cyst in crab meat	Cough (dry / rusty brown sputum), pulmonary pain, pleurisy, tuberculosis-like	Eggs in sputum	Praziquantel

Table IIIc.Cestodes - Mode of transmission, symptoms, diagnosis and treatment

Organism	Transmission	Symptoms	Diagnosis	Treatment
Tenia saginata	Cyst in beef	Epigastric pain, vomiting, diarrhea	Proglottids or eggs in stool or perianal area	Praziquantel/Niclosamide
Tenia solium	Cyst in pork	Epigastric pain, vomiting, diarrhea	Proglottids or eggs in stool or perianal area	Praziquantel/Niclosamide
T solium (Cysticercosis)	Oro-fecal	Muscle pain and weakness, ocular and neurologic problems	Imaging, anti cysticercal antibody (EIA)	Praziquantel/Albendazole, Corticosteroids
D latum	Cyst in fish	Abdominal pain, loss of weight, anorexia, malnutrition and B12 deficiency problems	Proglottids or eggs in stool or perianal area	Praziquantel
E granulosus	Oro-fecal	Large cysts produce various symptoms depending on the location of the organism.	Roentgenography, anti-hydatid fluid antibody (EIA), Casoni skin test	Surgery, formalin injection and drainage, Praziquantel/ Albendazole
E multiloculoris	Oro-fecal	As above	As above	Surgery, Albendazole

Table IV. Dosage schedule for intestinal infestations

Drugs	Dosage
Albendazole	Single oral dose 200mg in <2 years; 400 mg in >2years; for enterobiasisa 2nd dose after 2 weeks.
Mebendazole	100 mg twice daily orally × 3 days; 500 mg single dose; For enterobiasis a 2nddose after 2 weeks
Pyrantel pamoate	Single oral dose 10 mg/kg; 3 days for heavy N. americanus infection and strongyloidiosis
Ivermectin	200µg/kg single dose (6 mg tab); For hyperinfection in strongyloidiosis7–10days may require repeated courses; In onchocerciasis may be 3–6 months till asymptomatic.
Levamisole	2.5 mg/kg single dose
Piperazine Citrate	75 mg/kg orally × 2 days(results in necrosis of worms)
Praziquantel	10 – 20 mg/kg once only
Niclosamide	Single oral dose 1 gm in children weighing 11–34 kg and 1.5 gm in children more than 34 kg
Nitazoxanide	No additional advantage, costlier
Thiabendazole	25mg/kg/dose bid for 2 days; max 3 grams/day for heavy trichuriasis infection daily dose for 3 days; For trichinosis 400mg bid for 8–14 days; For echinococcosis 1-6 months

Table V. Dosage schedule of extra intestinal manifestations

In Cestodes	
Drugs	**Dosage**
Albendazole	400 mg bid in >2 years, 200 mg bid in <2 years × 4 weeks
Praziquantel	50 mg/kg/day × 14 days
Niclosamide	Single oral dose 1 gm in children weighing 11–34 kg and 1.5 gm in children more than 34 kg
In Trematodes	
Praziquental	50 mg/kg single or divided doses × 2 days

Parasitic infestations: issues at hand[1,4,8,9]

Combination therapy in deworming

Combination therapy has been advocated by some in order to prevent or overcome drug resistance. A number of studies have investigated the safety of drug combinations in the treatment of helminth infections: Albendazole and praziquantel can be safely co-administered for schistosomiasis and soil-transmitted helminthiasis; mebendazole andpraziquantel have been widely co-administered in many countries and reported to be safe; albendazole plus diethyl carbamazine (DEC) or albendazole wth ivermectin are also safe combinations in the treatment of lymphatic filariasis. Preliminary assessment of the co-administration of the three drugs (albendazole, ivermectin and praziquantel) indicate that there is no clinically relevant interaction between the three drugs when given concurrently as single oral doses in healthy volunteers. However many argue against it as there is no clear documented resistance of parasites reported in humans and the choice of changing to another single drug therapy is always available.

Drug resistance to deworming agents

This has been reported in livestock (where it is used at frequent intervals), but there is no unequivocal evidence in humans despite long term widespread use. However as the risk is real, blanket treatment should be targeted only to high risk group (school children), and not all. This will ensure susceptiblegene flow among a worm population, without drug pressure. Also, the drugs should be given not very frequently (>6 months interval).

Frequency of de-worming

The frequency of the treatment will depend on the prevalence and intensity of infection. In other words, it depends on the proportion of school-age children who are infected as well as the magnitude of infection in each child. The WHO recommends the following treatment guidelines:

For soil-transmitted helminths, schoolsin areas with high prevalence of infection (>50%) should deworm the children twice per year; with moderate prevalence of infection (20% to 50%) once per year; with low prevalence of infection (<20%), there is no need for mass drug administration, but should emphasize education campaigns and behaviour change, and encourage children to seek treatment when suspected.

For schistosomes, schools with high prevalence of infection (>50%) should deworm once per year. Schools with moderate prevalence of infection (10% to 50%) should deworm once every two years.Schools with low prevalence of infection (<10%) should deworm twice during primary school.

Benefits of deworming strategies

The health, educational, and economic consequences of helminth infections can be avoided through early intervention to treat the infections, particularly in women of reproductive age and children. Studies of pregnant women showed that deworming treatment reverses anemia and improves birth weight and child survival. In preschool children, use of deworming drugs can improve motor and language development and reduce malnutrition. Treating children of school age improves their nutritional status, physical fitness, appetite, growth, and intellectual development. Studies have shown that de-worming children reduced primary-school absenteeism by at least one-fourth in the first two years of the project. The gains were largest among young children, who suffered the most intense worm infections. In terms of cost-effectiveness as an educational intervention, de-worming proved to be far more effective at improving school attendance than other educational interventions. Additionally, because education has a high return on investment, de-worming offers large payoffs.

Vaccine status

Vaccines have had little impact on human parasitic infections. The reasons for this are many; these eukaryotic pathogens are genetically and biologically complex organisms, some with elaborate life cycles and well-honed immune evasion mechanisms. Additionally, our understanding of the mechanisms of immune control of many parasitic infections, what constitutes an effective immune response and how to induce high-quality immunological memory is not fully developed.[9] Progress has been made towards the development of a vaccine against malaria, cryptosporidiosis, leishmaniasis, toxoplasmosis and schistosomiasis. However most of these are in the trial phase. The maximum advancement has been made in case of malaria vaccine.

Points to Remember

- ***Parasitic infestations are an important cause of morbidity and mortality worldwide especially in the tropics.***
- ***Human parasites are divided into endoparasites (protozoa and helminths), which cause infection inside the body, and ectoparasites, which cause infection superficially within the skin.***
- ***Vector control, environmental sanitation and rational drug therapy are the keystones to effective control of these diseases.***
- ***Vaccines against various parasitic infections are under trial but none available as yet.***

References

1. Report of the third global meeting of the partners for parasite control. Deworming for health and development. Geneva, World Health Organization, 2005. (WHO/CDS/CPE/PVC/2005.14).
2. Beaver PC. Animal agents and vectors of human diseases. In: Beaver PC, Jung RC, Cupp EW., eds, Clinical parasitology, 9th edn, Philadelphia, Lea and Fabiger. 1984; pp18–30.
3. Kundu R. Diagnosis and management of malaria in children: Recommendations and IAP plan of action. DOI: http://dx.doi.org/10.1016/j.pid.2013.03.007.
4. Drugs for parasitic infection. Med Lett 2004; p12. Available at www.medicalletter.org
5. Hoetz PJ. Parasitic infections in temperate climates. In: Katz S , Gershon A , Hoetz P, eds. Krugman's Infectious Diseases of Children, 10th edn. St. Louis, Mosby-Year Book, 1998;pp311-325.
6. Bethony J,Brooker S, Albonico M, Geiger SM, Loukas A, Diemert D, et al. Soil-transmitted helminth infections: Ascariasis, trichuriasis, and hookworm. Lancet 2006; 367:1521-1532.
7. Keiser J, Utzinger J. Efficacy of current drugs against soil-transmitted helminth infections: systematic review and meta-analysis. JAMA 2008; 299:1937-1948.
8. Hotez PJ, Brindley PJ, Bethony JM, King CH, Pearce EJ, Jacobson J, et al. Helminthinfections: The great neglected tropical diseases. J Clin Inv 2008; 118 (4): 1311-1321.
9. Tarleton RL. New approaches in vaccine development for parasitic infections. Cell Microbiol 2005; 7:1379-1386.

GENERAL ARTICLES

HYPEROSMOLAR THERAPY IN CHILDREN WITH RAISED INTRACRANIAL PRESSURE

* ***Dipangkar Hazarika***

Abstract: *Raised intracranial pressure is a life threatening condition that can occur in many neurological and non-neurological illnesses. Hyperosmolar therapy in critically raised ICP is an important part of management and the same principles can be applied in both traumatic and non-traumatic conditions. Currently mannitol is the recommended first choice of a hyperosmolar agent in raised ICP. Some authors have argued that hypertonic saline might be more effective and safe compared to mannitol in particular situations.This article focuses on the practical useof hyperosmolar agents in the management of raised ICP in children.*

Keywords: *Intracranial pressure, Hyperosmolar therapy, Mannitol, Hypertonic saline.*

An increase in intracranial pressure (ICP) is commonly caused by an increase in volume of brain (cerebral edema), blood (intracranial bleeding), space occupying lesion, or cerebrospinal fluid (hydrocephalus). These mechanisms could be operating in single or in various combinations. Cerebral edema is the most important cause of raised ICP in non-traumatic brain injuries such as central nervous system (CNS) infections and metabolic encephalopathy. It can be vasogenic, cytotoxic, or interstitial. Patients with cerebral edema may have a combination of all three mechanisms operating.[1]

Most of the current treatment recommendations on raised ICP are based on consensus and clinical experience. Few specific treatment options have beensubjected to randomized trials.[1] Since there are limited outcome studies to support the current management of children with increased ICP from etiologies other than traumatic brain injury (TBI), it is the knowledge gained from treating TBI that is often applied to treat raised ICP of other etiologies as well.[1] Cerebral blood flow depends on Cerebral Perfusion Pressure (CPP). CPP is the difference between the Mean Arterial Pressure (MAP) and ICP. In the management of cerebral edema maintaining the CPP >40 mm Hg in infants and 50-60 mm Hg in children is essential for good outcome. It is not only important to reduce ICP but also to maintain the MAP in the upper normal range so as to maintain CPP in the normal range.

Hyperosmolar treatment is one of the important methods for treating cerebral edema and has been employed since early 1960.[2] Urea, glycerol and mannitol were used to treat this condition in the early years, but then urea and glycerol were soon abandoned because of low efficacy. Mannitol is still used extensively. Side effects such as rebound effect, serum electrolyte imbalance and hypovolemia have led to the continued search for other osmotically active agents. One of them is hypertonic saline.[3]

The Brain Trauma Foundation (BTF) has recommended that therapy to reduce ICP should begin at pressures more than 20 mm Hg. Currently, only two hyperosmolar agents are used for this purpose: mannitol and hypertonic saline (HTS). The BTF currently recommends mannitol as the mainstay in the management of intracranial hypertension, but HTS represents a potential alternative that is gaining favor.[4] The reported concentrations of HTS for clinical use range from 2% to 23.5%.[5] Research on animals and in children have shown that both mannitol and 3% NaCl are effective in reducing ICP, but that the effect achieved with hypertonic saline solution infusion is more accentuated and lasts longer.[6]

Mechanism of action of mannitol

Immediately after infusion of mannitol, there is an initialexpansion of plasma volume and a reduction in hematocrit and in blood viscosity, which may increase cerebral blood flow (CBF) and oxygen delivery to the brain reducing ICP within few minutes.[7] Rheologic and osmotic effects are additional effects.Infusion of mannitol increases serum osmolality during the second phase, which draws edema fluid from cerebral parenchyma. This process takes 15-30 minutes until gradients are established.[7]

* Assistant Professor
Department of Pediatrics,
Jorhat Medical College and Hospital,
Assam.

Mannitol

Although mannitol has been the cornerstone of osmotherapy in raised ICP, the optimal dosing of mannitol is not known.[8] Intravenous bolus of mannitol lowers ICP in 1 to 5 minutes with a peak effect at 20 to 60 minutes. The effect lasts 1.5 to 6 hours, depending on the clinical condition.[9]

A reasonable approach is to use an initial bolus of 0.25-1g/kg, higher dose for more urgent reduction of ICP followed by 0.25-0.5g/kg boluses repeated every 2-6 hourly as per requirement.[8] It should be administered approximately in 15- 20 minutes.

Precaution: Attention must be paid to the fluid balance to avoid hypovolemia and shock. There is also a concern of possible leakage of mannitol into the damaged brain tissue by opening the blood brain barrier (BBB), potentially leading to 'rebound' rises in ICP.[11] For this reason, when it is time to stop mannitol, it should be tapered and its use should be limited to 48 to72 hours.[8]

Apart from hypotension and rebound rise in ICP, mannitol can also lead to hypokalemia, hemolysis and renal failure.[8] Therefore it mustbe avoided in the presence of cardiac failure and renal failure.[12]

If mannitol is used in intracranial hemorrhage, there is a risk of increased bleeding as the brain edema reduces. Therefore, an emergency CT scan is mandatory if the patient does not regain full consciousness immediately after the dose of mannitol.[13] For optimal effect of mannitol, serum osmolality should be between 300–320 mOsm/kg. Keeping osmolality less than 320 mOsm/kg also helps to prevent complications.[1]

Side effects of mannitol: When osmolality is more than 320 mOsm/kg, complications such as hypovolemia, hyperosmolarity and renal failure may occur. The adverse effects of mannitol are more likely when it is present in the circulation for extended periods, such as in slow or continuous infusions or with repeated administration of high doses.[1]

Glycerol

Glycerol is another alternative osmotic agent for treatment of raised ICP. It is used orally (1.5 g/kg/day, q4–6hrly or 0.5ml/kg diluted in twice the volume of water or fruit juice) or intravenous forms. Given intravenously, it reduces ICP with effect lasting for about 70 minutes without any prolonged effect on serum osmolality.[10] Glycerol readily moves across the blood brain barrier into the brain. Though not proven, there is concern of rebound rise in ICP with its use.[8] Mannitol is to be given for the first 2–3 days followed by oral glycerol (either orally or through nasogastric tube) for a few days and then tapered off over the next few days.[12]

Hypertonic saline (HTS)

In 1988 Worthley, et al. first reported the use of HTS to reduce ICP in 2 patients who were unresponsive to mannitol. Since then, more recent studies have suggested that HTS is possibly more effective than mannitol for the reduction of ICP.[14]

Indications

Hypertonic saline has a clear advantage over mannitol in children who are hypovolemic or hypotensive[8] as it augments intravascular volume and may increase blood pressure in addition to decreasing ICP.[1] Other situations where it may be preferred are renal failure or serum osmolality >320 mOsm/Kg. It has been found effective in patients with serum osmolality of up to 360 mOsm/Kg.[15]

Hypertonic saline acts by creating an osmotic gradient at the intact blood brain barrier, reducing brain volume.[6] Early after administration HTS reduces blood viscosity, increasing the rheological properties, which improves cerebral blood flow (CBF) and cerebral oxygenation, causing auto regulatory vasoconstriction, thereby reducing ICP. Hypertonic saline is also thought to induce endothelial cell shrinkage, which also improves circulation.[16] It has an immunomodulatory role and reduction of CSF production.[17]

Studies using isotopic techniques and ion selective microelectrodes have shown that the blood-brain barrier (BBB) is impermeable to sodium (Na^+) and chloride (Cl^-) ions with the reflection coefficient for Na and Cl determined to be 1.0 and 0.9[18, 19, 20] meaning that with an intact BBB, very little Na crosses the barrier, thus allowing Na to pull fluid out of the interstitial space.[5]

It has been shown that both in animals with and without intracranial pathology, hypertonic saline (HS) reduces brain water content and in traumatized animal models it has more favorable results than mannitol.[21,22]

Dose: During stabilization or at any time during the treatment course, if there are signs and symptoms of cerebral herniation (pupillary dilation, systemic hypertension, bradycardia, extensor posturing) hyperventilation with FiO2 of 1.0, and intubating doses of either thiopental or pentobarbital and either mannitol (0.25-1.0 g/kg IV) or hypertonic saline (3% solution 5-10 mL/kg IV over 30-60

minutes) can be given, which is followed by continuous infusion.[23]

Administer hypertonic saline as a continuous infusion at 0.1 to 1.0 mL/kg/hr, to target a serum sodium level of 145–155 mEq/L.[24,25,26] with maximum target level up to160 mEq/L.[6, 27]

Infusion is given for 48-72 hours then tapered gradually at least 10% every 6 hourly, without causing any abrupt fall in sodium levels so as to avoid central or extra-pontine myelinolysis.[27] Mannitol and 3% NaCl can be used concurrently, keeping serum osmolality <320 mOsm/L.[23]

Side effects: Bleeding secondary to decreased platelet aggregation and prolonged coagulation, rebound rise in ICP, hypokalemia and hyperchloremic metabolic acidosis, central pontinemyelinolysis, acute volume overload, acute tubular necrosis and renal failure, subdural hematoma or effusion, cardiac failure or pulmonary edema[8] are documented side effects.

Myelinolysis occurs more frequently if there is a rapid transition from hyponatremia to hypernatremia. For myelinolysis to occur a daily serum-Na concentration load of 35-40 mEq/L is required.[28] The region most susceptible to myelinolysis is the pontine white matter with visualization on MRI.Central pontinemyelinolysis manifests clinically as lethargy and quadriplegia/paresis.[3]

Despite these concerns, current evidence suggests that hypertonic saline as currently used is safe and does not result in major adverse effects.[29]

The side effect profile of HTS appears to be more favorable than that of mannitol; the latter notoriously causes delayed hypovolemia secondary to its diuretic effect, which can be undesirable in trauma patients. Hypertonic saline improves mean arterial pressure and increases circulating blood volume without the delayed hypotensive effect observed with mannitol use.[5]

Precautions: Serum sodium and neurological status need to be closely monitored during therapy.[8] When the hypertonic saline therapy is no longer required, serum sodium should be slowly reduced to normal values over a period more than 2 days.[3] Hourly decline in serum sodium of not more than 0.5 mEq/L, with maximum decrease of 10 mEq/L/day is advised to avoid complications associated with fluid shifts.[30]

Monitoring of serum sodium and serum osmolality should be done every 2–4 h till target level is reached and then followed up with 12 hourly estimations.[31] Undercareful monitoring, hypertonic saline has been used for up to 7 days.[31]

Which one to use - HTS or mannitol?

During the last decade, HTS has received increasing attention as a good substitute for mannitol due to its excellent tonic properties and the lack of hypovolemic hypotension that mannitol causes. Various studies have reported various results when using different concentrations of HTS.[5]

3% HTS may be the osmotherapy of choice in hypotensive/hypoperfused patients for reducing ICP while maintaining MAP and CPP. Encouraged by the results of its use in traumatic brain injury as well as DKA, and in non-traumatic coma in adults, it is also being tried in non-traumatic coma in children.[13]

A recent study comparing role of HTS and mannitol suggested that 3% HTS treatment significantly raised the MAP, reduced ICP, greatly improved CPP, reduced cerebral edema and attenuated brain damage with a superior effect over mannitol.[32] A prospective, randomized study showed that 7.5% HTS administered as an isovolemic bolus (2 mL/kg) was more effective than 20% mannitol in reducing the ICP in trauma patients.[33]

Another prospective study conducted by Horn, et al using 7.5% saline administered as bolus infusion to patients with elevated ICP due to trauma and not responding to the standard treatment showed it to be effective in reducing the ICP and improving cerebral perfusion pressure (CPP).[34] With the aim of reducing the ICP to below 20 mmHg, Peterson, et al administered a 3% saline infusion to 68 children with trauma who did not respond to standard treatment. They found serum-Na concentrations of 150-170 mEq/L and a serum osmolarity of 300-330 mOsm/L to correlate with better prognosis.[31]

In another study comparingHTS (3%) with mannitol in 67 patients with cerebral edema of infective, hemorrhagic and metabolic origin,it was found that HTS is probably more effective and safe. None of the patients developed renal failure, congestive cardiac failure, pulmonary edema and hypokalemia.[3]

Upadhyay et al in their study compared mannitol (n=98) with 3% HTS (n=100) in the treatment of cerebral edema of varied etiologies including traumatic origin. They also found that HTS is more effective and safe.[35]

Mortazavi et al in their meta analysis on HTS for treating raised ICP found five pediatric studies that used HTS. Two studies were randomized control trials (RCTs),

one was a prospective observational trial and two were retrospective.A clinical benefit in ICP control or patient outcome was seen in all. Two RCTs demonstrated better ICP control with HTS than control fluid (RL or NS) in trauma patients, only 1 trial compared HTS and mannitol. All five pediatric studies supported the use of HTS for reduction of ICP. Only one retrospective study demonstrated a better outcome in terms of the mortality rate in patients treated with HTS.[5]

HTS has been administered as a continuous infusion or as a bolus in various studies. Although some studies have had ICP goals, others have had serum Na goals for HTS administration.[5]Concentrations of HTS used ranging from 3% to 20% in various studies. Doses ranged from 30 to 300 ml by volume and 1.5 to10 ml/kg by weight, with 2 ml/kg being the most common.[5,31] Yildizdas et al in their study used both as an infusion and in bolus form. Bolus dose of 1ml/kg (3%HTS) for 4-6 times in 15 minutes and then infusion dose of 0.5-2mL/kg/hour.[3]Upadhyay et al used 3% HTS at a loading dose of 5mL/kg stat followed by 2mL/kg every 6 hourly for two days and found it to be effective.[35] Various other studies use hypertonic saline as a continuous infusion at 0.1 to 1.0 mL/kg/hr, to target a serum sodium level of 145–155 mEq/L.[24, 25, 26]

Mortazavi et al in their meta analysis found that a majority of the studies showed a more favorable short-term ICP outcome for HTS, no matter what the concentration or administration mode (bolus or continuous drip). HTS also appears to have a favorable outcome in all types of intracranial hypertension, no matter the origin. However, there is no consensus on the most optimal concentration, because all concentrations appear to have favorable effects on ICP.[5]

Points to Remember

- ***Principles of treating traumatic brain injury are often applied to treat raised ICP of other etiologies also.***
- ***Mannitol is still used extensively but with potential risk of rebound effect, serum electrolyte imbalance and hypovolemia. It is to be avoided in cardiac and renal failure.***
- ***An emergency CT brain is mandatory, if traumatic patient does not regain full consciousness following mannitol use.***
- ***Use hypertonic saline in patient with hypovolemia, renal failure and serum osmolality >320 mosmol/kg.***
- ***More favorable short term outcome is for hypertonic saline, irrespective of concentration or mode of administration mode (continuous infusion or bolus).***

References

1. Singhi SC, Tiwari L. Management of intracranial hypertension. Indian J Pediatr 2009; 76:519-528.
2. Wise BL, Chater N. Use of hypertonic mannitol solutions to lower cerebrospinal fluid pressure and decrease brain bulk in man. Surg Forum 1961; 12:398-399.
3. Yildizdas D, Altunbasak S, Celik U, Herguner O. Hypertonic saline treatment in children with cerebral edema. Indian Pediatr 2006; 43:771-779.
4. Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons, Joint Section on Neurotrauma and Critical Care, AANS/CNS: Guidelines for the management of severe traumatic brain injury, J Neurotrauma 2004; 24: S1–S106.
5. Mortazavi, MM., Romeo AK, Deep A, Griessenauer CJ, Shoja M M, Tubbs RS, Fisher W. Hypertonic saline for treating raised intracranial pressure: literature review with meta-analysis. J Neurosurg 2012; 116:210–221.
6. Giugno K, Maia TR, Kunrath CL, Bizzi JJ. Treatment of intracranial hypertension. J de Pediatr 2003; 79:287-297.
7. Paczynski RP. Osmotherapy: basic concepts and controvensies. Crit Care Clin 1997; 13:105-129.
8. Sankhyan N, Raju KNV, Sharma S, Gulati S. Management of Raised Intracranial Pressure. Indian J Pediatr 2010; 77:1409–1416.
9. Knapp JM. Hyperosmolar therapy in the treatment of severe head injury in children: Mannitol and hypertonic saline. AACN Clin Issues 2005; 16:199–211.
10. Berger C, Sakowitz OW, Kiening KL, Schwab S. Neurochemical monitoring of glycerol therapy in patients with ischemic brain edema. Stroke. 2005; 36:e4–6.
11. Kaufmann AM, Cardoso ER. Aggravation of vasogenic edema by multiple – dose mannitol. J Neurosurg. 1992; 77:584–589.
12. Rao PN. Japanese encephalitis For Doctor, Health workers and Parents 16th edition May 2000. (Available at: http://indmed.nic.in & aphealth.org. Accessed on 10 July 2013).
13. Chokhani R. Altered Sensorium: An Approach. In: The Golden Hour Emergency Management Course, Eds, Udani S, Shandilya A, Mithiya B.2nd edn, Indian Academy of Pediatrics National Publication house, Gwalior, 2013; pp 43-49.
14. Worthley LI, Cooper DJ, Jones N. Treatment of resistant intracranial hypertension with hypertonic saline. Report of two cases. J Neurosurg 1988; 68:478–481.
15. Ziai WC, Toung TJ, Bhardwaj A. Hypertonic saline: First-line therapy for cerebral edema? J NeurolSci 2007; 261:157–166.

16. Ware ML, Nemani VM, Meeker M, Lee C, Morabito DJ, Manley GT. Effects of 23.4% sodium chloride solution in reducing intracranial pressure in patients with traumatic brain injury: a preliminary study. Neurosurgery 2005; 57:727–736.

17. Forsyth LL, Liu-DeRyke X, Parker D Jr, Rhoney DH. Role of hypertonic saline for the management of intracranial hypertension after stroke and traumatic brain injury. Pharmacotherapy 2008; 28:469–484.

18. Betz AL. Sodium transport in capillaries isolated from rat brain. J Neurochem 1983; 41:1150-1157.

19. Betz AL. Sodium transport from blood to brain: Inhibition by furosemide and amiloride. J Neurochem 1983; 41: 1158-1164.

20. Fenstermacher JD, Johnson JA. Filtration and reflection coefficients of the rabbit blood-brain barrier. Am J Physiol 1966; 211:311-346.

21. Qureshi AI, Wilson DA, Traystman RJ. Treatment of elevated intracranial pressure in experimental intracerebral hemorrhage: Comparison between mannitol and hypertonic saline. Neurosurgery 1999; 44:1055-1064.

22. Zornow MH, Scheller MS, Shackford SR. Effect of a hypertonic lactated Ringer's solution on intracranial pressure and cerebral water content in a model of traumatic brain injury. J Trauma 1989; 29:484-488.

23. Kochanek PM, Bell MJ. Neurologic emergencies and stabilization. In: Nelson Textbook of Pediatrics, edsKliegman, Stanton, Geme, Schor, Behrman, 19th Edn, Elsevier, New Delhi 2012; pp296-304.

24. Larive LL, Rhoney DH, Parker D, Coplin WM, Carhuapoma JR. Introducing hypertonic saline for cerebral edema. Neurocrit Care 2004; 1:435–440.

25. Qureshi A, Suarez J, Bhardwaj A, Mirski M, Schnitzer MS, Hanley DF et al. Use of hypertonic saline/ acetate infusion in the treatment of cerebral edema: effect on intracranial pressure and lateral displacement of the brain. Crit Care Med 1998; 26:440–446.

26. Suarez JI. Hypertonic saline for cerebral edema and elevated intracranial pressure. Cleve Clin J Med.2004;71 Suppl : S9-13.

27. Udani S. Head injury in children. In: IAP Specialty series on Pediatric Intensive Care, Eds, Udani S, Ugra D, Chugh K, Khilnani P, 2nd edn, Jaypee Brothers, New Delhi, 2013; pp321-340.

28. Soupart A, Pennickx R, Namias B, Stenuit A, Perier O, Decaun G, et al. Brain myelinolysis following hypernatremia in rats. J Neuropathol ExpNeurol 1996; 55:106-113.

29. Strandvik GF. Hypertonic saline in critical care: a review of the literature and guidelines for use in hypotensive states and raised intracranial pressure. Anaesthesia 2009; 64: 990 - 1003.

30. Marcoux KK. Management of increased intracranial pressure in critically ill child with acute neurological injury. AACN Clin Issues 2005; 16:212-231.

31. Peterson B, Khanna S, Fischer B, Marshall L. Prolonged hypernatremia controls elevated intracranial pressure in head injured pediatric patients. Crit Care Med 2000; 28: 1136–1143.

32. Liu S, Li L, Luo Z, Wang M, She H, Yu X et al. Superior effect of hypertonic saline over mannitol to attenuate cerebral edema in a rabbit bacterial meningitis model. Crit Care Med 2011; 39:1467-1473.

33. Vialet R, Albanese J, Thomachot L, Antonini F, Bourgoun A, Aliez B, et al. Isovolemic hypertonic solutes (sodium chloride and mannitol) in the treatment of refractory posttraumatic intracranial hypertension: 2 mL/kg 7.5% saline is more effective than 2 mL/kg 20% mannitol. Crit Care Med 2003; 31:1683-1687.

34. Horn P, Munch E, Vajkoczy P, Herrman P, Quintel M, Schilling L, et al.Hypertonic saline solution for control of elevated intracranial pressure in patients with exhausted response to mannitol and barbiturates. Neurol Res 1999; 21:758-764.

35. Upadhyay P, Tripathi VN, Singh RP, Sachan D. Role of hypertonic saline and mannitol in the management of raised intracranial pressure in children: A randomized comparative study. J PediatrNeurosci. 2010; 5:18-21.

NEWS AND NOTES

Neonatology Association of Tamilnadu

Expert Talk 2015

Theme: Neonatal Sepsis

Date: 22nd February, 2015 Venue: GRT Convention Center, T.Nagar, Chennai

Contact:

Dr. S. Giridhar

Organizing Secretary

Phone (O): 044-45989890, 09841027228 Email: giridharsethu@hotmail.com

DRUG PROFILE

COUGH AND COLD REMEDIES IN CHILDREN - USE WITH CAUTION

**** Jeeson C Unni***

Abstract: *Cough and cold are common symptoms that cause parental anxiety and therefore cough and cold medications targeting these are a major income for the pharmaceutical industry. Many of these medications are disbursed over-the-counter in India and they are often prescribed by pediatricians. This article attempts to review relevant literature pertaining to efficacy and side effects of these drugs in young children and usefulness of honey.*

Keywords: *Cough, Children, Antihistamines, Antitussives, Expectorants, Mucolytics, Decongestants*

Cough is one of the commonest symptoms for which a pediatrician is consulted.[1] Care-givers have prescribed 'cough-relievers' for decades starting with home remedies like Plectranthus amboinicus ('pathorchur' in Hindi, panikkoorkka in Malayalam, doddapatre soppu in Kanada, karpooravalli in Tamil), honey, carom seeds (ajwain) and tulsi leaves, turmeric with milk, etc; and cold and cough medicines which are sold over the counter (OTC). However, FDA warns against use of OTC cold and cough medicines in children below 2 yrs age[2] because serious and potentially life-threatening side effects could occur. Further, there is no evidence that they are effective.[3] This article examines the facts regarding the use of these cold and cough medications in children and adolescents.

Medications to be reviewed

Table I gives the 4 classes of cough and cold medications and their generic products, that will be discussed in this article.

Antihistamine combinations

A Cochrane review showed that antihistamine-analgesic-decongestantant combinations have some general benefit in adults and older children with the common cold but not in young children.[4] Another Cochrane review suggests that OTC medications containing codeine and antihistamines should not be used in young children as an adjunctive treatment for acute pneumonia.[5] Further, there is no evidence for the use of antihistamines for treatment of cough associated with acute sinusitis in children.[6] Nocturnal cough in URI is self-limiting and both dextromethorphan and promethazine produce no better relief than no treatment.[7] Antihistamine-decongestant combination was no better than a placebo in reducing symptoms of URI in preschool children[8,9] and produced significantly more sleepiness than the placebo. In spite of being in the market for more than 65 years there are very few studies on effectiveness of diphenhydramine for treatment of cough and none of these studies have targeted children. Even in adults, the effect is not substantiated.[10]

Table I. Cough and cold medications

Antihistamines	Brompheniramine Chlorpheniramine Dexchlorpheniramine Diphenhydramine Doxylamine Pheniramine Promethazine Triprolidine
Antitussives	Codeine Dextromethorphan Dihydrocodeine Pentoxyverine Pholcodine
Expectorants / Mucolytics	Ammonium chloride, Bromhexine, Guaifenesin, Ipecacuanha, Senega, Ammonia
Decongestants	Oxymetazoline Phenylephrine Pseudoephedrine Xylometazoline

* Editor-in-Chief
IAP Drug Formulary,
Cochin.

Antitussives

Most cough suppressant preparations are marketed as mixtures of dextromethorphan or codeine with antihistamines, decongestants and/or expectorants. Although codeine and dextromethorphan are efficacious for cough suppression in adults,[11] similar efficacy has not been demonstrated in children. A study comparing codeine, dextromethorphan and placebo at a low dose given at bedtime for 3 days in children 18 months to 12 years of age, with significant night cough of less than 14 days duration found no benefit with these antitussives.[12] Studies using larger dosages have not been performed. It is important to note that suppression of cough may be hazardous and contraindicated in many respiratory ailments. The IAP drug formulary mentions dry unproductive cough as an indication for use of dextromethorphan but does not recommend use of codeine for any form of cough.[13] Neither diphenhydramine nor dextromethorphan has been shown to alleviate nocturnal cough or improve sleep quality for the sick child or for the care-giver when compared with placebo groups.[14,15] In a more recent study dextromethorphan as compared with placebo did not alleviate nocturnal cough or help to sleep, but honey was shown to significantly improve nocturnal symptoms and sleep quality as compared with placebo.[16] The most recent evidence seems to indicate that the most common ingredients in cough and cold medications are not effective for the treatment of cough in children, but honey may be beneficial. In addition, other than the risk of botulism in children younger than one year to honey does not seem to carry the potential toxicity and side effects.

Expectorants/Mucolytics

Mucolytics may be beneficial but there is insufficient evidence to recommend them as an adjunctive treatment for acute pneumonia - One trial found that a mucolytic reduced cough frequency and symptom scores.[3-5] Two trials compared the expectorant guaifenesin with placebo; one indicated significant benefit whereas the other did not.[3]

Decongestants

Nasal decongestants may be less hazardous than some of the oral medicines, but they still present a safety risk such as physical injury to the nasal passages. However, there are hardly any RCTs addressing this modality of treatment. Decongesants are not effective for treating cough associated with acute sinusitis in children.[6]

Toxicity of cough medications in young children

Most of the commonly used cough and cold medications in the prescribed doses are not very toxic in children and they rarely cause poisoning or death on inadvertent excess administration. Cases of toxicity, if they occur, are due to improper dosing. Codeine appears to be associated with a high frequency of severe adverse effects and toxicity.[17,18] Diphenhydramine, though implicated in toxicity in children,[17] rarely produced severe side effects in children less than 6 yrs age given doses less than 7.5mg/kg.[19] Dextromethorphan toxicity must be suspected in a child who has ingested 5-7.5mg/kg of the drug and present with infrequent vomiting or somnolence.[20] It is imperative to consider drug abuse as a cause when an adolescent is being treated for dextromethorphan toxicity.[21] Pseudoephedrine, predominantly, and other over-the-counter cold medications have been implicated in the deaths of very young children.[22]

Summary

There is scant evidence for the utility of the numerous, much prescribed medications available in the market for treating cough and cold in children. The side effects, though rare, could be catastrophic. Pediatricians need to be careful in prescribing these drugs to young children.

Points to Remember

- ***No evidence exists for use of cough and cold medications.***
- ***As far as possible, use of these medications in very young children must be avoided.***
- ***Check that the correct dosage is prescribed even when they are prescribed for older children.***
- ***Cough and cold medicines should be in child-resistant packaging.***
- ***Medications that need to be sparingly used include codeine, dextromethorphan, pseudoephedrine, diphenhydramine and chlorpheniramine.***

References

1. Worrall G. Acute cough in children. Can Fam Physician. 2011; 57(3): 315–318.
2. OTC Cough and Cold Products: Not For Infants and Children Under 2 Years of Age.http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm048682.htm. Accessed on 19/10.14.

3. Smith SM, Schroeder K, Fahey T. Over-the-counter (OTC) medications for acute cough in children and adults in ambulatory settings. Cochrane Database of Systematic Reviews 2012, Issue 8. Art. No.: CD001831. DOI: 10.1002/14651858.CD001831.pub4.
4. De Sutter AIM, Van Driel ML, Kumar AA, Lesslar O, Skrt A. Oral antihistamine-decongestant-analgesic combinations for the common cold. Cochrane Database of Systematic Reviews 2012, Issue 2. [DOI: 10.1002 14651858. CD004976. pub3].
5. Chang CC, Cheng AC, Chang AB. O ver-the-counter (OTC) medications to reduce cough as an adjunct to antibiotics for acute pneumonia in children and adults. Cochrane Database Syst Rev. 2014 Mar 10;3:CD006088. doi: 10.1002/14651858.CD006088.pub4.
6. Shaikh N, Wald ER, Pi M. Decongestants, antihistamines and nasal irrigation for acute sinusitis in children. Cochrane Database Syst Rev 2012;9:CD007909. doi: 10.1002/14651858. CD007909. pub3.
7. Bhattacharya M, Joshi N, Yadav S. To compare the effect of dextromethorphan, promethazine and placebo on nocturnal cough in children aged 1-12 y with upper respiratory infections: a randomized controlled trial. Indian J Pediatr 2013 Nov; 80(11):891-5. doi: 10.1007/s12098-013-1002-2. Epub 2013 Apr 17.
8. Clemens CJ, Taylor JA, Almquist JR, Quinn HC, Mehta A, Naylor GS. Is an antihistamine-decongestant combination effective in temporarily relieving symptoms of the common cold in preschool children? J Pediatr 1997; 130(3): 463-466.
9. Hutton N, Wilson MH, Mellits ED, Baumgartner R, Wissow LS, Bonuccelli C, et al. Effectiveness of an antihistamine-decongestant combination for young children with the common cold: a randomized, controlled clinical trial. J Pediatr 1991; 118(1): 125-130.
10. Björnsdóttir I, Einarson TR, Gudmundsson LS, Einarsdóttir RA. Efficacy of diphenhydramine against cough in humans: a review. Pharm World Sci 2007; 29(6): 577-583. Epub 2007 May 8. Review.
11. Eddy NB, Friebel H, Hahn KJ, Halbach H. Codeine and its alternates for pain and cough relief. Bull WHO 1969; 40: 425–454.
12. Taylor JA, Novack AH, Almquist JR, Rogers JE. Efficacy of cough suppressants in children. J Pediatr 1993 122: 799–802.
13. IAP Drug Formulary 2015. Eds Jeeson C Unni, Menon PSN, Nair MKC, Bansal CP. 2012, Publication of IAP. Pixel Studio, Cochin.
14. Yoder KE, Shaffer ML, La Tournous SJ, et al. Child assessmentof dextromethorphan, diphenhydramine, and placebofor nocturnal cough due to upper respiratory infection. Clin Pediatr (Phila) 2006; 45:633-40.
15. Paul IM, Yoder KE, Crowell KR, et al. Effect of dextromethorphan, diphenhydramine, and placebo on nocturnal cough and sleep quality for coughing children and their parents. Pediatrics 2004; 114:e85-90.
16. Paul IM, Beiler J, McMonagle A, et al. Effect of honey, dextromethorphan, and no treatment on nocturnal cough and sleep quality for coughing children and their parents.Arch Pediatr Adolesc Med 2007;161:1140-1146.
17. Friedrichsdorf SJ, Nugent AP, Strobl AQ. Codeine-associated pediatric deaths despite using recommended dosing guidelines: three case reports. J Opioid Manag 2013; (2): 151-155. doi: 10.5055/jom.2013.0156.
18. Isbister GK, Prior F, Kilham HA. Restricting cough and cold medicines in children. J Paediatr Child Health. 2012 Feb; 48(2):91-8. Epub 2010 Jun 27.
19. Bebarta VS, Blair HW, Morgan DL, Maddry J, Borys DJ. Validation of the American Association of Poison Control Centers out of hospital guideline for pediatric diphenhydramine ingestions. Clin Toxicol (Phila) 2010; 48(6): 559-562. doi:10.3109/15563650.2010.497149.
20. Chyka PA, Erdman AR, Manoguerra AS, Christianson G, Booze LL, Nelson LS, Woolf AD, Cobaugh DJ, Caravati EM, Scharman EJ,Troutman WG; American Association of Poison Control Centers. Dextromethorphan poisoning: An evidence-based consensus guideline for out-of-hospital management. Clin Toxicol (Phila). 2007; 45(6): 662-677.
21. Montgomery EJ, Wasserman GS. Toxicity and use of over-the-counter cough and cold medication in the pediatric population. Mo Med. 2008; 105(6): 514-517.
22. Wingert WE, Mundy LA, Collins GL, Chmara ES. Possible role of pseudoephedrine and other over-the-counter cold medications in the deaths of very young children. J Forensic Sci 2007; 52(2): 487-490.

NEWS AND NOTES

National Conference on Down Syndrome

Event Date: 22nd February, 2015

Event Venue: Calicut

Enquiries to

Dr. Shaji Thomas John

Email : doctorshaji@hotmail.com

DERMATOLOGY

COMMON DISORDERS OF ECCRINE GLANDS IN PEDIATRIC PRACTICE

*** Vijayabhaskar C**

Abstract: *In the day-to-day pediatric practice disorders of eccrine glands such as hyperhidrosis, bromhidrosis and miliaria are commonly seen. Hyperhidrosis of palms and soles in children and hyperhidrosis of axillae in adolescent age group are commonly encountered. Primary hyperhidrosis of palms and soles are commonly encountered where the child has difficulty in carrying out the day-to-day task in school and socialising which could be managed with topical aluminium salts and iontophoresis. Bromhidrosis is yet another condition where excessive bad odor is emanated from the skin which could be managed with proper clothing and bathing with antibacterial soaps. Anhidrosis may have a primary cause such as ectodermal dysplasia where the symptoms like hyperthermia must be managed by keeping the patient in cool environment with proper clothing. Miliaria is common in hot environment and has to be managed with proper ventilation, cotton clothes, calamine lotion and antihistamines.*

Keywords: *Eccrine glands, Hyperhidrosis, Anhidrosis, Bromhidrosis, Miliaria.*

Eccrine glands are situated all over the body except clitoris, glans penis, labia minora, external auditory canal and lips and are present abundantly over the palms, soles and over the axillae. There are 2 to 5 million eccrine glands distributed in the skin. These glands maintain the homeostatic balance by evaporation. They are controlled by the sympathetic nervous system. Sweating can be altered by thermal and emotional stimuli. There are conditions associated with increased, decreased or excessively bad-odored sweating. The common conditions dealt with in this article are primary hyperhidrosis, bromhidrosis, anhidrosis and miliaria.

* Associate Professor of Venereology, Chengalpattu Medical College, Chengalpattu.

Primary hyperhidrosis

Syn: Primary pediatric hyperhidrosis, Idiopathic hyperhidrosis

Primary hyperhidrosis is defined as excessive sweating in localized areas, especially palms, soles and/or axillae and is not associated with any systemic disorder. The exact etiology is not known. There is excessive sweating in response to emotional or heat stimuli. The sweating may vary from mild to severe. Children often find it difficult to write in the book or on papers as it gets wet due to hyperhidrosis. The situation is socially not acceptable as they cannot even shake hands with others and later in life it could interfere with the occupation. In more than 60% to 80% of patients family history is present and suggests a pattern of autosomal dominant with incomplete penetrance. The criteria for diagnosis of primary hyperhidrosis are given in Box 1.

Box 1. Criteria for the diagnosis of primary hyperhidrosis

1. Focal visible excessive sweating
2. Present for at least 6 months
3. No apparent secondary cause
4. At least 2 of the following symptoms:
   - Bilateral and symmetric
   - Impairs activities of daily life
   - At least 1 episode per week
   - Age of onset < 25
   - Positive family history
   - Stops during sleep

This hyperhidrosis may be volar (palmoplantar) and axillary and sometimes could be generalized. The onset of volar hyperhidrosis is from childhood and axillary hyperhidrosis starts at the time of puberty or thereafter. The volar hyperhidrosis involves the palms and soles and lateral aspect and tips and distal skin of fingers.

Axillary hyperhidrosis is common in the adolescent age group. The right side produces more sweat than the left and sometimes one side may be hyperhidrotic and another side may be anhidrotic or hypohidrotic.

Treatment

There are a number of treatment options available from topical application to surgical management. The commonly applied topical antiperspirants contain 20% aluminium chloride hexahydrate. They are applied daily for 3 to 5 nights continuously and later used on alternate days or when required. Systemic anticholinergic drugs could be used but they have limitations due to the side effects that occur. Oral glycopyrrloate or propanthelene bromide could be used but the severe systemic side effects like dry eyes, dry mouth and bowel and bladder disturbances limit their use.

Iontophoresis is considered one of the safe and effective mode of preventing hyperhidrosis. Tap water iontophoresis over 20 minutes two to three times a week is helpful. Iontophoresis is thought to block the sweat ducts in the stratum corneum. This procedure could be performed by dermatologist or pediatrician or the procedure could be taught to the parents if they want to own a unit.

Botulinum toxin A could be injected intradermally particularly for axillary hyperhidrosis and could be painful. This should be repeated once in 3 to 6 months.

Thoracic sympathetectomy could be done for very severe disease.

Bromhidrosis

Bromhidrosis is defined as excessive and offensive bad odour emanating from the skin. It could be of two types namely apocrine and eccrine bromhidrosis.

Apocrine bromhidrosis results due to bacterial degradation of the apocrine sweat mostly noted in all post pubertal individuals.

Eccrine bromhidrosis is excessive odour resulting from bacterial action on stratum corneum when it gets macerated due to excessive sweat. The common site of involvement is seen over the plantar aspect of feet and over the intertriginous area.

The different types of bromhidrosis are listed in Box 2.

Box 2. Types of bromhidrosis

- Apocrine
  - Axillary
- Eccrine
  - Keratinogenic
    - Plantar
    - Intertriginous
  - Metabolic
    - Phenylketonuria (musty or mousy odour)
    - Maple syrup urine disease (sweet odour)
    - Methionine adenosyltransferase deficiency (boiled cabbage odor)
    - Methionine malabsorption syndrome (oasthouse syndrome)
    - Trimethylaminuria (fishy odor)
    - Dimethylglycine dehydrogenase deficiency (fishy odor)
    - Isovaleric acidemia (sweaty feet odor)
  - Exogenous
    - Foods, e.g. garlic, asparagus, curry
    - Drugs, e.g. penicillins, bromides
    - Chemicals, e.g. dimethyl sulfoxide (DMSO)

Treatment

Eccrine bromhidrosis: Cleansing with an antibacterial soap which contains triclosan may help. Frequent changing of clothes and use of cotton clothes will improve the condition.

Apocrine bromhidrosis: Topical antibiotics in the form of clindamycin can be used. Deodorants and antiperspirants are used.

Metabolic and exogenous causes could be appropriately managed by addressing the primary cause.

Anhidrosis

It is defined as absence of sweat from the surface of skin after appropriate stimuli. It occurs due to deficiency or abnormality of the eccrine glands as in hypohidrotic ectodermal dysplasia. There could be abnormality of the nervous pathways from the peripheral or central nervous system to the eccrine glands. The main symptom in anhidrosis is hyperthermia. Apart from dealing with the appropriate pathological condition the patients symptom could be managed by giving cool baths, air conditioning and light clothing.

Miliaria

It is a common condition caused by sweat retention characterised by papulovesicular eruption secondary to obstruction of the eccrine glands. Three types of miliaria are described depending on the obstruction of the sweat ducts at different locations. The three types are described in Table I.

Table I. Three types of miliaria

Type	Location of obstruction	Cutaneous lesions	Patient population(s)	Most common locations
Crystallina	Stratum corneum	Non-pruritic, clear, fragile, 1mm vesicle	Neonates < 2 weeks of age. Children and adults in hot climates	Face and trunk
Rubra	Epidermis	Pruritic, erythematous, 1 – 3 mm papules; may have pustules	Neonates 1 – 3 weeks of age. Children and adults in hot climates	Neck and upper trunk
Profunda	Dermo-epidermal junction	Non-pruritic, white, 1-3 mm papules	Adults in hot climates; often with multiple bouts of miliaria rubra	Trunk and proximal extremities

Miliaria is common in children. Excessive sweating particularly in a humid environment can lead to maceration of the stratum corneum and to blockage of the eccrine duct.

Miliaria crystalline: It presents as small and clear vesicles which rupture easily and commonly seen over the face and upper trunk of infants. Congenital miliaria crystallin has been described. There are no symptoms and systemic risks.

Miliaria rubra: This is one of the common forms seen in hot environments in children. The lesions appear as erythematous macules and papules with punctuate vesicles common over neck and upper trunk but can be seen all over the body including the face. Burning sensation and itching sensation is associated with the lesions. The lesions appear within days to weeks after exposure to hot environment. Miliaria pustulosa is a variant of the miliaria rubra with pustules which are sterile but may get secondarily infected.

Miliaria profunda: Chronic or recurrent miliaria rubra the occlusion occurs in the deeper part of the eccrine duct leading to appearance of white papules of 1 to 3 mm in diameter. The lesions appear on initiation of sweating and disappears after 2 to 3 hours of cessation of sweating.

Treatment

Miliaria crystalline: Reassurance and no treatment is required.

Miliaria rubra: Patient should be kept in a cool environment with loose cotton clothing. In the long run the keratinous plugs that are formed are shed and normal sweating occurs. Topical calamine lotions are advocated three to four times daily. Occlusive ointments and moisturisers are to be avoided which may further occlude the sweat ducts. Short course of antihistamines may be given for itching. When miliaria pustulosa with secondary infection occurs a course of penicillin group antibiotics or macrolides can be given.

Note - For Miliaria - either table or text can be taken – both seem like a lot of info for such a benigh condition.

Points to remember

- ***Hyperhidrosis, bromhidrosis and miliaria are commonly encountered problems in pediatric practice.***
- ***Majority of the hyperhidrosis is primary without any cause and palmoplantar hyperhidrosis is frequently encountered which poses a major problem for school going children and can be symptomatically managed with topical aluminium salts or iontophoresis.***
- ***Bromhidrosis can make a child psychologically depressed. It is treated with proper clothing, frequent bathing and with soaps with antibacterial property.***
- ***Miliaria is commonly encountered from neonates to adolescent age groups in hot and humid environments. It is treated with topical calamine lotions, proper ventilation, proper clothing and antihistamines.***

Bibliography

1. Paller AS, Mancini AJ, Hurwitz Clinical Pediatric Dermatology, 4th edn. Saunders; Philadelphia: 2011.
2. Schachner LA, Hansen RC, Pediatric Dermatology, 3rd edn. Mosby; London: 2003.
3. Burns, Tony, Stephen Breathnach, Neil Cox, Christopher Griffiths (eds). Rook's Textbook of Dermatology.edition. Blackwell Publishing, 2010.
4. Bolognia JL, Jorizzo JJ, Schaffer JV. Dermatology: 3rd edn. Saunders; 2012.
5. Cafardi JA. The Manual of Dermatology: 1st edn. Springer; New Delhi: 2013.

SURGERY

PITFALLS IN THE DIAGNOSIS AND MANAGEMENT OF ACUTE APPENDICITIS

*Madhavan TRK
**Senthilnathan SV
*** Soundappan S
****Hariharan G

Abstract: *Appendicitis is the most common pediatric abdominal surgical emergency worldwide. The diagnosis of acute appendicitis is predominantly based on clinical findings. Whilst a clinical diagnosis can often be made, there are groups of patients in whom the clinical diagnosis is difficult and who provide a degree of diagnostic uncertainty. High index of suspicion and early diagnosis in infants and children is essential to prevent complications like appendiceal perforation, abscess formation, peritonitis, sepsis, bowel obstruction and death. Appendectomy is the treatment of choice and is increasingly done as a laparoscopic procedure.*

Keywords: *Diagnosis, Scoring systems, Management, Children.*

Acute appendicitis is the most common cause of acute abdomen requiring surgical intervention during childhood, accounting for 1% to 8% of children who present to the pediatric emergency room with acute abdominal pain.[1] Appendicitis in the pediatric age group varies considerably in its clinical presentation, contributing to delay in diagnosis and increased morbidity. The methods of diagnosis and treatment of appendicitis also vary significantly among clinicians and medical centers according to the patient's clinical status, the medical center's capabilities and the physician's experience and technical expertise. Recent trends include the increased use of radiologic imaging, minimally invasive and non operative treatments, shorter hospital stays and home antibiotic therapy. Little consensus exists regarding many aspects of the care of the child with complicated appendicitis.

* Professor
** Professor & HOD,
Pediatric Surgery,
Institute of Child Health and Hospital for Children, Chennai
*** Consultant Pediatric Surgeon and
Senior Lecturer in Pediatric Surgery,
The Sydney Children's Hospital,
Network and University of Sydney.
**** Professor
Pediatric Surgery & Deputy Director of Medical Education.

The clinical diagnosis of acute appendicitis is often not straightforward, as approximately a third of children with the condition have atypical clinical findings. There is no single historical or physical finding or laboratory test that can definitely lead to the diagnosis. Despite considerable recent expansion of knowledge concerning appendicitis, accurate diagnosis remains suboptimal, especially in children. Initial misdiagnosis rates range from 28% to 57% for children 2 to 12 years old, to nearly 100% for those ≤2 years despite the multiple diagnostic modalities now available.[2,3]

Clinical presentation

The child may initially have mild gastrointestinal symptoms before the onset of pain (e.g., decreased appetite, subtle changes in bowel habits). Anorexia is a helpful sign, particularly in children, because a child with hunger rarely has appendicitis. Any severe gastrointestinal symptom before the onset of pain, however, should suggest an alternative diagnosis. Distention of the appendix results in activation of its visceral pain fibers. Typical early visceral pain is non-specific in the periumbilical region, poorly localized as a deep, dull pain in the T-10 dermatome. The continued distention of the appendiceal wall elicits nausea and vomiting, which typically follow the onset of pain within a few hours. Nausea is common, but vomiting is typically not severe.

Because of a lack of reliable history, rates of perforation as high as 80% to 100% have been reported in children less than 3 years of age . Children aged 10 to 17 years have a lower rate of perforation at 20 %.[4] Signs of perforated appendicitis include a temperature higher than 38.6°C, leukocyte count greater than 14,000 and the presence of more generalized peritoneal signs.

There should be a very high clinical suspicion for appendicitis in children, particularly in infants. Serial abdominal examinations, possible admission for observation and laboratory testing are a must when in doubt. In addition, the symptom of 'diarrhea' is often overstated by parents

and always needs to be clarified by the clinician. Diarrhea is typically of short duration and often results from irritation of the terminal ileum or cecum; however, it may also indicate a pelvic abscess.

Terminology

Simple appendicitis: Inflammed appendix, in the absence of gangrene, perforation or abscess around the appendix.

Complicated appendicitis: Perforated or gangrenous appendicitis or the presence of peri appendicular abscess.

Negative appendicectomy: Term used for surgery done for suspected appendicitis, in which the appendix is found to be normal on histological evaluation.

Embryology and anatomy

During embryogenesis, the appendix first becomes visible during the eighth week of gestation as a continuation of the inferior tip of the cecum. The appendix rotates to its final position on the posteromedial aspect of the cecum, about 2 cms below the ileocecal valve, during late childhood. The variability in this rotation leads to multiple possible final positions of the appendix. The appendix is intraperitoneal in 95% of cases, but the exact location varies widely. In 30% of cases the tip of the appendix is in the pelvis, behind the cecum in 65% and it is truly extra peritoneal in 5% in the retrocolic or retrocecal position.[2] In cases of malrotation or situs inversus, the malpositioned appendix may give rise to signs of inflammation in unusual locations.

Diagnosis

Physical examination

Clinically, the most relevant distinction is between simple and complicated appendicitis. Children with appendicitis usually lie in bed with minimal movement. Older children may limp or flex the trunk and walk, whereas infants may flex the right leg over the abdomen. With the knees bent to relax the abdominal muscles, gentle palpation of the abdomen should begin at a point away from the location of perceived pain. Palpating the abdomen in an area remote from the site of pain may elicit tenderness in the right lower quadrant (Rovsing sign of referred pain), indicating peritoneal irritation. Although patients often have diminished or absent bowel sounds, this is not uniform and auscultation of the abdomen is of little benefit. However, auscultation of the chest to examine for lower respiratory infection is useful because right lower lobe pneumonia can mimic appendicitis. Cutaneous hyperesthesia, a sensation derived from the T10 to L1 nerve roots, is often an early although inconsistent sign of appendicitis. Localized tenderness is essential for diagnosis and is noted either on palpation or percussion. Tenderness can be mild and even masked by more generalized abdominal pain, especially during initial stages.

The Mc Burney point is the most common location of tenderness. Retrocecal appendicitis may be detected by tenderness midway between the twelfth rib and the posterior superior iliac spine. Pelvic appendicitis produces rectal tenderness. A child with malrotation will have localized tenderness that corresponds to the position of the exudative drainage from the inflammed appendix.

The appendix can take a variety of anatomical positions and as a result the clinical presentation is influenced by the surrounding structures that are involved in the inflammatory process.

Anatomical position of the appendix and possible changes in clinical presentation (Fig.1)

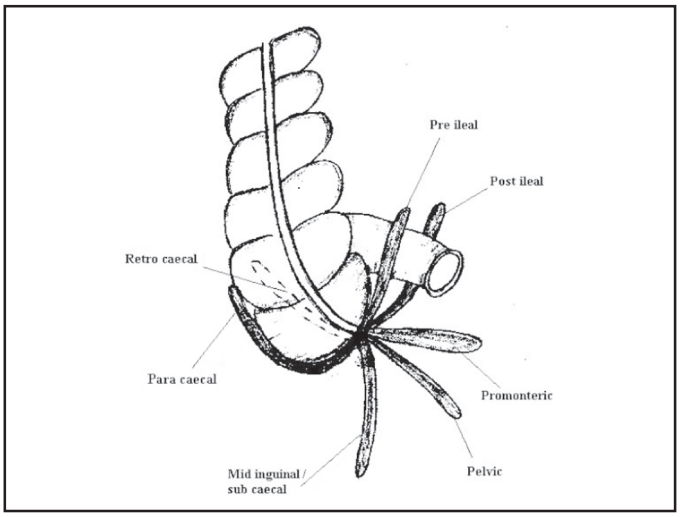


Fig.1. Anatomical positions of the appendix

Retrocecal/Retrocolic

Right loin pain is often present with tenderness on examination. Muscular rigidity and tenderness to deep palpation are often absent due to protection from the overlying cecum. The psoas muscle may be irritated in this position leading to hip flexion and exacerbation of the pain on hip extension (psoas stretch sign).

Subcecal and pelvic appendix

Suprapubic pain and urinary frequency may predominate. Diarrhea may be present due to irritation of the rectum. Abdominal tenderness may be lacking but rectal or vaginal tenderness may be present on the right. Microscopic haematuria and leucocytes may be present on urinalysis.

Pre - and post-ileal

Signs and symptoms may be lacking. Vomiting may be more prominent and diarrhoea due to irritation of the distal ileum may be present.

As the disease progresses to perforation, peritonitis ensues. The pattern of pain depends on the location of the appendix. Perforation may result in temporary relief of symptoms as the pain of the distended viscus is relieved. Initially, peritonitis is reflected as local muscular rigidity. This progresses from simple involuntary guarding to generalized rigidity of the abdomen.

Rectal exam while not useful as a routine, may be a helpful diagnostic maneuver in questionable cases such as when a pelvic appendix or abscess is suspected or when uterine or adnexal pathologic conditions are being considered in older girls.

Laboratory studies: The sensitivity of an elevated leukocyte count ranges from 52% to 96% and that of a left-shift of neutrophil count ranges from 39% to 96%. The latter is of better diagnostic value, but misinterpretation of the values is still common. Normal leukocyte count occurs in 5% of patients with appendicitis. Greater specificity and sensitivity have been reported using a neutrophil-lymphocyte ratio greater than 3.5.[2]

The role of various imaging modalities in the diagnosis of acute appendicitis is described in Table I and ultrasound image of appendicitis is shown in Fig. 2.

Scoring Systems

Several scoring systems exist for the diagnosis of appendicitis : however, 2 systems have been evaluated in pediatric patients. The first is the Alvarado score, which

Table.I Imaging studies in diagnosis of acute appendicitis[2,5]

Investigation	Diagnostic criteria	Evidence	Remarks
Plain radiography	None	No role in diagnosis; in some cases a fecolith may be shown	Abnormal gas pattern in right lower quadrant, lumbar scoliosis away from the right lower quadrant, obliteration of the psoas shadow or fat stripe on the right are helpful. CXR to rule out pneumonia may be indicated
Barium enema contrast radiograph	May show absent or incomplete filling of the appendix, irregularities of the appendiceal lumen, and an extrinsic mass effect on the cecum or terminal ileum.	Sensitivity and specificity of this technique are low	Best used in the diagnosis of non-specific abdominal pain.
USG abdomen	Aperistaltic and non-compressible structure with diameter >6 mm; presence of an appendicolith is helpful	Sensitivity of 86%; specificity of 81%	Techniques like graded compression, self-localization and transvaginal or transrectal ultrasound approaches have improved results
CT abdomen	Enlarged appendix (>6mm), appendiceal wall thickening (>1mm), periappendiceal fat stranding and appendiceal wall enhancement or calcified appendicolith	Sensitivity of 94% and specificity of 95%	No good evidence for routine use .
MRI	Not confirmed	Restricted to cases in which radiation and diagnostic difficulties preclude use of other modalities (eg: pregnancy)	

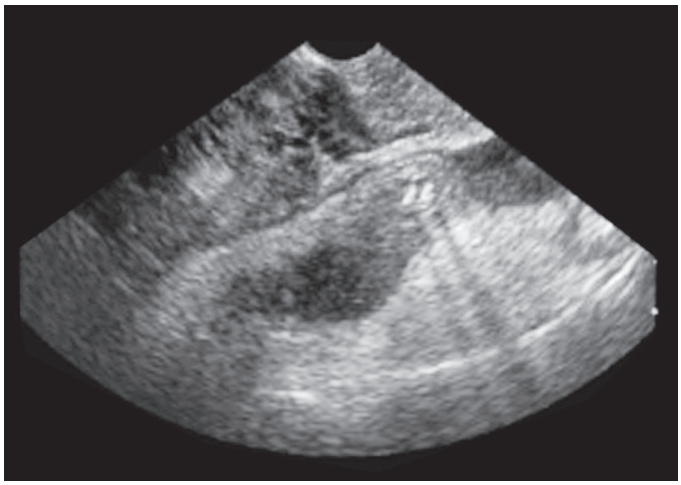


Fig.2. Ultrasound image of appendicitis in an 8-year-old girl.

Note the dilated noncompressible appendix and the presence of a fecolith with posterior acoustic shadowing.

Table.II Alvarado/MANTRELS score[6]

Variables	Score
Migration of pain to the right lower quadrant	1
Anorexia	1
Nausea/Vomiting	1
Tenderness in the right lower quadrant	2
Rebound pain	1
Elevation of temperature (≥ 37.3°C)	1
Leukocytosis (WBC > 10,000/µL)	2
Shift of WBC count to the left (>75% neutrophils)	1
Maximum score	**10**

was initially developed for use in the adult population. The Alvarado score is composed of 8 components with a total score of 10 (Table II). Alvarado scores of 1 to 4 are negative for appendicitis,whereas scores from 9 to 10 are diagnostic of appendicitis. In cases of intermediate scores 5 to 8, further diagnostic studies are required. Using these specifications, a 93% sensitivity, 100% specificity, 100% positive predictive value and 96% negative predictive value are obtained.[1]

The pediatric appendicitis score (PAS) is composed with a total score of 10 (Table III). A score of 1 to 3 is

Table.III Pediatric appendicitis score[6] (Samuel score)

Variables	Score
Migration of pain to the right lower quadrant	1
Anorexia	1
Nausea/vomiting	1
Tenderness in the right lower quadrant	2
Elevation in temperature	1
Leuckocytosis (WBC/10000/µL)	1
Shift of WBC count to the left (not defined)	1
Maximum score	**10**

considered negative for appendicitis, whereas scores from 8 to 10 are considered positive. The intermediate scores of 4 to 7 require further diagnostic testing. With these thresholds, the sensitivity for appendicitis is 97 % with a specificity of 97.6% , a positive predictive value of 97.2%, and a negative predictive value of 97.6%. Although both of these systems have been shown to be useful in the diagnosis of appendicitis, they do not replace an experienced clinician.[1]

Differential diagnosis

The differential diagnosis is varied, but is divided into 5 general categories: inflammatory, infectious, vascular, congenital and genitourinary conditions. Inflammatory mimickers of appendicitis include mesenteric adenitis (primary or secondary), inflammatory bowel disease, intussusception, omental infarction or epiploic appendagitis. Infectious causes include viral infections, bacterial infections and parasitic infections. Among vascular causes, Henoch – Schonlein purpura can initially present as severe abdominal pain before the characteristic purpuric rash appears. Congenital causes include Meckel diverticulitis and duplication cysts. Genitourinary causes include pyelonephritis, nephrolithiasis, ovarian torsion, ovarian tumors, hemorrhagic ovarian cysts, pelvic inflammatory disease and infected urachal remnants. Constipation should not be forgotten when evaluating pediatric patients because it is often a culprit in abdominal pain.

Despite advances in diagnostic imaging, surgery for appendicitis does not always reveal an inflamed appendix. Formerly accepted rates of laparotomy that did not reveal appendicitis range from 15% to 40%.[2] Recent literature report negative appendectomy rates to be less than 10%.[2]

The diagnostic accuracy for appendicitis is lowest among young women because of the variety of gynecologic conditions that can cause lower abdominal pain. Ectopic pregnancy should be considered in all teenage girls with these symptoms. They may present with vaginal bleeding, amenorrhea, dizziness, nausea and vomiting. Rupture of ovarian cysts and ovarian torsion may also present with lower abdominal pain.

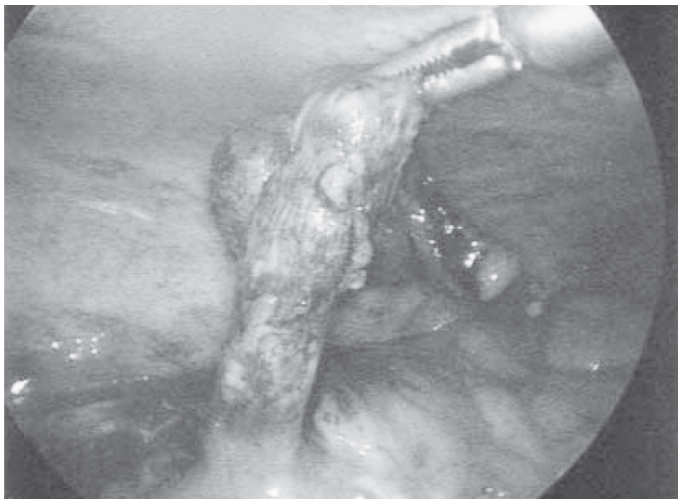


Fig.3. Laparoscopic appendectomy

Management

Antibiotics

The use of antibiotics for the treatment of appendicitis is clearly beneficial. Intra-operative cultures have not been shown to alter the treatment outcome. The best regimen and duration of use of antibiotics is a subject of continued controversy. There is a trend toward decreasing the duration of antibiotic therapy. Only perioperative antibiotics are required for simple appendicitis. The recommended duration is from a single, preoperative dose to 24 hours of post-operative antibiotic therapy for simple appendicitis.[2,7]

For complicated appendicitis, recent studies have suggested that as little as 48 hours of coverage is adequate. Others suggest that treatment be continued as clinically indicated using the leukocyte count and presence of fever as guides. There is also a trend to use oral antibiotics instead of intravenous antibiotics when gastrointestinal function returns.[2,7]

Appendectomy

The most widely accepted treatment of appendicitis is appendectomy. If a normal appendix is found, the peritoneal cavity should be inspected for inflammatory bowel disease, mesenteric adenitis, Meckel diverticulitis, or in females, pathologic conditions of the ovary.

When dealing with either simple or perforated appendicitis, the laparoscopic approach has been found to be safe and efficacious. Advantages of laparoscopic appendectomy include shorter hospitalizations, decreased (Fig. 3) post-operative pain, decreased wound complications, increased ability to diagnose uncertain cases, surgical ease in an obese patient and faster postoperative recovery. Laparoscopic appendectomy is a safe and effective means of performing an appendectomy and its utilization has increased dramatically over the past decade.

Management of patients with a palpable abdominal mass is another controversial topic. It occurs in a small but significant fraction of patients with complicated appendicitis, especially in young children after perforation. Some advocate immediate appendectomy, whereas others perform the procedure only if a mass is confirmed with the patient under anesthesia. Some recommend treatment with intravenous antibiotics until the leukocyte count is normal and the patient remains afebrile for 24 hours. If the patient's condition worsens or the mass enlarges on serial ultrasonography, the mass is drained percutaneously, followed by interval appendectomy. Interval appendectomy prevents repeated episodes of appendicitis and affords the surgeon the opportunity to evaluate the patient for other conditions that can masquerade as an appendiceal mass.

Complications

The incidence of complications increases with the degree of severity of the appendicitis. The complications include wound infection, intra-abdominal abscess formation, postoperative intestinal obstruction, prolonged ileus, and rarely enterocutaneous fistula.

Conclusions

Diagnosing appendicitis in children can pose considerable challenges even to the experienced clinician. A delayed or missed diagnosis can have complications resulting in morbidity and medicolegal claims. The clinician should be aware of atypical presentations especially in infants and small children. Neither single test nor a combination of tests can distinguish all cases of acute appendicitis from other conditions. An awareness of the limitations of imaging, blood tests and scoring systems is essential. A thorough history, repeated clinical examinations in conjunction with appropriate investigations are essential to diagnose acute appendicitis in infants and children.

Points to Remember

- ***The classic signs and symptoms of appendicitis occur in less than half of pediatric patients.***

The most sensitive symptoms include migrating pain to the right lower quadrant and fever. Rebound tenderness on examination also increases the likelihood of appendicitis.

- ***Increased WBC count and left shift are the most accurate laboratory values when assessing for appendicitis.***
- ***In the majority of children with suspected appendicitis, a combination of clinical history, physical findings and laboratory studies should provide sufficient data for making the diagnosis.***
- ***In infants and young children, difficulty in communication and anatomical factors (short omentum and mobile intra-peritoneal caecum) make progression of the disease more rapid. Generalized peritonitis will occur with delay in diagnosis or treatment.***
- ***When the diagnosis is unclear, serial abdominal examinations permit the surgeon to decrease the number of unnecessary laparotomies without increased risk to the patient.***
- ***Ultrasonography is more specific and CT abdomen is more sensitive in the diagnosis of acute appendicitis.***

References

1. Gardikis S1, Giatromanolaki A, Kambouri K, Tripsianis G, Sivridis E, Vaos G. Acute appendicitis in preschoolers: a study of two different populations of children. Italian J Pediatr 2011;37:35.
2. James C.Y. Dunn. Appendicitis. In:Arnold Coran A, Adzick NS. Krummel T, Laberge JM, Shamberger R, Caldamone A (eds.) Coran: Pediatric Surgery, 7th edn 2012;pp-.
3. Rothrock SG, Pagane J. Acute appendicitis in children: emergency department diagnosis and management. Ann Emerg Med. 2000; 36:39-51.
4. Victoria K. Pepper, Amy B. Stanfill, Richard H. Pearl, Diagnosis and Management of Pediatric Appendicitis, Surg Clin N Am 2012; 92:505-526.
5. Carlos J. Sivit, Marilyn J. Siegel, Kimberly E. Applegate, Kurt D. Newman, When Appendicitis Is Suspected in Children RadioGraphics 2001; 21:247–262.
6. Humes DJ, Simpson J. Clinical Presentation of Acute Appendicitis: Clinical Signs-Laboratory Findings-Clinical Scores, Alvarado Score and Derivate Scores In: C. Keyzer and P. A. Gevenois (eds.), Imaging of Acute Appendicitis in Adults and Children, Medical Radiology. Diagnostic Imaging, DOI: 10.1007/174_2011_211, _ Springer-Verlag Berlin Heidelberg 2011
7. Steven L. Lee, Saleem Islam, Laura D. Cassidy, Fizan Abdullah, Marjorie J. Arca. Antibiotics and appendicitis in the pediatric population: an American Pediatric Surgical Association Outcomes and Clinical Trials Committee Systematic Review. J Pediatr Surg 2010; 45:2181-2185.

CLIPPINGS

Dexamethasone for acute asthma exacerbations in children: A meta-analysis.

This systematic review and meta–analysis aimed to determine whether intramuscular or oral dexamethasone is equivalent or superior to a 5–day course of oral prednisone or prednisolone. The primary outcome of interest was return visits or hospital readmissions. Six randomized controlled trials in the emergency department of children less than 18 years of age comparing dexamethasone with prednisone/prednisolone for the treatment of acute asthma exacerbations were included.

There was no difference in relative risk (RR) of relapse between the 2 groups at any time point (5 days RR 0.90, 95% confidence interval [CI] 0.46-1.78, Q = 1.86, df = 3, I2 = 0.0%, 10-14 days RR 1.14, 95% CI 0.77-1.67, Q = 0.84, df = 2, I2 = 0.0%, or 30 days RR 1.20, 95% CI 0.03-56.93). Patients who received dexamethasone were less likely to experience vomiting in either the emergency department (RR 0.29, 95% CI 0.12-0.69, Q = 3.78, df = 3, I2 = 20.7%) or at home (RR 0.32, 95% CI 0.14-0.74, Q = 2.09, df = 2, I2 = 4.2%).

Practitioners should consider single or 2–dose regimens of dexamethasone as a viable alternative to a 5–day course of prednisone/prednisolone.

Keeney GE, Gray MP, Morrison AK, Levas MN, Kessler EA, Hill GD, Gorelick MH, Jackson JL.. Dexamethasone for acute asthma exacerbations in children: A meta-analysis. Pediatrics 2014; 133(3): 493-499.

RADIOLOGY

MUCOPOLYSACCHARIDOSES

**** Vijayalakshmi G***
***** Natarajan B***
***** Jeya Rajiah***
***** Kasivisalakshi KP***

Many years have passed since the first 'Radiologist talks to you' column was started in 1999 and Professor Elizabeth John began with plain X-ray evaluation. I took over and since 2002 we have been through an almost complete round of radiological evaluation of various conditions using various modalities. There have been many new pediatricians and new subscribers joining the expanding readership of IJPP. So, we have decided to do a few topics under plain radiography. As you would all agree, no new modality has totally replaced the humble plain X-ray.

In this issue, we will see how to evaluate mucopolysaccharidoses with a set of X-rays. Mucopolysaccharidoses (MPS) is a group of inherited disorders of metabolism characterised by lysosomal enzyme deficiencies. Their genetic bases are now well defined. MPS manifest clinically in late infancy or early childhood. They escape routine antenatal detection. However, chorionic villus biopsy or amniotic fluid sampling can be done for the specific enzyme deficiency in mothers with previously affected children.

Dysplasias are disorders of bone and cartilage formation. Therefore the entire skeleton is likely to throw up a long list of abnormalities that can be confusing. A lot of them are common to a number of conditions, so it would be very useful if we follow a standard routine and search for a few clinching features. In the Institute of Child Health & Hospital for Children, Chennai we follow and teach the system that was formulated by Professor Elizabeth John. When there is a suspicion of dysplasia we take a set of X-rays consisting only of the pelvis, dorso-lumbar spine AP and lateral, both hands AP and sometimes the skull. We start with a study of the X-ray pelvis which will definitely show a positive finding in all dysplasias. This will guide towards a diagnosis or will at least narrow down the diagnosis. Then one can study the dorso-lumbar spine followed by the hands. With this one would be able to come to a conclusion and also be able to direct biochemical and gene testing.

The pelvis has a classic shape in all MPS - a signature finding not seen in other dysplasias. The ilium is narrow in its lower part tapering inferiorly. This is a finding in all the types of MPS (Fig.1). Specific findings exist for the Hurlers syndrome (MPS 1H) and Morquio's disease (MPS Type 4A and 4B). Platyspondyly or flattening of vertebrae is a feature of these MPS. In Morquio's disease all or most of the vertebrae are flat with anterior beaking that protrudes from the middle of the anterior surface of the body of the vertebra (Fig.2). In Hurler's only some of the vertebrae

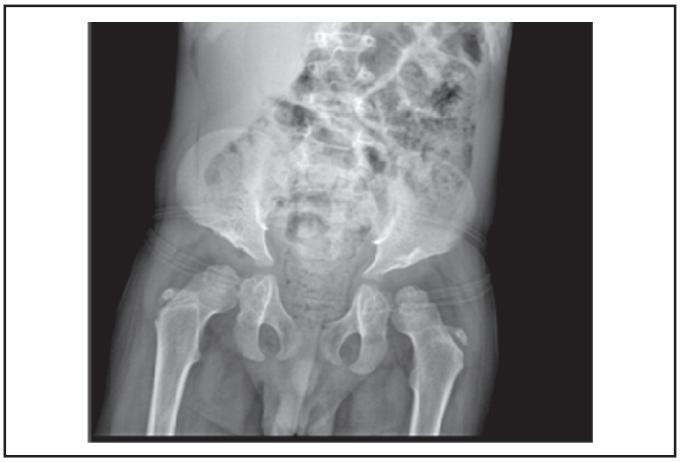


Fig.1. MPS pelvis

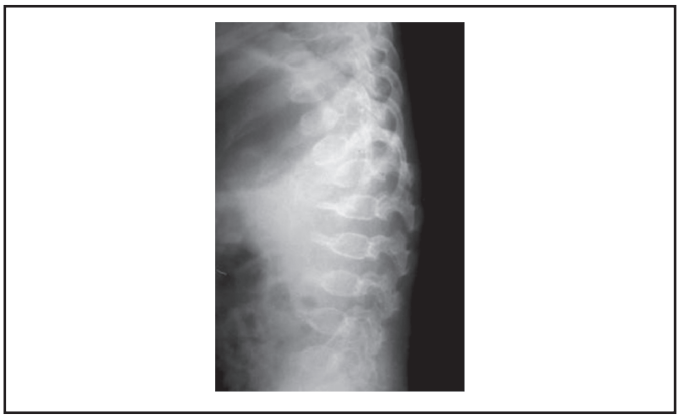


Fig.2. Spine in Morquio's disease

* Professor
* Asstistant Professors,
Department of Radiology,
Institute of Child Health & Hospital for Children, Chennai.

are flattened mostly in the dorso-lumbar region and the beaking is inferior (Fig. 3). In the X-ray of the hands the metacarpals are short and show proximal hypoplasia or tapering. It is necessary to recall that normal metacarpals like other long bones are wide at both ends while the

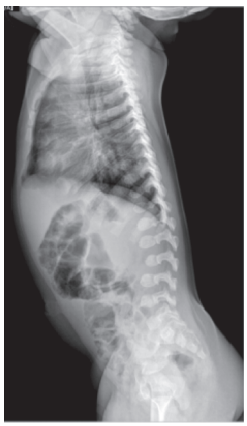


Fig.3. Spine in Hurler's syndrome

diaphyses are narrow or constricted. This middle constriction is maintained in Morquio's disease (Fig. 4) and lost in Hurler's (Fig. 5). Metacarpals in Hurler's are described as 'bullet'shaped.

With the help of the above mentioned features you can diagnose the MPS group and specifically differentiate

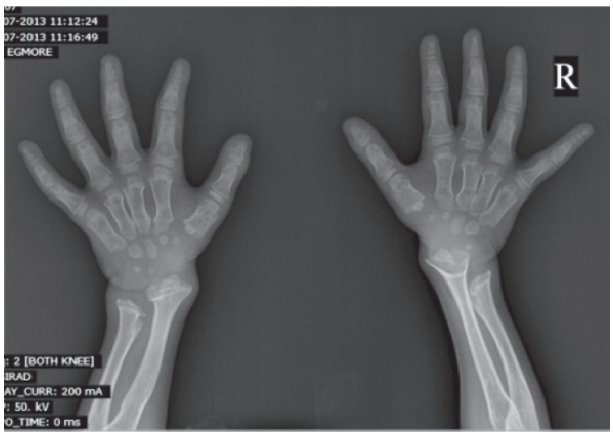


Fig.4. Morquios disease - Middle constriction maintained in metacarpals

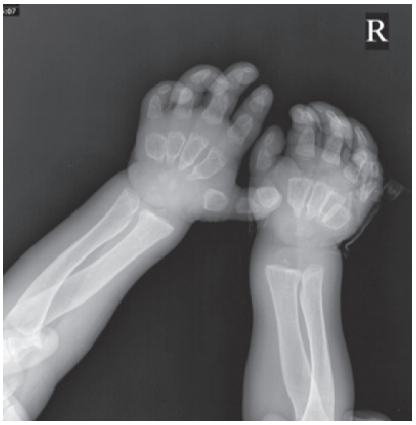


Fig 5. Hurler's syndrome - Bullet shaped metacarpals

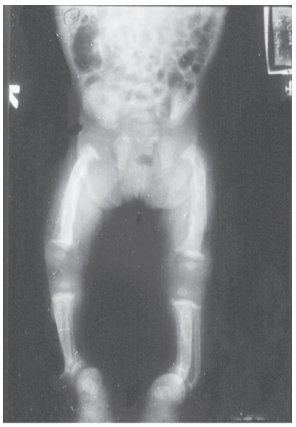


Fig 6. Mucolipidosis Type 2

between Morquio's and Hurlers. Other radiological findings that have been described are J- shaped sella and paddle shaped ribs in Hurler's (thick anteriorly and thin posteriorly), slanting irregular acetabular roof and sloping articular surfaces of the distal radius and ulna that face each other. There is a delay in skeletal maturation as well.

'Mucolipidosis Type 2' or 'I-cell disease' is also an enzyme deficiency and is grouped under the dysostosis multiplex group along with MPS. It has a characteristic periosteal cloaking that makes the diaphyses appear widened. Vertebrae show inferior beaking and metacarpals show proximal tapering (Fig. 6). Those with the disease die in infancy.

CASE STUDY

TRANSTHORACIC DRAINAGE OF LIVER ABSCESS IN CHILDREN

*Anirudhan A
*Poornima P
** Jaidurairaj M
*** Mohan P

Abstract: *In developing countries, pyogenic liver abscess in children is a common problem. Though conservative management is the corner stone of treatment, there are many indications for surgical drainage. Right posterosuperior segment (VII) liver abscess is one such location where non- operative drainage is seldom useful. There are reports of transthoracic drainage of such abscesses in the literature for adults. However there are no such reports in pediatric literature. We report transthoracic drainage of posterosuperior segment liver abscess in two children with precise anatomic localization, good exposure, adequate drainage and dramatic recovery in both the cases.*

Keywords: *Pyogenic liver abscess, Segment VII, Children, Transthoracic drainage.*

Pyogenic liver abscess (PLA) in children in contrast to that in adults has a unique set of predisposers, clinical profile and outcome. Its incidence has decreased considerably in the antibiotic era. The initial treatment is always broad spectrum antibiotics, followed by diagnostic or therapeutic USG-guided aspiration or percutaneous catheter drainage. However, surgical intervention is sought for inaccessible sites, impending/actual rupture or ineffective medical therapy. We report our experience with transthoracic drainage of right posterosuperior liver abscess with persistent segment VII abscess.

Case 1

A six-year-old girl child was admitted with complaints of fever, right upper quadrant abdomen pain of one week duration. She was sick looking and febrile with intercostal tenderness and tender hepatomegaly. CBC revealed leukocytosis and anaemia.

USG abdomen showed multiple liver abscesses. Three of them were near the segment VII and one in the left lobe of liver (segment IV). Under IV sedation and antibiotic cover, aspiration was done and 100ml of thick pus was drained out. Pus culture growth showed Staphylococcus aureus. The child continued to be febrile despite antibiotics and repeat aspirations and hence a CECT abdomen was done. It revealed persistent abscess in the segment VII and a segment IVB abscess with a subcapsular collection (Fig.1). It was then decided to surgically drain the abscess. We felt the best exposure could be through a transdiaphragmatic route.

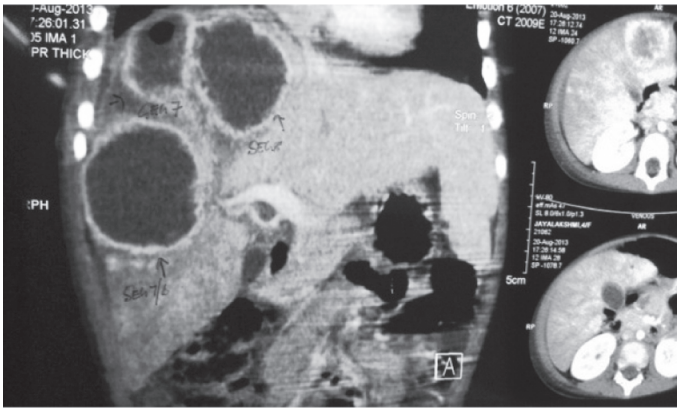


Fig.1.Coronal reconstruction image showing multiple abscesses in the segment VII.

Under GA, patient in the left lateral position, through the right 7th intercostal space, chest and diaphragm were opened and needle aspiration (Fig.2) was done to locate the abscess. The abscess cavity was opened wide and 200ml of thick pus was drained out. Segment IV abscess cavity palpated under anaesthesia and percutaneously drained. Thoracotomy wound closed with an ICD tube tip lying in the abscess cavity. Subsequently, though the child improved, she continued to have low grade fever. A repeat USG couple of days later showed that two of the abscess cavities remained undrained. Thoracotomy wound was re-explored and the persistent abscess cavities were drained. No significant bleeding was encountered. The child

* Senior Resident
** Assistant Professor
*** Professor
Department of Pediatric Surgery,
Institute of Child Health and Hospital for Children,
Chennai.

dramatically improved and had an uneventful recovery which was confirmed by post-op USG (Fig.3).

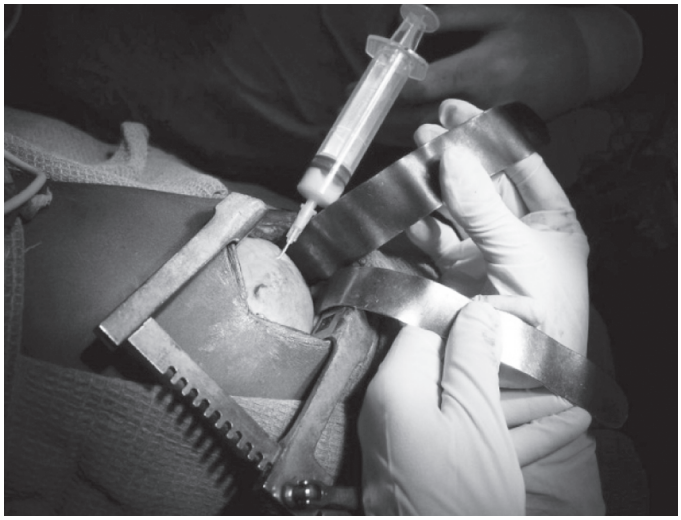


Fig.2. Abscess being aspirated through diaphragm after thoracotomy

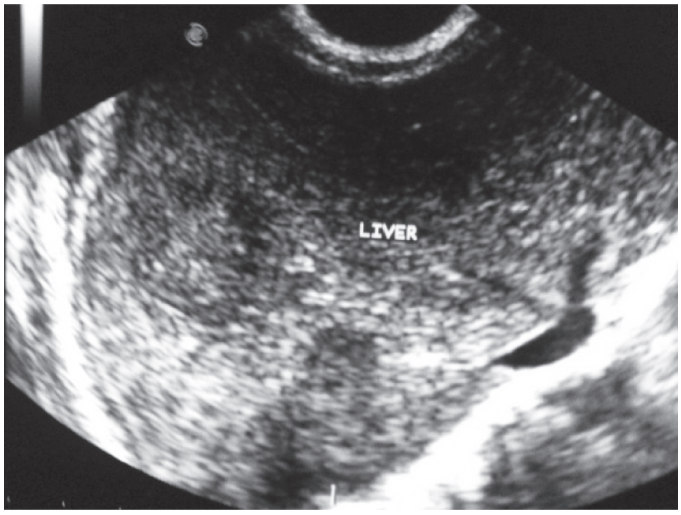


Fig.3. Post-OP USG shows reduction of abscess and regeneration of liver parenchyma.

Case 2

4years old male child was diagnosed as a case of solitary liver abscess in the right posterosuperior segment of liver (Fig.4). Failing conservative measures, child was explored through the right 7th ICS, thoracotomy was done, the diaphragm opened and the abscess cavity opened widely and drained. An ICD tube was left in the pleural cavity and removed on the 7th POD. The child improved well with no issues.

Discussion

PLA in children has an incidence of 79 per 100000 admissions.[1] Predisposing causes in children are unique such

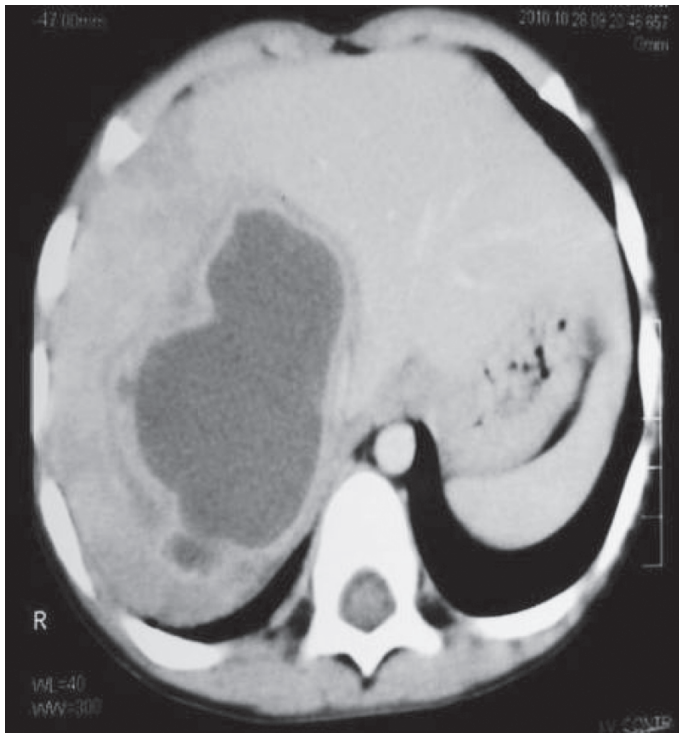


Fig.4.Axial view showing solitary abscess in the segment VII.

as parasitic infections, chronic granulomatous disease, skin infection and protein-calorie malnutrition.[2] Pyogenic liver abscesses are much more common in children than amoebic abscesses. Staphylococcus aureus is the commonest pathogen. The clinical triad includes high swinging fever, right upper quadrant pain and tender palpable liver. Leukocytosis, anaemia and raised liver enzymes are routinely seen in the blood tests. USG abdomen is the imaging modality of choice followed by CECT abdomen to find out small unsuspected abscesses. Most of them respond to antibiotics, percutaneous aspiration or catheter drainage. Open drainage is indicated in cases falling under the Kapoor criteria[3] which include the following:1.thick pus which could not be aspirated 2. ongoing sepsis after antibiotics and percutaneous drainage 3. multiloculated abscesses 4. left lobe abscess and 5. ruptured abscess.

Inaccessible site such as segement

VII liver abscess is another added criterion for surgical drainage. For posterosuperior segment liver abscess, open window hepatostomy (OWH)[4] in post-transplant patients and other resilient abscesses have been described already in the literature[5,6]. Similar to our patients, three cases of resilient liver abscess failing conservative measures and treated by thoracic approach in Italy have been reported in the above mentioned case series. In those cases the abscess cavity was exteriorized by suturing the diaphragmatic defect

and pleura to the skin. However in our patients, a transthoracic drainage was done and an ICD tube was left in the pleural cavity. Complete resolution of the abscess with uneventful recovery was noticed in both the cases. The advantages of transthoracic drainage over laparotomy for segment VII abscess are: 1. good anatomic localization, 2. less of hepatic parenchyma traversed, 3. less bleeding complications, 4. less inadvertent bile duct injury and 5.no risk of post-operative adhesions.

Trans-diaphragmatic drainage of segment VII liver abscess is a viable therapeutic option which gives good exposure, adequate drainage and avoids the complications of a laparotomy.

Points to Remember

- ***Liver abscess involving segment VII often requires surgical intervention and thus early surgical referral is recommended.***
- ***In multiple abscesses or resistant cases, CECT abdomen for anatomic localization is recommended.***
- ***Liver abscess at these sites, can present as empyema.***
- ***Protein energy malnutrition, parasitic infection and chronic granulomatous disease must be kept in mind by practicing physicians in case of liver abscess in children.***

References

1. Kumar A, Srinivasan S, Sharma AK. Pyogenic liver abscess in children – South Indian experiences. J Pediatr Surg 1998 33(3):417-421.
2. MP Sharma, Arvind Kumar, Liver abscess in children: Symposium on Hepatology and Gastroenterology II. Indian J Pediatr 2006; 73; 813-817.
3. Ajaz A Malik, Shams UL Bari. Pyogenic liver abscess: changing patterns in approach. World J GI Surg 2010; 2(12): 395-401.
4. Romagnoli R, Patrono D, Transthoracic open window hepatostomy: a salvage approach to right lobe abscesses after liver transplantation. Liver Transpl 2009; 15(7): 818-821.
5. Bala A, Saxena P, Transthoracic drainage of large Streptococcus Milleri liver abscess. J Thorac Cardiovasc Surg 2006; 131 (3):744-745.
6. Ranson JH, Madyag MA. New diagnostic and therapeutic techniques in the management of pyogenic liver abscesses. Annals of Surg 1975; 181 (5): 508-518.

CLIPPINGS

Oral paracetamol versus oral ibuprofen in the management of patent ductus arteriosus in preterm infants: A randomized controlled trial.

The aim of this study is to compare the efficacy and safety of oral paracetamol and oral ibuprofen for the pharmacological closure of patent ductus arteriosus (PDA) in preterm infants.

This prospective, randomized, controlled study enrolled 90 preterm infants with gestational age d”30 weeks, birthweight d”1250 g, and postnatal age 48 to 96 hours who had echocardiographically confirmed significant PDA. Each enrolled patient received either oral paracetamol (15 mg/kg every 6 hours for 3 days) or oral ibuprofen (initial dose of 10 mg/kg, followed by 5 mg/kg at 24 and 48 hours).

After the first course of treatment, the PDA closed in 31 (77.5%) of the patients assigned to the oral ibuprofen group vs 29 (72.5%) of those enrolled in the oral paracetamol group (P = 0.6). The reopening rate was higher in the paracetamol group than in the ibuprofen group, but the reopening rates were not statistically different (24.1% [7 of 29] vs 16.1% [5 of 31]; P = 0.43). The cumulative closure rates after the second course of drugs were high in both groups. Only 2 patient (2.5%) in the paracetamol group and 3 patients (5%) in the ibuprofen group required surgical ligation.

Oncel MY, Yurttutan S, Erdeve O, Uras N, Altug N, Oguz SS, Canpolat FE, Dilmen U. Oral paracetamol versus oral ibuprofen in the management of patent ductus arteriosus in preterm infants: A randomized controlled trial. J Pediatr 2014;164(3):510-514.

CASE STUDY

INTRA-CRANIAL CALCIFICATION AND GLOBAL DEVELOPMENTAL DELAY IN A CHILD WITH NEPHROGENIC DIABETES INSIPIDUS

**** Samuel P. Oommen***
***** Sunithi Mani***
****** Anna Simon***

Abstract: *Although intracranial calcifications and global developmental delay are seen together in many conditions, this is unusual in nephrogenic diabetes insipidus. Intracranial calcification has been speculated to be a consequence of episodes of hyperosmotic dehydration and the amount of calcification has been shown to correlate with the degree of mental retardation in nephrogenic diabetes insipidus. We present a case history of a 3½-year-old boy who presented with intracranial calcifications and developmental delay and was subsequently diagnosed with nephrogenic diabetes insipidus.*

Keywords: *Intracranial calcifications, Nephrogenic diabetes insipidus, Global developmental delay.*

Intracranial calcification and developmental delay are commonly seen together in intrauterine infections, neurocutaneous syndromes and metabolic conditions. Nephrogenic diabetes insipidus is an unusual cause of intracranial calcification and developmental delay.[1-6]

A 3½-year old boy was referred for evaluation of developmental delay. He was the third child born to non-consanguineous parents and his birth weight was 3kg. He had three previous episodes of seizures precipitated by fever and one episode of urinary tract infection. The first sibling, a boy, had died during the neonatal period following diarrhea. The second sibling, a 5 year old girl child was well. There was no other significant family history. During evaluation we noticed polyuria and polydipsia, although these were not part of his initial presenting complaints.

On examination he was alert. His head circumference was 42.2cm, weight was 7.4kg and height was 77cm (all below the third percentile). His development was equivalent to a nine months old child. There were no neurocutaneous markers or dysmorphic features. He had hypotonia with brisk reflexes.

CT (brain) showed, confluent and feathery calcifications involving subcortical white matter and the basal ganglia (Fig.1) and he was initially referred for evaluation of TORCH infection. Investigations revealed significant hypernatremia on several occasions (between 153–163mEq/L), increased serum osmolality (343–350mOsm/kg) with low concurrent urine osmolality (80–198mOsm/kg). Hemogram, serum potassium, arterial

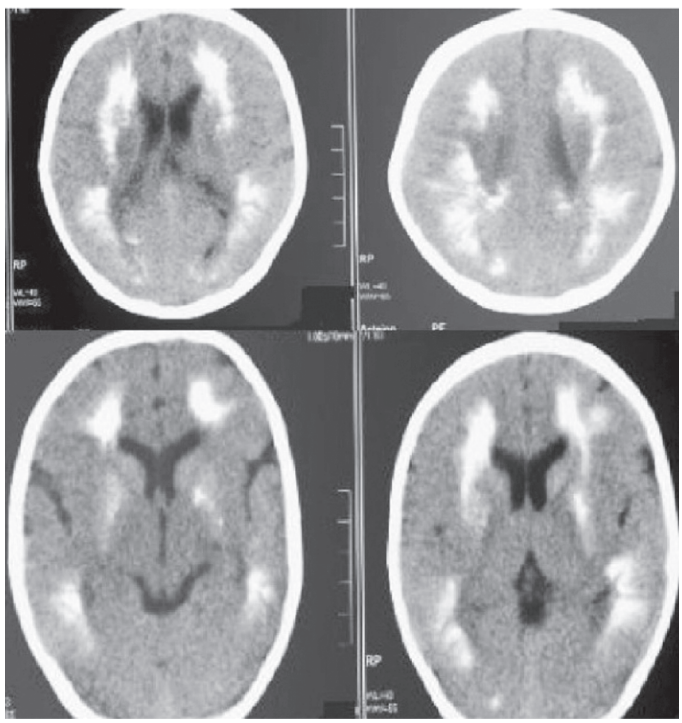


Fig.1. CT sections of the brain showing extensive confluent calcifications in the white matter (subcortical to periventricular) in a symmetric distribution. Globus pallidus calcification is also present.

* Associate Professor,
Developmental Pediatrics Unit
** Assistant Professor
Department of Radiology
*** Professor
Pediatric Endocrinology Unit,
Department of Child Health,
Christian Medical College, Vellore.

blood gas, creatinine and ultrasound of the kidneys were normal. Normal serum calcium, phosphorus and alkaline phosphatase ruled out hyperparathyroidism, pseudohypo parathyroidism and hypo-parathyroidism which can cause intracranial calcification. Eye examination did not show cataracts or evidence of TORCH infection. Cardiac and hearing evaluations were normal as was MRI (Fig.2). There were no white matter changes in the MRI corresponding to the extensive calcifications seen on CT (susceptibility weighted images were not done).

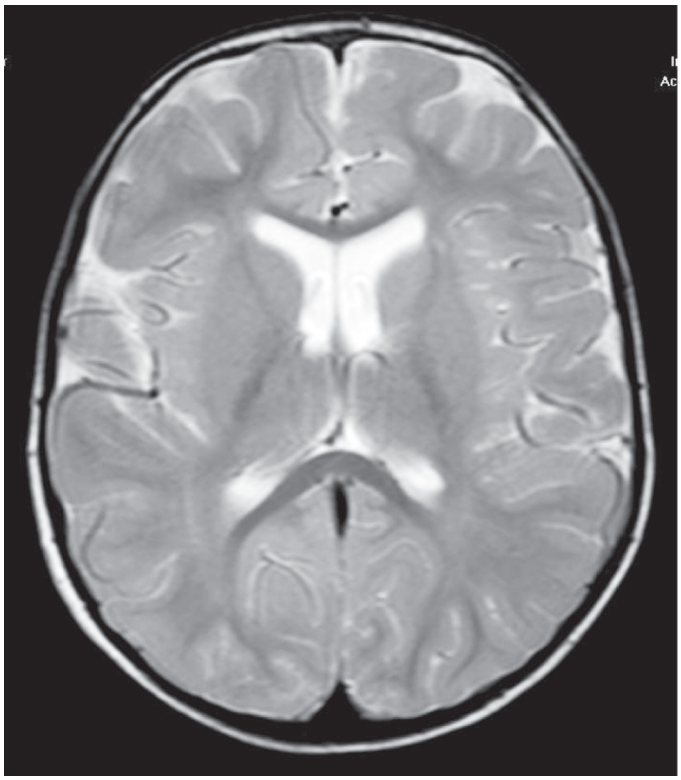


Fig.2. T2W axial MRI at the level of the basal ganglia shows no signal changes in the globus pallidus or in the areas of white matter calcification seen on the CT sections.

Based on the clinical features of polyuria, polydipsia, hypernatremia, serum hyperosmolality and low concurrent urine osmolality, diabetes insipidus was suspected. This was confirmed by water deprivation test. Nephrogenic diabetes in the areas of white matter calcification seen on the CT sections. Insipidus was confirmed by absence of response to vasopressin. Polyuria and hypernatremia resolved after starting hydrochlorthiazide. Parents were counseled about preventing dehydration and being compliant with the medications. When he was seen two years later, he had improved remarkably. His height had increased by 15cm. He was walking independently and attending school.

Discussion

Nephrogenic diabetes insipidus, manifests within few weeks of life as irritability, poor feeding, poor weight gain, polyuria, polydipsia and intermittent high fever due to dehydration.[2] Intracranial calcifications have been reported in nephrogenic diabetes insipidus[2-6] and in central diabetes insipidus.[7] It is hypothesized that endothelial damage following hypernatremic dehydration leads to necrosis and subsequent dystrophic calcifications.[1] Repeated episodes of severe brain dehydration results in developmental delay.[8] Many children with intracranial calcifications have some amount of mental retardation which correlates with the amount of calcium deposition.[3,4,9] White matter involvement although uncommon, occurs due to gliosis and results in spasticity and psychomotor retardation.[6] Calcification can be prevented by avoiding episodes of dehydration and starting hydrochlorthiazide by one month of age.[9]

MRI signals depend on the presence of mobile protons and these are deficient in areas of calcification. Thus even in extensive intracranial calcification, MRI appearances of calcification are variable and non-specific[10] on conventional sequences (T1, T2 and FLAIR). Calcification can be detected on susceptibility weighted images (SWI).

This child's kidney functions and metabolic parameters (other than serum sodium and osmolality) were normal. There was history of death of a previous male sibling following dehydration. Therefore he may be having the X-linked form of congenital nephrogenic diabetes insipidus.

Conclusion

Nephrogenic diabetes insipidus should be considered as a differential in children with psychomotor retardation and intracranial calcification. Early initiation of therapy and avoiding dehydration can prevent brain damage.

References

1. Schofer O, Beetz R, Kruse K, Rascher C, Schütz C, Bohl J. Nephrogenic diabetes insipidus and intracerebral calcification. Arch Dis Child 1990; 65(8):885–887.
2. Knoers N, Monnens LA. Nephrogenic diabetes insipidus: clinical symptoms, pathogenesis, genetics and treatment. Pediatr Nephrol Berl Ger 1992; 6(5): 476–482.
3. Tohyama J, Inagaki M, Koeda T, Ohno K, Takeshita K. Intracranial calcification in siblings with nephrogenic diabetes insipidus: CT and MRI. Neuroradiology 1993; 35(7):553–555.
4. Bajpai A, Kabra M, Thapliyal R, Gulati S, Kalra V. Nephrogenic diabetes insipidus presenting with developmental delay and intracranial calcification. Indian J Pediatr. 2005;72(6):527–528.

5. Ray M, Dixit A, Singhi P. Nephrogenic diabetes insipidus with intracranial calcifications. Indian Pediatr 2002; 39(2):197–202.
6. Bindu PS, Kovoor JME. Nephrogenic diabetes insipidus: a rare cause of intracranial calcification in children. J Child Neurol. 2007; 22(11):1305–1307.
7. Al-Kandari SR, Pandey T, Badawi MH. Intracranial calcification in central diabetes insipidus. Pediatr Radiol 2008 Jan;38(1):101–103.
8. Hoekstra JA, van Lieburg AF, Monnens LA, Hulstijn-Dirkmaat GM, Knoers VV. Cognitive and psychosocial functioning of patients with congenital nephrogenic diabetes insipidus. Am J Med Genet 1996; 61(1):81–88.
9. Mendonca EV, Stone RC, Rosa FC. Prevention of intracranial calcifications and brain damage associated with nephrogenic diabetes insipidus. Pediatr Nephrol Berl Ger 1994; 8(2):263.
10. Oot RF, New PF, Pile-Spellman J, Rosen BR, Shoukimas GM, Davis KR. The detection of intracranial calcifications by MR. AJNR Am J Neuroradiol 1986; 7(5):801–809.

CLIPPINGS

Impact of Inpatient Bronchiolitis Clinical Practice Guideline Implementation on Testing and Treatment.

Objective: To determine the association between institutional inpatient clinical practice guidelines (CPGs) for bronchiolitis and the use of diagnostic tests and treatments.

Methods: A multicenter retrospective cohort study of infants aged 29 days to 24 months with a discharge diagnosis of bronchiolitis was conducted between July 2011 and June 2012. An electronic survey was sent to quality improvement leaders to determine the presence, duration, and method of CPG implementation at participating hospitals. The Wilcoxon rank-sum test was used to perform bivariate comparisons between hospitals with CPGs and those without CPGs. Multivariable analysis was used to determine associations between CPG characteristics and the use of tests and treatments; analyses were clustered by hospital.

Results: The response rate to our electronic survey was 77% (33 of 43 hospitals). The majority (85%) had an institutional bronchiolitis CPG in place. Hospitals with a CPG had universal agreement regarding recommendations against routine tests and treatments. The presence of a CPG was not associated with significant reductions in the use of tests and treatments (eg, complete blood count, chest radiography, bronchodilator use, steroid and antibiotic use). A longer interval duration since CPG implementation and presence of an easily accessible online CPG document were associated with significant reductions in the performance of complete blood count and chest radiography and the use of corticosteroids. Other implementation factors demonstrated mixed results.

Conclusion: Most children's hospitals have an institutional bronchiolitis CPG in place. The content of these CPGs is largely uniform in practice recommendations against tests and treatments. The presence of institutional CPGs did not significantly reduce the ordering of tests and treatments. Online accessibility of a written CPG and prolonged duration of implementation reduce tests and treatments.

Vineeta Mittal, Matt Hall, Rustin Morse,Karen M. Wilson, Grant Mussman, Paul Hain, et al. Impact of Inpatient Bronchiolitis Clinical Practice Guideline Implementation on Testing and Treatment. J Pediatr 2014;165 (3): 570-576.e3.

NEWS AND NOTES

International Pediatric Nephrology Training Course and

3rd Indian Simulation Based Pediatric Dialysis Course, February 28 - March 1, 2015

Contact:

Dr. Sidharth Kumar Sethi

Course Director

Consultant, Pediatric Nephrology Kidney and Urology Institute

Medanta, The Medicity Hospital, Gurgaon, Haryana, India 122001.

Ph: 09868306235 E mail: sidsdoc@gmail.com

AUTHOR INDEX

SUBJECT INDEX

Details of the bank for online transaction

Name of the Account	:	South Pedicon 2015
Account Number	:	914010032144133
Name of the Bank	:	Axis Bank Ltd.,
Name of the Branch	:	Tiruvannamalai (TN)
MICR CODE	:	606211002
IFS CODE	:	UTIB0000799

In Case of Online Transfer kindly send the bank acknowledgment along with **Registration Form**

DD to be drawn in favourof **SOUTH PEDICON - 2015** payable at **VELLORE**

Conference Secretariat

Dr. S.Narmada
Organising Secretary - South Pedicon - 2015
Nalam Medical Centre & Hospital
No.44, Arcot Road, Phase - II,
Sathuvachari,
VELLORE - 632 009.
Tamil Nadu.
Cell : 97912 08103 / 94430 98899 / 94428 08963

Contact Persons

Dr. G.KIRUBAKARAN
E-Mail : drgkirubakaran@gmail.com

Dr. S.NARMADA
E-Mail : dr.narmadhaashok@gmail.com

Dr. P.SURESHBABU
E-Mail : sureshbabu31@gmail.com

South Pedicon - 2015

Dear Esteemed members of IAP,

Welcome to South Pedicon 2015 !

The members of IAP North Arcot and Kanchipuram take great pride in inviting you all for the 40th Tamilnadu State Conference and 29th South Pedicon. The event is to be held in Vellore in the prestigious **Vellore Institute of Technology from 6th August 2015 to 9th August 2015**. We cordially invite you to join us in this academic extravaganza as we hold our academic deliberations in a serene background without the hustle and bustle of urban life.

The conference will cover a range of topics meticulously planned by our Scientific committee involving academic heads from Christian Medical college, Government Medical college and academically oriented private practitioners. This unique blend brings you a wide spread of topics useful for everyone from the aspiring postgraduates, the specialists involved in advanced care of the very sick children and the office practitioners.

We invite abstracts for the papers and posters that will steer us into evidence based practice and contribute to enriching our knowledge.

Vellore is accessible with in 3 hours to Tourist places like Tirupati, Pondicherry, Kanchipuram, Mahabalipuram, Chennai, so that your family members can also enjoy the trip along with you.

Enjoy our hospitality as we bring to you the legacy of the rich Tamil heritage in our entertainment,

Dip in our delicacies as we bring to you the world famous Arcot Nawab cuisine,

Relax in our serenity and blend into our sophistication.

Yours in academy Service

IAP TNSC

Dr. S.Yoganandan
President - 2015

Dr. S.Aram Chenthil
Secretary - 2015 - 16

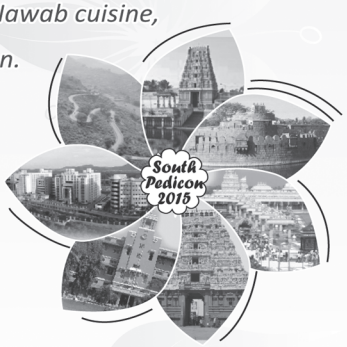
Dr. A.Somasundaram
Treasurer - 2015 - 16

Organising Committee South Pedicon 2015.

Dr. G.Kirubakaran
Organising Chairperson

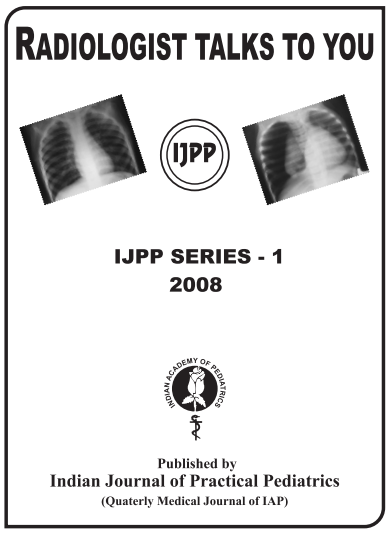
Dr. S.Narmada
Organising Secretary

Dr. P.Suresh Babu
Organising Treasurer

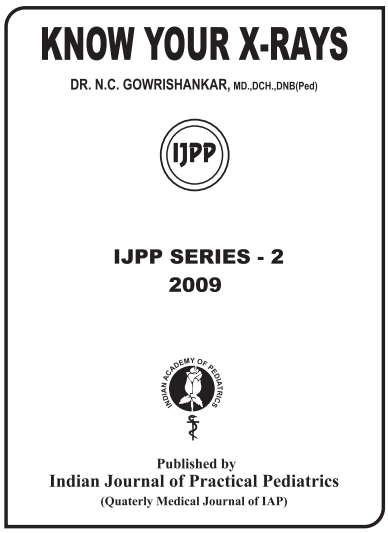


Date	IAP MEMBER	NON IAP MEMBER	PG STUDENT	ACCOMPANYING PERSON	SENIOR CITIZEN
TILL 30.04.2015	5000	5500	4500	3500	FREE
TILL 15.07.2015	5500	6000	5000	3500	FREE
SPOT (FROM 15.07.2015)	6000	6500	5500	4000	3500

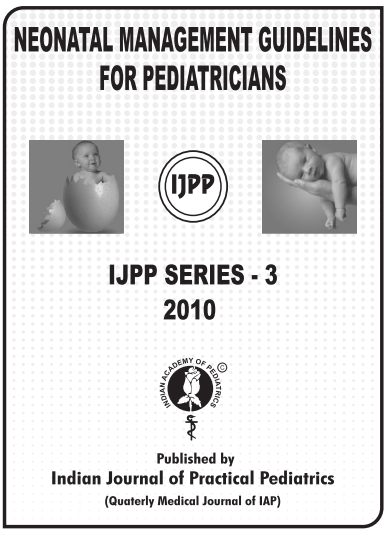
Note :
1. *70 years and above as on 6.8.2015 considered as Senior citizens(please attach age proof)*
2. *Separate registration mandatory for workshops*
3. *Letter from HOD mandatory for Postgraduate registration*
4. *Complimentary kits will not be provided for spouse and spot registration*



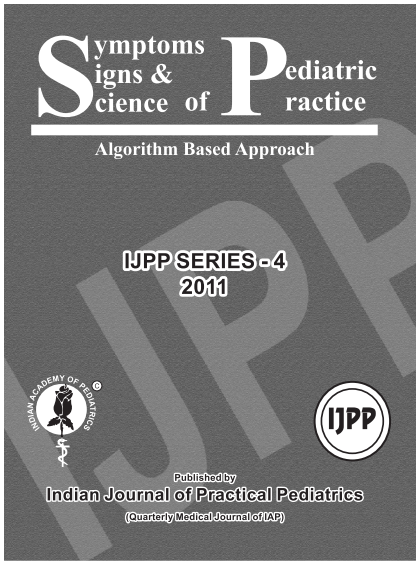
Price : Rs.200/-



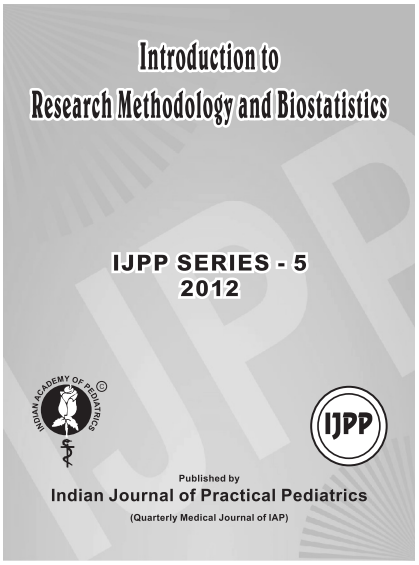
Price : Rs.150/-



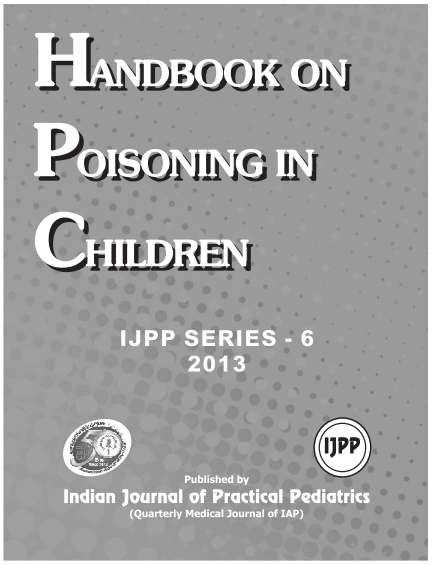
Price : Rs.250/-



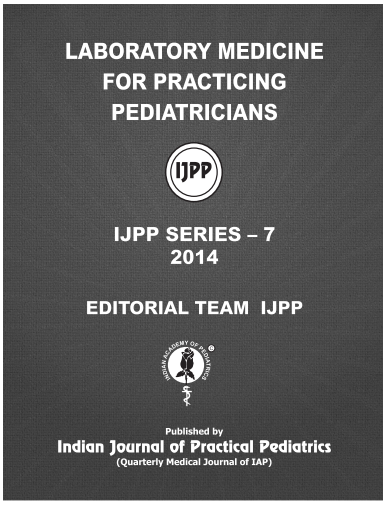
Price : Rs.300/-



Price : Rs.400/-



Price : Rs.400/-



Price : Rs.500/-

Copies available at
Indian Journal of Practical Pediatrics
1A, Block II, Krsna Apartments,
50, Halls Road, Egmore, Chennai 600 008, Tamil Nadu, India.
Phone: 044-28190032, 42052900 Email: ijpp_iap@rediffmail.com

INDIAN JOURNAL OF PRACTICAL PEDIATRICS

SUBSCRIPTION TARIFF

JOURNAL OFFICE
1A, Block II, Krsna Apartments,
50, Halls Road, Egmore,
Chennai 600 008, Tamilnadu, India.
Phone: +91-44-28190032, 42052900.
Email: ijpp_iap@rediffmail.com

Official Journal of the Indian Academy of Pediatrics
A quarterly medical journal committed to practical pediatric problems and management update

Subscription for ☐ ONE year ☐ TEN years

For office use

Ref. No.

Cash / DD for Rs.

DD No.

Receipt No. & Date

Name.....

Address.....

.....

City .....State

.....

Pin ..... Phone (R) ..... (O).....

Mobile ..... Email .....

Designation ..... Qualification.....

I am enclosing a DD No. …….. dated …… drawn on ……..……....

favoring **Indian Journal of Practical Pediatrics** for Rs……....

Signature

Subscription rate

Individual	Annual	Rs.500/-
	Ten Years	Rs.5000/-
Institution	Annual	Rs.600/-
	Ten Years	Rs.6000/-
Foreign	Annual	US $ 65/-

(Subscription period is between January and December only)

Send your subscription, only by crossed demand draft, drawn in favour of **INDIAN JOURNAL OF PRACTICAL PEDIATRICS**, payable at **Chennai** and mail to **Dr. P. RAMACHANDRAN,** Editor-in-Chief, 1A, Block II, Krsna Apartments, 50, Halls Road, Egmore, Chennai 600 008, Tamilnadu, India.

INDIAN JOURNAL OF PRACTICAL PEDIATRICS

ADVERTISEMENT TARIFF

Official Journal of the Indian Academy of Pediatrics - A quarterly medical journal committed to practical pediatric problems and management update

Name .....

Address .....

.....

.....

.....

City .....

State ..... Pin .....

FULL PAGE

	B/W	Colour*
Ordinary	10,000	15,000
Back cover	-	25,000
Second cover	-	20,000
Third cover	-	20,000

* Advertisements should be given in the Coreldraw / Photoshop / PDF format.

Signature

Kindly send your payment by crossed demand draft only drawn in favour of **"Indian Journal of Practical Pediatrics"** payable at **Chennai.**

MANAGING EDITOR
Indian Journal of Practical Pediatrics
1A, Block II, Krsna Apartments,
50, Halls Road, Egmore,
Chennai - 600 008, Tamilnadu, India.
Phone : 044-2819 0032, 42052900
Email : ijpp_iap@rediffmail.com