INDIAN JOURNAL OF PRACTICAL PEDIATRICS

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

Vol.21 No.3 **JUL.- SEP. 2019**

Dr.N.C.Gowrishankar
Editor-in-Chief

Dr.S.Thangavelu
Executive Editor

CONTENTS

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

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

INSTRUCTIONS TO AUTHORS

General

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

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

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

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

Manuscript

1st Page –

Title

Name of the author and affiliation

Institution

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

Word count

No. of figures (colour / black and white)

No. of references

Authors contribution

2nd Page –

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

3rd Page -

Acknowledgement

Points to remember (not more than 5 points)

Text

References

Tables

Legends

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

(4 x 6 inches – Maxi size) Glossy print

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

Text

Only generic names should be used

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

References

Recent and relevant references only

Strictly adhere to Vancouver style

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

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

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

Tables

Numbered with Roman numerals and typed on separate sheets.

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

Figures and legends

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

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

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

Article Categories

Review article

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

Case report (covering practical importance)

250 – 600 words, 8 – 10 recent references

Clinical spotters section

150 – 200 words write up

With 1 or 2 images of clinically recognizable condition

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

Letters to the Editor

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

Check List

Covering letter by corresponding author

Declaration (as enclosed) signed by all authors **

Manuscript (4 copies)

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

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

Author's contribution / Authorship Criteria

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

**** Declaration by authors**

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

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

Selection procedures

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

INFECTIOUS DISEASES - II

EMERGING INFECTIOUS DISEASES

***Raju C Shah**
****Meet Patel**

Abstract: *Emerging infectious diseases are infections that have recently appeared within a population or those whose incidence or geographic range is rapidly increasing or threatens to increase in the near future. People coming in to closer contact with wild animals and travelling much more frequently are major contributors. Many emerging diseases arise when infectious agents in animals are passed to humans.*

The second annual review in WHO by expert committee consider that given their potential to cause a public health emergency and the absence of efficacious drugs and/or vaccines, there is an urgent need for accelerated research and development for 8 diseases emerged recently. In this article we will discuss about four emerging diseases which include Ebola virus, Middle East Respiratory Syndrome Corona Virus (MERS-CoV), Nipah and Zika virus.

Keywords: *Emerging Infectious diseases, Zoonoses, Contagious, Ebola, MERS, Nipah, Zika.*

Emerging infectious diseases (EID) are infections that have recently appeared within a population or those whose incidence or geographic range is rapidly increasing or threatens to increase in the near future. The new infectious diseases and those which are re-emerging after a period of quiescence are also grouped under emerging infectious diseases.[1]

Changes in human behaviour and customs will continue to provide opportunities for microbes to produce unexpected epidemics. Notably, 60 to 80 percent of new human infections likely originated in animals.[2]

* Medical Director,
Ankur Institute of Child Health

** Associate Consulting Pediatrician,
Ankur Institute of Child Health, Ahmedabad.
email: rajucshah@gmail.com

Causes of emerging infections:[3]

- Previously undetected or unknown infectious agents
- Known agents that have spread to new geographic locations or new populations
- Agents whose role in specific diseases has previously gone unrecognized.
- Re-emergence of agents whose incidence of disease had significantly declined in the past, but has reappeared. This class of diseases is known as re-emerging infectious diseases.

Since the 1970s, about 40 infectious diseases and agents have been discovered, including severe acute respiratory syndrome (SARS), Middle east respiratory syndrome (MERS), ebola, chikungunya, avian flu, swine flu, Zika and most recently Nipah. The World Health Organization warned in its 2007 report that infectious diseases are emerging at a rate that has not been seen before.[3]

Coming into closer contact with wild animals, travelling more frequently and far greater distances than in the past increase the potential for emerging infectious diseases to spread rapidly and cause global epidemics which is a major concern.

Agents of bioterrorism like anthrax, smallpox and tularemia also has the potential for reemergence and of serious concern.

Factors for the emergence or re-emergence of infectious diseases

Factors that have contributed to these changes are population growth, migration from rural areas to cities, international air travel, poverty, wars and destructive ecological changes due to economic development, unregulated land use evolution of pathogens over time etc.

For an emerging disease to become established the following events have to occur (Fig.1).

The infection also has to be able to sustain itself within the population, with more and more people continued to get infected.[4]

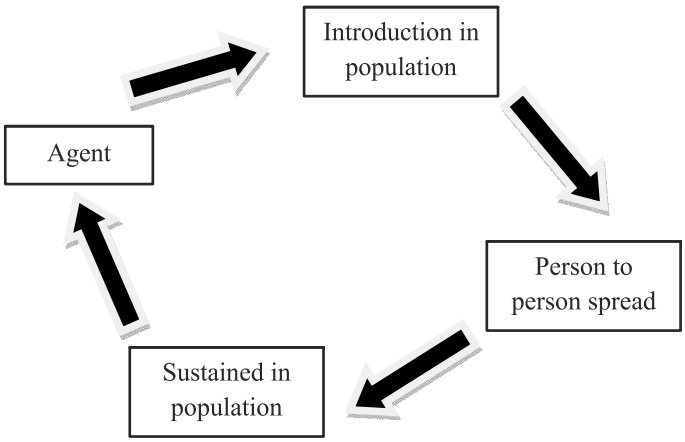


Fig.1. Events leading to emerging infectious diseases

Many emerging diseases arise when infectious agents in animals are passed on to humans (zoonoses). As the human population expands in number and into new geographical regions, the possibility that humans will come into close contact with infected animals increases. When this is combined with increase in human density and mobility, it poses a serious threat to human health.

The WHO expert committee during their second annual review in 2018, opined that given their potential to cause a public health emergency and the absence of efficacious drugs and / or vaccines, there is an urgent need for accelerated research and development for[4]:

- Crimean-Congo hemorrhagic fever (CCHF)
- Ebola virus disease and Marburg virus disease
- Lassa fever
- Middle-east respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome (SARS)
- Nipah and henipaviral diseases
- Rift Valley fever (RVF)
- Zika
- Disease X

Disease X represents the knowledge that a serious international epidemic could be caused by a pathogen currently unknown to cause human disease and so the research and development (R&D) blueprint explicitly seeks to enable cross-cutting R&D preparedness that is also relevant for an unknown "Disease X" as far as possible.[4]

This article will cover Ebola virus, Middle-east respiratory syndrome corona virus (MERS-CoV), Nipah and Zika virus.

Ebola virus disease

Ebola virus disease (EVD) is a rare and deadly disease most commonly affecting people and nonhuman primates (monkeys, gorillas and chimpanzees). Ebola virus disease (EVD) was discovered in Central Africa in 1976 when two consecutive outbreaks of fatal hemorrhagic fever occurred. The first outbreak occurred in the Democratic Republic of Congo (DRC) in a village near the Ebola river, which gave the virus its name. The second outbreak occurred in what is now South Sudan, approximately 500 miles (850 km) away.[5]

Initially, public health officials assumed that these outbreaks were isolated events associated with an infected person who travelled between the two locations. However, later it was discovered that the two outbreaks were caused by two genetically distinct viruses: Zaire ebolavirus and Sudan ebolavirus.[6] Factors like population growth, encroachment into forested areas and direct interaction with wildlife (such as bushmeat consumption) may have contributed to the spread of the Ebola virus.[6]

Since its discovery in 1976, the majority of cases and outbreaks of Ebola Virus Disease have occurred in Africa. The 2014-2016 Ebola outbreak in West Africa began in a rural setting of southeastern Guinea, spread to urban areas and across borders within weeks and became a global epidemic within months.[6]

Ebola viruses are highly contagious once early symptoms such as fever develop. The infected patient sheds viruses in all body secretions (bodily fluids); direct contact with any of these secretions may cause the virus transmission to uninfected individuals.[7]

The cause of Ebola hemorrhagic fever is Ebola virus infection that results in coagulation abnormalities, including gastrointestinal bleeding, development of a rash, cytokine release, damage to the liver and massive viremia that damages the endothelial cells of blood vessels. As the massive viremia continues, coagulation factors are compromised and the microvascular endothelial cells are damaged or destroyed, resulting in diffuse bleeding internally and externally (bleeding from the mucosal surfaces like nasal passages, mouth, gums and conjunctiva). This uncontrolled bleeding leads to blood and fluid loss ultimately leading to hypotensive shock that causes death in many Ebola-infected patients.[7]

Unfortunately, early symptoms of Ebola virus disease are nonspecific and include fever, headache (severe), weakness, vomiting, diarrhea, abdominal discomfort or pain, decreased appetite and joint and muscle discomfort.[7]

As the disease progresses, patients may develop other symptoms and signs such as rash or skin and eye bleeds, hiccups, sore throat, cough, hemotyis/hemotemesis (GI bleed), chest pain, mental confusion, bleeding both inside and outside the body (for example, mucosal surfaces, eyes) and difficulty in breathing and swallowing.[7]

The symptoms and signs may appear from about 2 to 21 days after exposure with an average incubation period of 8 to 10 days. It is unclear why some patients can survive and others die from this disease, but patients who die usually have a poor immune response to the virus. Patients who survive have symptoms that can be severe for a week or two; recovery is often slow (weeks to months) and some survivors have chronic problems such as fatigue and eye problems.[7]

Diagnostic studies[8] that may be helpful include the following: Complete blood count (CBC) with differential, bilirubin, liver enzymes, blood urea nitrogen (BUN), creatinine, ABG, Studies for isolating the virus - Tissue culture (only to be performed in one of a few high-containment laboratories throughout the world), reverse-transcription polymerase chain reaction (RT-PCR) assay, serologic testing – Enzyme-linked immunosorbent assay (ELISA) for antigens or for immunoglobulins (IgM and IgG). Other studies are immunochemical testing of postmortem skin and electron microscopy.

Ebola hemorrhagic fever often has many complications; organ failure, severe bleeding, jaundice, delirium, shock, seizures, coma, and death (about 50%-100% of infected patients). Survivors may experience weakness, fatigue, headaches, hair loss, hepatitis, sensory changes and inflammation of organs (e.g., the testicles and the eyes).[7] Male patients may have detectable Ebola viruses in their semen for as long as six months after they survive the infection. Chances of being infected with Ebola from semen is very low.[7]

Treatment

The CDC recommends the following supportive medical treatment for Ebola-infected patients:

Providing intravenous fluids (IV), maintaining electrolyte balance and oxygen status and blood pressure and treating other infections if they occur.

Anyone suspected of having Ebola hemorrhagic fever should be isolated, and caregivers should wear protective garments. Currently, there is no specific medical treatment for Ebola hemorrhagic fever according to the CDC.[5]

The main way to prevent getting Ebola hemorrhagic fever is to not travel to areas where it is endemic and by staying away from any patients who may have the disease. Medical caregivers may protect themselves from infection by strict adherence to barriers to the virus (wearing gloves, gowns, goggles, and a mask). Contact surfaces should be disinfected with alcohol-based (70%) wipes.[8]

The recommendations from the CDC to prevent getting Ebola (EVD) from an infected person are shown in Box 1.[5]

In addition, after leaving an area affected by EVD, individuals should monitor their health for 21 days; if a person develops any symptoms, he or she should immediately seek medical care and inform the medical caregivers of his or her exposure to Ebola.[8]

In December 2016, a human clinical trial of rVSV-ZEBOV vaccine[9] against Ebola disease was found to be apparently effective and relatively safe for . The researchers used people (contacts) exposed to Ebola patients during the outbreak in a trial following similar procedures ("ring of exposure") used to eliminate smallpox. Researchers randomly assigned the Ebola case exposure patients to get the vaccine at either day 0 or 21 days later after being identified as a new case exposure. Although many vaccinated people developed side effects of injection-site pain, mild headache, fatigue and muscle pain, most

Box 1. Steps to prevent Ebola virus disease

Avoid the following:

- Contact with blood and body fluids (urine, feces, saliva, sweat, vomit, breast milk, semen and vaginal fluids)
- Items that may have contacted an infected person's blood or body fluids (such as clothes, bedding, needles and medical equipment)
- Funeral or burial rituals that require handling the body of someone who died from EVD
- Contact with bats and nonhuman primates or blood, fluids and raw meat prepared from these animals (bushmeat) or meat from an unknown source
- Contact with semen from a man who had EVD

individuals recovered within a few days and none developed long-term problems. The study involved 11,841 people. The vaccine was 100% effective in patients who obtained the vaccine at day 0 and those day 0 individuals who had no symptoms within 10 days (due to the approximate average incubation period of Ebola). There were 23 new cases of Ebola in patients who got the vaccine 21 days later. Many investigators consider this vaccine to be a safe and effective vaccine. There is a stockpile of 300,000 doses in reserve for future outbreaks. The vaccine is in limited supply and is not licensed by the FDA. Health care professionals use this vaccine in the same way to limit the spread of Ebola in the DRC in the 2018 outbreak. Time will tell if the "ring of exposure" method of vaccination will stop the outbreak.[5]

Middle East Respiratory Syndrome Corona Virus (MERS-CoV)

Middle East Respiratory Syndrome (MERS) is a viral respiratory illness first reported in Saudi Arabia in 2012. The virus that causes MERS is called Middle East Respiratory Syndrome Corona virus (MERS-CoV). Corona viruses are common viruses that most people get at some point of time in their life. Human Corona viruses usually cause mild to moderate cold-like illnesses. However, MERS-CoV is different from any other corona virus previously found in people.[10]

The largest outbreak outside Arabian Peninsula occurred in the Republic of Korea in 2015. It was linked to a traveller returning from the Arabian Peninsula. MERS-CoV is a type of corona virus, similar to the one that caused SARS (severe acute respiratory syndrome) and the common cold. MERS-CoV has not been previously identified in humans. Like the SARS virus, MERS-CoV is most similar to corona viruses found in bats. It has been detected in camels and several cases of MERS-CoV in those who handle camels have been reported. Other livestock do not seem to be affected. [10] MERS-CoV likely came from an animal source in the Arabian Peninsula. Researchers have found MERS-CoV in camels from several countries. Studies continue to provide evidence that infections in camel may play a role in human infection with MERS-CoV. However, more information is needed. [10]

Typical MERS symptoms include fever, cough and shortness of breath. Pneumonia is common, but not always present. Gastrointestinal symptoms, including diarrhoea, have also been reported. Initially, the illness resembles influenza with fever and a mild cough. The breathing disorder often progresses to severe shortness of breath and inability to maintain oxygenation. Progression may be rapid, or it may take several days. Severely affected people develop a potentially fatal form of respiratory failure, known as adult respiratory distress syndrome. In addition to affecting the alveoli in the lungs, the virus also infects other organs in the body, causing renal failure, pericarditis or disseminated intravascular coagulation. People with compromised immune system such as severe rheumatoid arthritis or organ transplantation may not experience respiratory symptoms but can have fever or diarrhea.[11]

Some of the laboratory-confirmed cases of MERS-CoV infection are asymptomatic. Most of these asymptomatic cases have been detected following aggressive contact tracing of a laboratory-confirmed case. Approximately 35% of reported patients with MERS-CoV infection have died. Although most of human cases of MERS-CoV infections have been attributed to human-to-human infections in health care settings, current scientific evidence suggests that dromedary camels are a major reservoir host for MERS-CoV and an animal source of MERS infection in humans. However, the exact role of dromedaries in transmission of the virus and the exact route(s) of transmission are unknown. The virus does not seem to pass easily from person to person unless there is close contact, such as that occurs when providing unprotected care to a patient. Health care associated outbreaks have occurred in several countries, with the largest outbreaks seen in Saudi Arabia, United Arab Emirates and the Republic of Korea.[11]

The incubation period is about five days, but can occasionally be from two to 14 days. The contagious period for MERS-CoV is not known but may last as long as virus is being shed.[10] MERS is contagious and can spread from person to person by respiratory droplets, either by breathing airborne droplets, or contact of respiratory secretions with moist membranes of the mouth, nose and eyes. It is contagious from camel to human via respiratory droplets as well as meat, milk and urine of an infected animal, even though the animal may not appear sick.[12]

Treatment

Like SARS, patients with MERS-CoV often require oxygen supplementation and severe cases require mechanical ventilation and intensive-care-unit support. No medication has been proven to be of use in treating MERS-CoV and treatment is based upon the patient's medical condition. Management of the individual with MERS is aided by infectious disease, pulmonary and critical-care specialists.[12]

MERS is associated with a rapidly progressive severe respiratory illness, and mortality compared to the SARS-CoV outbreak of 2003 is very high. Since the MERS outbreak in Saudi Arabia from 2012 a total of 933 individuals had been affected with 401 deaths as of March 2015, a mortality rate of about 50%.[10] Pneumonia and renal failure are the complications of MERS-CoV. Good hand hygiene using soap and water or an alcohol-based hand sanitizer, avoidance of close contact with sick people and avoidance of touching one's eyes, nose, and mouth can prevent the spread of viruses. Caregivers of patients who are not hospitalized should perform frequent hand hygiene as stated above and wear a face mask for direct care until the patient has recovered.

In the Arabian Peninsula and surrounding countries where MERS-CoV has been found, the World Health Organization (WHO) recommends precautions in handling live camels or their raw meat and dairy products. Anyone who does so, should frequently wash hands and consider using respiratory protection, as well as barriers to protect skin and clothing. Clothing worn during handling of camels or their products should be kept away from household contacts and washed daily. All products intended for human consumption should be cooked thoroughly or pasteurized. [10]

In the health-care setting, a suspected case of MERS is placed in airborne infection isolation room (AIIR). This is a patient care room used to isolate people with suspected or confirmed airborne infectious diseases. The air is under negative pressure, meaning that contaminated air is continually sucked into the room instead of letting it leak out into the hospital environment. This air is exhausted outside, or it circulates back into the room after passing through a high-efficiency particulate air (HEPA) filter to decontaminate it. If an AIIR not available, the patient must wear a face mask and is isolated in a single-patient room with the door closed. The number of staff assigned and the patient's movements outside the room must be minimized. Before entering the isolation room, health-care workers caring for the patient must wear a gown, gloves, eye shield, and mask or a portable air purifier that filters out small infectious particles (N95 mask). Before leaving the room, any disposable gear such as gowns, gloves and mask must be discarded. Hands must be cleansed with soap and water or an alcohol-based hand sanitizer after leaving the room and before attending to another patient.[12]

Nipah virus disease

Nipah virus (NiV) is a member of the family Paramyxoviridae, genus Henipavirus and is related to Hendra virus that infects horses.[13]

History: People first discovered NiV in a village named Kampung Sungai Nipah in 1999 in Malaysia; the virus was named after the village. This first recorded outbreak began in 1998-1999 and reached Singapore. A new strain occurred in 2001 in Bangladesh and India. Small outbreaks of NiV have happened in these countries since 2001.[14] An outbreak in India (state of Kerala) occurred in May 2018. Fruit bats and rabbits are the likely sources of NiV that infected people.[15]

NiV is a zoonotic virus; the virus often infects animals such as pigs and fruit bats (Pteropodidae), but they may be asymptomatic (not show any symptoms). In addition, flying foxes of the genus Pteropus in the Malaysian peninsula can carry NiV. Nipah virus (NiV) can also be transmitted through contaminated food or directly between people.

In infected people, it causes a range of illnesses from asymptomatic (subclinical) infection to acute respiratory illness and fatal encephalitis. The virus can also cause severe disease in animals such as pigs, resulting in significant economic losses for farmers.[16] Although Nipah virus has caused only a few known outbreaks in Asia, not only it infects a wide range of animals but also causes severe disease and death in people, making it a public health concern.

Transmission is thought to have occurred via unprotected exposure to secretions from the pigs, or unprotected contact with the tissue of a sick animal. In outbreaks in Bangladesh and India, consumption of fruits or fruit products (such as raw date palm juice) contaminated with urine or saliva from infected fruit bats was the most likely source of infection.[15] There are currently no studies on viral persistence in body fluids or the environment including fruits. Human-to-human transmission of Nipah virus has also been reported among family and care givers of infected patients. During the later outbreaks in Bangladesh and India, Nipah virus spread directly from human-to human through close contact with people's secretions and excretions. In Siliguri, India in 2001, transmission of the virus was also reported within a health-care setting, where 75% of cases occurred among hospital staff or visitors. From 2001 to 2008, around half of the reported cases in Bangladesh were due to human-to-human transmission through providing care to infected patients. [15]

Infected people initially develop symptoms[16] fever, headaches, myalgia (muscle pain), vomiting, sore throat, dizziness, drowsiness, altered consciousness and neurological signs that indicate acute encephalitis. Some people can also experience atypical pneumonia and

severe respiratory problems, including acute respiratory distress. Encephalitis and seizures occur in severe cases, progressing to coma within 24 to 48 hours.[16]

The incubation period (interval from infection to the onset of symptoms) is believed to range from 4 to 14 days. However, an incubation period as long as 45 days has been reported.

Though Nipah virus infection was well established as having effects on the nervous system, involvement of other organ systems was seen to various degrees.

MRI brain reveals extensive involvement of the cortex, temporal lobe, and pons. Patients who relapsed or had late onset encephalitis also had multiple areas of patchy and confluent cortical involvement.[17] Most people who survive acute encephalitis make a full recovery, but long term neurologic conditions have been reported in survivors. Approximately 20% of patients are left with residual neurological consequences such as seizure disorder and personality changes. A small number of people who recover subsequently relapse or develop delayed onset encephalitis.

The case fatality rate is estimated at 40% to 75%. This rate can vary by outbreak depending on local capabilities for epidemiological surveillance and clinical management.

Initial signs and symptoms of Nipah virus infection are nonspecific and the diagnosis is often not suspected at the time of presentation. This can hinder accurate diagnosis and creates challenges in outbreak detection, effective and timely infection control measures, and outbreak response activities.[16] Nipah virus infection can be diagnosed with clinical history during the acute and convalescent phase of the disease. The main tests used are real time polymerase chain reaction (RT-PCR) from body fluids and antibody detection via enzyme-linked immunosorbent assay (ELISA). Other tests used include polymerase chain reaction (PCR) assay and virus isolation by cell culture. [16] There are currently no drugs or vaccines specific for Nipah virus infection although WHO has identified Nipah as a priority disease for the WHO Research and Development Blueprint.[16]

Prevention: Based on the experience gained during the outbreak of Nipah involving pig farms in 1999, routine and thorough cleaning and disinfection of pig farms with appropriate detergents may be effective in preventing infection. [16]

If an outbreak is suspected, the animal premises should be quarantined immediately. Culling of infected animals - with close supervision of burial or incineration of carcasses - may be necessary to reduce the risk of transmission to people. Restricting or banning the movement of animals from infected farms to other areas can reduce the spread of the disease. As Nipah virus outbreaks have involved pigs and/or fruit bats, establishing an animal health/wildlife surveillance system, using a One Health approach, to detect Nipah cases is essential in providing early warning for veterinary and human public health authorities.[16] In the absence of a vaccine, the only way to reduce or prevent infection in people is by raising awareness of the risk factors and educating people about the measures they can take to reduce exposure to the Nipah virus.

Health-care workers caring for patients with suspected or confirmed infection, or handling specimens from them, should implement standard infection control precautions at all times.

As human-to-human transmission has been reported, in particular in health-care settings, contact and droplet precautions should be used in addition to standard precautions. Airborne precautions may be required in certain circumstances.[17] Samples taken from people and animals with suspected Nipah virus infection should be handled only by trained staff working in suitably equipped laboratories. [16]

Update on the Nipah Virus Outbreak in Kerala, India (2018)[17,18,19]

Nipah virus outbreak in Kerala was first alerted when three members of a family, two brothers (age 26 and 28) and their aunt (age 50), died on May 5th, May 18th and May 19th of 2018 respectively, in a private hospital in Kozhikode district, Kerala. They died with signs of viral encephalitis. Laboratory testing was initially conducted at the Manipal Centre for Viral Research using blood and fluid samples from this patient. The presence of the Nipah virus in patients was confirmed from RT-PCR tests conducted at the Manipal Institute of Virology and the National Virology Institute, Pune. It is interesting to note that the distance from Kerala to the known "Nipah belt" in western/northwestern Bangladesh and the bordering areas of west Bengal is ~2,600 km (1600 miles).

As the incubation period of Nipah virus infection varies from 4 to 14 days, it was difficult to definitively determine who was the true "index case" and how was the infection acquired. Although more studies are required to prove or disprove that all the human cases are related and resulted from a single spillover event, early genetic analysis seems to indicate that the outbreak was caused by a virus

closely related to the Nipah virus-BD strain. There were 19 confirmed cases with 17 deaths giving a presumptive mortality rate of ~90%. To fight the outbreak, M 102.4-a human monoclonal antibody for which clinical trials are still going on—was imported from Australia.

Though the first set of samples did not detect the virus in bats, later tests proved that fruit bats in the area were the source of the virus. At least 31 species of bats have been documented in Kerala (including 5 species of fruit bats). The bats tested so far are insectivorous bats. A fruit bat colony 4-5 km from the site of the outbreak was yet to be tested.[17]

Longitudinal studies of Hendra virus in Australia revealed that the viral load in the bat population could go through short periods of "spikes". As the timing of the assumed initial spillover event could not be conclusively determined, it is also possible that the viral load in the bat population has dropped recently, leading to negative findings. There is a vast literature showing that bats are the natural reservoirs for henipaviruses.[14]

ZIKA virus disease

The epidemic history of Zika virus began in 2007, with its emergence in Yap Island in the western Pacific, followed in 2013–14 by a larger epidemic in French Polynesia, south pacific, where the first severe complications and non-vectorborne transmission of the virus were reported. Zika virus emerged in Brazil in 2015 and was declared a national public health emergency after local researchers and physicians reported an increase in microcephaly cases.[20]

Zika virus, a member of the family Flaviviridae and genus flavivirus, was first isolated in 1947 from a sentinel monkey in the Zika forest in Uganda, east Africa. Subsequent epidemiological studies suggested that Zika virus had a broad geographical distribution in sub-Saharan Africa and southeast Asia. Silent transmission in the absence of severe disease and large outbreaks allowed Zika virus infection to go undetected while spreading throughout Africa and Asia, with fewer than 20 human infections confirmed in 60 years. The virus strains that emerged in the Pacific, Americas, Africa (Cape Verde), and southeast Asia (Singapore) were all from the Asian lineage.[20,21]

Zika virus infects human embryonic cortical neural progenitor cells, inducing cell death and providing evidence that human neurons are susceptible to the virus. The virus seems to mainly target neuronal progenitors in the developing brain and, in rare instances, some areas of the adult brain. Early infection is associated with proliferation arrest and an increase in neuronal progenitor death. Similar results were observed in cortical neurospheres.[20]

Vector-borne Zika

Zika virus is part of the mosquito-borne group of flaviviruses that are mainly transmitted in the urban environment by aedes (subgenus stegomyia) mosquitoes, which also transmit dengue virus, chikungunya and yellow fever virus. Conflicting studies suggest that mosquitoes belonging to other genera, mainly culex mosquitoes, which transmit West Nile and Japanese encephalitis viruses, might be involved in Zika virus transmission.[20]

Non-vector-borne

Sexual: Sexual transmission of Zika virus was suspected in 2008, when a scientist infected in Senegal transmitted the virus to his wife upon returning to the USA. Zika virus sexual transmission has since been documented when people living in non-endemic areas became infected after sexual intercourse with partners returning from endemic areas.

Sexual transmission is possible from both asymptomatic and symptomatic infections through genital, oral and anal intercourse and male to male, male to female, and female to male contact. [20]

Transfusion: The potential for Zika virus transfusion-transmitted infection was suspected in French Polynesia after viral RNA was detected in 2·8% of asymptomatic blood donors in 2014 and further confirmed in Puerto Rico in 2016 with 1·1% of blood donors identified as viraemic. In 2017, Zika virus RNA-positive asymptomatic blood donors were detected in Florida and Texas. Transfusion-transmitted infection was confirmed in Brazil in 2016. [20]

Materno-fetal: Perinatal transmission of Zika virus was first reported during the French Polynesian outbreak in 2013. Intrauterine transmission was subsequently confirmed during the Brazilian outbreak. Viral RNA was detected in the amniotic fluid of pregnant women suffering from symptoms compatible with Zika virus infection and later in fetal brains and products of miscarriages, supporting materno–fetal transmission of the virus. [20]

Contact with infected body fluids: Non-sexual direct person to person transmission has been reported only once through contact with body fluids of a highly viraemic, severely ill patient, but this mode of transmission remains to be confirmed. [20]

The clinical presentation of uncomplicated Zika virus infection has been extensively described. Because of its non-specific nature, infection is often not detected, or is misdiagnosed. The percentage of asymptomatic infections has been reported to be around 80%.[20]

Laboratory diagnosis

In the absence of an antigenic detection test, acute phase diagnosis relies on molecular detection of Zika virus RNA. Blood and urine are the samples of choice. The virus can be detected only briefly in plasma or serum during acute illness. Compared with serum, urine was reported to increase the detection rate of viral RNA within the first week after symptom onset and expand the window of detection, as Zika virus RNA was detectable up to 39 days after exposure. However, discrepant results were found in Puerto Rico, with a lower sensitivity of urine than blood. In blood, Zika virus RNA has been reported up to 107 days after symptom onset in pregnant women and up to 60 days after birth in a virus-infected neonate. Zika virus RNA can be detected for an increased duration in whole blood compared to serum, therefore whole blood testing should be considered for both men and women, especially for diagnosis of Zika infection in pregnant women living in or returning from endemic areas. As the timing of infection is difficult to establish, a negative RT-PCR does not exclude infection. [20]

Serology relies on detection of specific IgM by ELISA, which detects IgM antibodies as early as 4-5 days and up to 12 weeks or more after symptom onset. All positive or inconclusive IgM ELISA results should be confirmed by a plaque reduction neutralisation test (PRNT), a technique only available in few laboratories. Zika virus infection might also be responsible for false positive dengue virus serology. Serology is difficult to interpret in endemic areas and in returning travellers with a previous history of flavivirus infection, as most cases are secondary flavivirus infections. [20]

For Zika virus infection diagnosis, RT-PCR should be performed, and serum should be tested for IgM. In pregnant women infected with the virus, both RT-PCR, on serum and whole blood, and serology should be considered at any time; however, laboratory confirmation of fetal infection during pregnancy is challenging. Detection of Zika virus RNA in blood, urine and amniotic fluid can be negative or transient, despite proven fetal infection. Conversely, the virus can be detected in pregnant mothers' amniotic fluid without fetal abnormalities. Sensitivity, specificity and negative and positive predictive values of detection of Zika virus RNA in amniotic fluids are unknown, challenging maternal counselling. [20]

For infants with possible congenital Zika virus infection, RT-PCR should be performed within the first 2 days of birth on both serum and urine, and IgM ELISA should be performed on serum. Molecular and serology diagnosis tests are commercially available. [20]

A potential link between maternal Zika virus infection and a congenital syndrome was identified in October, 2015 in Brazil, when neurologists and physicians in the state of Pernambuco observed an increase in microcephaly cases. The Brazilian Ministry of Health declared a national health emergency in November, 2015. In February, 2016, this microcephaly epidemic was declared a public health emergency of international concern by WHO.[20] The temporal association between the Zika virus outbreak and severe congenital CNS malformations was also reported in a retrospective analysis. Analysis of the Zika virus and microcephaly epidemics in French Polynesia, Brazil Recife and in returning travellers in the USA suggested that the risk of fetal brain anomalies was greatest during the first trimester.[20]

Detection of viral RNA in the amniotic fluid, placenta, brain tissue of fetuses and infants with microcephaly and the high rates of microcephaly among children born to mothers with proven acute Zika virus infection during pregnancy, provided strong evidence linking CNS anomalies to maternal infection. By use of Shepard's criteria for the assessment of potential teratogens, it was concluded that a causal relationship existed between prenatal infection with Zika virus and serious brain anomalies. The clinical presentation of Zika virus infection is similar in pregnant and non-pregnant women and congenital infection is possible even in asymptomatic women. The prognosis and adequate management of virus-exposed fetuses remains to be established and should include close ultrasound monitoring, amniocentesis, and fetal blood analysis.[20] As of March, 2017, the WHO registered 2656 congenital syndromes associated with Zika virus infections in 31 countries.[21]

Complications in adults

Guillain-Barré syndrome was the first reported severe complication of Zika virus infection in adults. The link between Zika virus and Guillain-Barré syndrome was confirmed by a case-control study conducted in French Polynesia. The pathogenesis of Zika virus-associated Guillain-Barré syndrome is still unknown: direct neuropathogenic mechanisms, hyperacute immune response, immune disregulation and molecular mimicry against nervous antigens are all hypotheses.[21,22]

Vaccines and drugs against Zika virus

Vaccine development has been well supported by international funding agencies. A DNA vaccine has entered phase 1 clinical trials and there are more than 40 vaccine candidates in the pipeline, some of which are being fast tracked for licensure.[23]

Using large screening strategies, several compounds have been found to have in-vitro activity against Zika virus, but there are no antiviral drugs that have shown activity against the virus in vivo.[21]

Knowledge gaps

Although important advances have been made since Zika virus emerged in the Pacific, gaps remain in the knowledge of the epidemiology, virology, and biology of infections.[21,22] WHO declared Zika virus a public health emergency of international concern in February, 2016, subsequently declaring the virus an ongoing challenge requiring intense action, but no longer a public health emergency of international concern, in November, 2016. Virus transmission has been decreasing in Latin America and the Caribbean over the past months because of the seasonality of arbovirus outbreaks.[21]

Points to Remember

- ***Many emerging diseases arise when infectious agents in animals are passed to humans (referred to as zoonoses).***
- ***Ebola viruses are highly contagious. The infected patient sheds infectious viruses in all body secretions. The main way to prevent is to avoid travel to areas where it is endemic.***
- ***MERS - initially, the illness resembles influenza often progresses to dyspnea, hypoxia and RDS.***
- ***Nipah virus infects a wide range of animals, causes severe disease and death in people.***
- ***Zika virus infects human embryonic cortical neural progenitor cells, inducing cell death and providing evidence that human neurons are susceptible to the virus.***

References

1. World Health Organization, Regional Office for South-East Asia. Combating emerging infectious diseases in the South-East Asia Region. New Delhi: WHO-SEARO, 2005.
2. Morens DM, Fauci AS (2013) Emerging Infectious Diseases: Threats to Human Health and Global Stability. PLoS Pathog 9(7): e1003467. https://doi.org/10.1371/journal.ppat.1003467
3. Emerging Infectious Diseases. https://www.bcm.edu Emerging Infections and Biodefense. Accessed on 4th July, 2019.
4. 2018 Annual review of diseases prioritized under the Research and Development Blueprint Informal consultation. http://www.who.int/csr/research-and-development/documents/prioritizing_diseases_progress/en/. Accessed on 4th July, 2019.
5. What is ebola virus disease –History of ebola virus disease in humans-CDC. https://www.cdc.gov/vhf/ebola/about.html. Accessed on 17th June, 2019.
6. Davis PK, Ebola Hemorrhagic Fever (Ebola Virus Disease), Medicine net. Jerry R (Medical Editor) Balentine. https://www.medicinenet.com/ebola_hemorrhagic_fever_ebola_hf/article.htm. Accessed on 19th June, 2019.
7. https://www.who.int/news-room/fact-sheets/detail/ebola-virus-disease. Accessed on 19th June, 2019.
8. https://www.webmd.com/a-to-z-guides/ebola-fever-virus-infection Article on –what is ebola virus disease-Prevention,Vaccine,Treatment. Accessed on 21st June, 2019.
9. Henao-Restrepo AM, Camacho A, Longini IM, Watson CH, Edmunds WJ, Egger M, et al. Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open label, cluster-randomised trial (Ebola Ca Suffit!). The Lancet. 2017;389:505-518.
10. http://apps.who.int/mediacentre/factsheets/mers-cov/en/index.html Middle East respiratory syndrome coronavirus (MERS-CoV).
11. https://www.who.int/features/qa/mers-cov/en/. Middle East respiratory syndrome coronavirus (MERS-CoV). Accessed on 21st June, 2019.
12. https://www.cdc.gov/coronavirus/mers/index.html-Middle East Respiratory Syndrome (MERS). Accessed on 21st June, 2019.
13. http://www.searo.who.int/entity/emerging_diseases/links/CDS_Nipah_Virus.pdf?ua=1-Nipah Virus Infection. Accessed on 21st June, 2019. https://doi.org/10.1128/JCM.01875-17.
14. Ang BSP, Lim TCC, Wang L. 2018. Nipah virus infection. J Clin Microbiol 56:e01875-17.
15. https://gvn.org/update-on-the-nipah-virus-outbreak-in-kerala-india/-UPDATE ON THE NIPAH VIRUS OUTBREAK IN KERALA, INDIA. Accessed on 21st June, 2019.
16. https://www.who.int/news-room/fact-sheets/detail/nipah-virus-World. Health Organisation-Nipah virus. Accessed on 21st June, 2019.
17. https://www.cdc.gov/vhf/nipah/pdf/factsheet.pdf. National Center for Emerging and Zoonotic Infectious Diseases. Division of High-Consequence Pathogens and Pathology (DHCPP)- Nipah Virus (NiV). Accessed on 21st June, 2019.

18. http://www.searo.who.int/india/topics/emergencies/ministry-of-health-and-family-welfare-press-release-2 june 2018.pdf-Ministry of Health and Family Welfare-public health measures for Nipah Virus disease. Accessed on 21st June, 2019.
19. http://kkaggarwal.com/Editorial/west-nile-virus-another-impending-outbreak-in-india/-West Nile virus: Another impending outbreak in India?- Accessed on 21st June, 2019.
20. Baud D, Gubler DJ, Schaub B, Lanteri MC, Musso D. An update on Zika virus infection. Lancet 2017; 390: 2099–2109 Published Online 21st June, 2017.
21. https://www.who.int/news-room/fact-sheets/detail/zika-virus. Accessed on 15th March, 2019.
22. www.cdc.gov/zika/CS289371-C/ August 21, 2018. Accessed on 21st June, 2019.
23. https://rarediseases.info.nih.gov/diseases/12894/zika-virus-infection-National center for advancing translational sciences-Genetic and rare disease information centre (GARD)- Zika virus infection. Accessed on 21st June, 2019.

CLIPPINGS

Sodium and potassium excretion predict increased depression in urban adolescents.

Using urinary biomarkers as objective indicators of sodium and potassium intake, the present results provide preliminary evidence supporting the importance of these two dietary factors in the development of adolescent depression. This study examined the prospective role of urinary sodium and potassium excretion in depressive symptoms among urban, low income adolescents, and whether these relationships vary by gender. A total of 84 urban adolescents (mean age 13.36 years; 50% male; 95% African American) self reported on their depressive symptoms at baseline and 1.5 years later. At baseline, the youth also completed a 12 h (overnight) urine collection at home which was used to measure sodium and potassium excretion. After adjusting for baseline depressive symptoms, age, BMI percentile, and pubertal development, greater sodium excretion and lower potassium excretion predicted more severe depressive symptoms at follow up, with no significant gender differences. The results suggest that consumption of foods high in sodium and low in potassium contributes to the development of depressive symptoms in early adolescence, and that diet is a modifiable risk factor for adolescent depression. Interventions focusing on diet may improve mental health in urban adolescents. Replication of these findings using larger cohorts and multiple urine samples in future studies will be important. Although more research is needed to identify specific nutrients that contribute to depression and the underlying mechanisms of these effects, these results suggest that reducing the consumption of sodium rich foods, and increasing the consumption of potassium rich foods (e.g., fruits, vegetables, and whole grains) may help reduce the prevalence of depression in adolescents and its burden on public health. The results also point to the utility of using urinary biomarkers in future studies of dietary factors in health outcomes.

Mrug S, Orihuela C, Mrug M, Sanders PW. Sodium and potassium excretion predict increased depression in urban adolescents. Physiol rep 2019; 7(16):e1421.

Accuracy comparison between age-adapted SOFA and SIRS in predicting in-hospital mortality of infected children at China's PICU.

In this retrospective and observational cohort study, researchers included children admitted for infection to China's pediatric intensive care unit (PICU) between 2009 and 2017. Validation for the accuracy of age-adapted sequential organ failure assessment (SOFA) and systemic inflammatory response syndrome (SIRS) in predicting the poor prognosis among these individuals was analysed by the authors. Overall 1,831 children admitted to PICU because of infection were included. The study concluded the following. The observed accuracy of age-adapted SOFA score of $\geq$ 2 was more than that of SIRS criteria in predicting in-hospital mortality of PICU-admitted children. Also, the former yielded a higher sensitivity in identifying children with severe infection.

Wu Z, Liang Y, Li Z, Liu G, Zheng J, Zuo Y, et al. Accuracy comparison between age-adapted SOFA and SIRS in predicting in-hospital mortality of infected children at China's PICU. Shock 2019; 52(3):347-352.

INFECTIOUS DISEASES - II

SCRUB TYPHUS: THE RE-EMERGING INFECTION

*Atul Kulkarni
**Ashutosh V Yajurvedi

Abstract: *Scrub typhus is an important re-emerging infection caused by the Orientia tsutsugamushi transmitted by the bite of trombiculid mite. The larval stage of the mite (Chigger) can also transmit infection. The clinical manifestation is a triad of fever, myalgia and headache and the spectrum can range from a mild disease to multiorgan dysfunction and death. Eschar is pathognomonic of scrub typhus. Even though difficult to diagnose in early phases, delayed diagnosis is synonymous with complication and death. Doxycycline is the drug of choice which causes rapid defervescence of fever. Prevention can be achieved by avoidance of mite bite.*

Keywords: *Scrub typhus, Doxycycline, Chigger, Eschar.*

Scrub typhus is one of the oldest known mite borne acute febrile illnesses caused by Orientia (Previously known as rickettsia) tsutsugamushi. Literature about scrub typhus which comes from China dates back to 3rd century.[1] World war II was the period during when the understanding of scrub typhus greatly increased because of thousands of cases and deaths in Asia-pacific region.[2]

Epidemiology

Russia, Afghanistan, Pakistan, India, China, Tibet, Japan, Korea, Indonesia, Taiwan, Sri Lanka and Northern Australia are endemic to scrub typhus and forms the famous tsutsugamushi triangle.[3,4] It is said that about 3% of population in this triangle are having scrub typhus at any given moment. India being a part of this triangle, is endemic to scrub typhus. The name scrub was given to disease due to the residence of vector in typical terrain between woods and clearings. The disease is now increasingly seen in urban areas, one of the reasons being increasing ecotourism in these endemic areas.

Etiology

Scrub typhus is caused by Orientia tsutsugamushi. It is a Gram negative coccobacillus which has antigenically different features from that of typhus group rickettsia. O. tsutsugamushi has many features similar to other rickettsia while some are different. The characteristic similarity to rickettsia is that it cannot grow in cell free media. The unique feature of O. tsutsugamushi is that is has trilaminar outer membrane. Budding is the process by which the organism leaves the host cells and new cells phagocytose the organism while it is still covered in host cell membrane. To date, there have been more than 20 antigenically distinct strains reported, including the initially characterized prototypic strains Karp, Gilliam and Kato.[2] The infection with one strain does not give protective immunity from reinfection with other strains.

Vectors: Larval trombiculid mites of the genus Leptotrombidium are both reservoir as well as vector of scrub typhus. These larval mites are also known as chiggers. Through transovarian transmission chiggers maintain infection. Out of sixty different species of trombiculids, eight are implicated in the causation of scrub typhus. These mites are usually found in the geographically sharply outlined areas at woods and clearings.

Because of long incubation period and greater ease of transportation, tourist visiting endemic area may carry infection to countries where it is not usually seen making the clinicians to miss the diagnosis due to relative unfamiliarity of the disease.

Pathogenesis/pathophysiology[5]

Vascular endothelial cells of small and medium sized vessels are the typical target site of scrub typhus. Rickettsial viability and effector function of the host cell cytoskeletal actin are the two prerequisites for the entry of rickettsia into endothelial cells. Rickettsia induce phagocytosis in host cells for its entry into cells. After internalization, rickettsia needs to be in cytosol of the host cell not only for growth due to the availability of nutrients, adenosine triphosphate, amino acids and nucleotides but also for

* Associate Professor,
Ashwini Rural Medical College, Solapur
** Consultant Pediatrician,
Yajurvedi Hospital, Solapur
email: dratulkulkarni@rediffmail.com

avoiding the formation of phagolysosomal fusion and eventual death of organism. Because of the surface protein, host actin polymerization occurs which pushes the organism to cell surface. Later there is bending of the cell membrane outwards forming budding which then releases organism causing destruction of the cells. Organism later invades other cells. The pathophysiological effect of this is vasculitis, increased vascular permeability, hypoalbuminemia, reduced oncotic pressure with subsequent edema and hypotension. Vascular endothelial injury leads to consumption of platelets leading to thrombocytopenia. Hyponatremia is due to renal loss, fluid shift and cellular exchange of sodium for potassium.

The exact mechanism of host cell damage is not certain but it is speculated that free radical, phospholipase and protease cause cellular damage. The characteristic pathological effect produced by rickettsia is microvasculitis within various affected organs. This is characteristically seen in brain, cardiac and skeletal muscles, kidneys, liver and lungs producing clinical manifestations of scrub typhus.

Clinical manifestation

It is the triad of fever, headache and myalgia. The incubation period is 7-10 days (Range 6-19 days) after the bite of chigger. The clinical manifestations vary greatly ranging from mild clinically inapparent disease to a highly fatal disease with multiorgan dysfunction. The data from World War II and preantibiotic era shows that the severity of the disease is strain dependent. There is linear relationship between the level of rickettsial DNA in blood sample taken at admission and mortality.[6]

Fever is usually abrupt in onset and is associated with chills. Fever usually follows prodromal symptoms like anorexia and malaise and lasts longer in untreated patients. Eschar is pathognomonic of scrub typhus but the frequency of finding one is variable to the extent of 50%-80%.[7] If not looked carefully, clinician can easily miss the eschar. It is the initial site of attachment of chigger which looks like a papule initially and later develops to have central necrosis before finally presenting the characteristic black crusted lesion. It is painless. The common sites are inguinal folds, buttocks, axillae, below the breast, head and neck region (Fig.1). There is associated regional lymphadenopathy. Eschar should be actively searched if regional lymphadenopathy is found at examination. About 40%-50% of the cases develop rash on day 5 to day 8. Rash is typically macular or maculopapular and is nonitchy. Distribution is centripetal starting from abdomen and spreading all over. Face is also commonly involved. The rash can be petechial on rare occasion.[8]

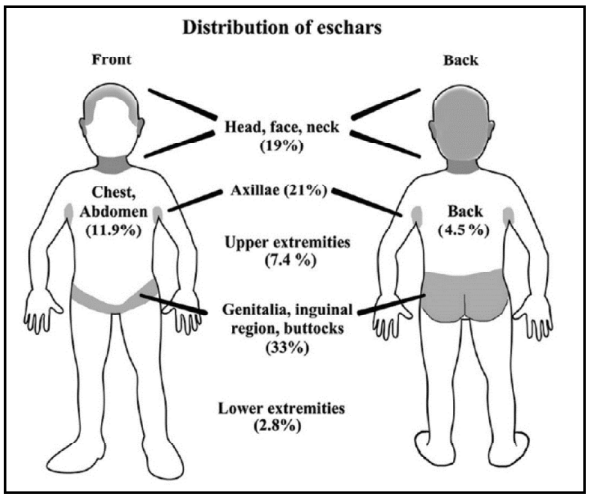


Fig.1. Sites of eschar in scrub typhus

Other systems can also be involved. About 20-25% of patients may have GI symptoms in the form of nausea, vomiting and/or diarrhoea. There can be mucosal ulceration or actively bleeding ulcer which correlates with the severity as well as occurrence of cutaneous lesions.[9] Hepatic involvement in a form of transaminitis is seen. Acute kidney injury can also be seen. There can be involvement of respiratory system leading to cough with occasional cases presenting with acute respiratory distress syndrome (ARDS). Some may have bilateral reticular opacities on x-ray chest. Relative bradycardia is also a feature of scrub typhus. Cardiac involvement leads to myocarditis. Pericardial effusion has been seen in autopsied patients but clinical effusion is an unusual finding.

Table I. Complications of scrub infection

System	Complications
CVS	Myocarditis CCF
CNS	Encephalitis Hearing defects Vasculitic infarcts
Liver	Hepatitis Hepatic failure
Respiratory	Pneumonia ARDS Pulmonary edema
Renal	Acute kidney injury
Skin	Vasculitis Gangrene
GIT	Mucosal ulceration GI bleed
Hematological	Thrombocytopenia DIC

Vasculitis of CNS vessels can lead to meningoencephalitis. Acute hearing loss and tinnitus unrelated to encephalitis has been described in scrub typhus.[10] Complications have been summarized in Table I.

Cases can be divided as suspected, probable and confirmed.[11] A suspected case is one which is having a compatible clinical scenario (Box 1) in suggestive epidemiological setting (Box 2), in the absence of definitive alternate diagnosis. If the suspected case has eschar or rapid deferevesence of fever within 48 hours of starting anti-rickettsial drug, or suggestive laboratory features (Box 3), or Weil Felix test showing agglutination with OX K with titre above 1:80, it should be considered as a probable case. Demonstration of rickettsial DNA in whole blood or tissue samples or four-fold rise in antibody titres on acute and convalescent sera detected by immunofluorescence assay (IFA) or immunoperoxidase assay (IPA) in suspected case makes it a confirmed case of scrub typhus. As PCR and IFA are scarcely available in India, properly performed paired serological tests like ELISA have high positive predictive value.

Differential diagnosis

Rickettsial fever can mimic a great number of febrile illnesses. Most important of these are meningococcemia, measles and enteroviral exanthems. Other diseases in the differential diagnosis are typhoid fever, secondary syphilis, leptospirosis, toxic shock syndrome, scarlet fever, rubella, Kawasaki disease, parvo-viral infection, idiopathic thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome, Henoch-Schoenlein purpura, aseptic meningitis, hepatitis, dengue fever, infectious mononucleosis, drug reactions, malaria, tularemia, anthrax and other causes of pyrexia of unknown origin.[12]

Diagnosis[11,13]

Rickettsial infections are difficult to diagnose early in the course of the illness due to lack of specific and sensitive test in that period. High index of suspicion is the most important tool for those clinicians working in the endemic region. The complete blood count can be normal or show leucopenia with shift to left in the early phases while there will be leucocytosis later. Other findings on complete blood picture are anemia and thrombocytopenia. Markers of inflammation like ESR and CRP are elevated. The other nonspecific findings are hyponatremia, hypoproteinemia and high transaminases. CSF analysis is usually required in children with signs of meningoencephalitis. It shows pleocytosis (10-300 cells/ microL) with high albumin (200mg/dL).

Box 1. Compatible clinical scenario

One or more of the following:

- Undifferentiated fever of more than 5 days
- Sepsis of unclear etiology
- Fever with rash
- Fever with edema
- Dengue-like disease
- Fever with headache and myalgia
- Fever with hepatosplenomegaly and / or lymphadenopathy
- Aseptic meningitis/meningoencephalitis /acute encephalitic syndrome
- Fever with cough and pulmonary infiltrates or community acquired pneumonia
- Fever with acute kidney injury
- Fever with acute gastrointestinal or hepatic involvement

Box 2. Suggestive epidemiological features

One or more of the following within 14 days of illness onset:

- Mite bite
- Visit to areas which are common habitats of vectors like woodlands and clearings
- Animal sheds in proximity of homes.
- Living in or travel to areas endemic for scrub typhus.
- Occurrence of similar clinical cases simultaneously or sequentially in family members, coworkers, neighborhood or pets.

Box 3. Suggestive laboratory features

- Normal to low total leukocyte count with a shift to left in early stages and leukocytosis later on
- Thrombocytopenia
- Raised ESR and CRP
- Hyponatremia
- Hypoalbuminemia
- Elevated hepatic transaminases

All available serological tests have some inherent constraints and clinician must be cognizant of these. Weil Felix test, in spite of having low specificity and sensitivity, is an economical test and serves the purpose of diagnosis in many cases. It is a heterophile antibody test which uses the principle that rickettsia and proteus share common antigens. Agglutination with OX K and not at all with OX-2 and OX-19 clinches the diagnosis of scrub typhus. A titre of above 1:80 may suggest infection but higher titre (1:320) or rising titre has better predictive value. The problem remains unsolved as diagnosis is retrospective not helping in management. Local titres need to be defined.

Enzyme linked immunosorbent assay (ELISA): Outer membrane of O.tsutsugamushi has outer membrane protein 56-kDa. Trivalent ELISA using whole cell antigen and r56 from different strains can also be done. It is quite sensitive and specific but expensive.

IgM and IgG ELISA: ELISA techniques, particulary immunoglobulin M (IgM) capture assays are probably the most sensitive tests available for rikettsial diagnosis and the presence of IgM antibodies, indicates recent infection with Rickettsia. In cases of infection with O.tsutsugamushi, a significant IgM antibody titire is observed at the end of 1st week, whereas IgG antibodies appear at the end of 2nd week. The cut-off value is optical density of 0.5. Baseline titres need to be established keeping in view the regional variations.[13]

Table II. Summary of anti-rickettsial drugs

Name of drug	Dose, route and duration	Comments
Doxycycline	2.2 mg/kg/dose q12h per oral or IV (Max 200 mg/day) 5 to 7 days or for at least 3 days after the patient is afebrile	• Drug of choice • Rapid defervescence within 48 hours • IV formulation for sick patients
Azithromycin	10mg/kg /day q24h (max 500mg) 5 to 7 days or for at least 3 days after the patient is afebrile	• Preferred drug in pregnancy • Recommended when doxycycline resistance is present
Tetracycline	25-50 mg/kg/day div q6h oral (Max 2 g/day) 5 to 7 days or for at least 3 days until the patient is afebrile	• Rapid defervescence within 48 hours • IV formulation for sick patients
Chloramphenicol	50-100 mg/kg/day q6h (Max 3 g/day) 5 to 7 days or for at least 3 days after the patient is afebrile	• Most common alternative for tetracycline • Most common adverse effect is agranulocytosis
Clarithromycin	15mg/kg /day q12h 5 to 7 days or for at least 3 days after the patient is afebrile	
Rifampicin	10 mg/kg OD (max 300mg) 5 to 7 days or for at least 3 days after the patient is afebrile	• Doxycycline resistance cases • Shorter duration of fever with rifampicin in northern Thailand when compared with doxycycline.
Fluoroquinolones	Not recommended in pediatric age group	

Immunofluorescence assay (IFA) is supposed to be the reference standard test. But the exorbitant cost, sparse availability and technically demanding nature of the test makes it less useful for use in clinical practice. Titres start rising between 5-10 days of illness and peaks at 3-4 weeks.

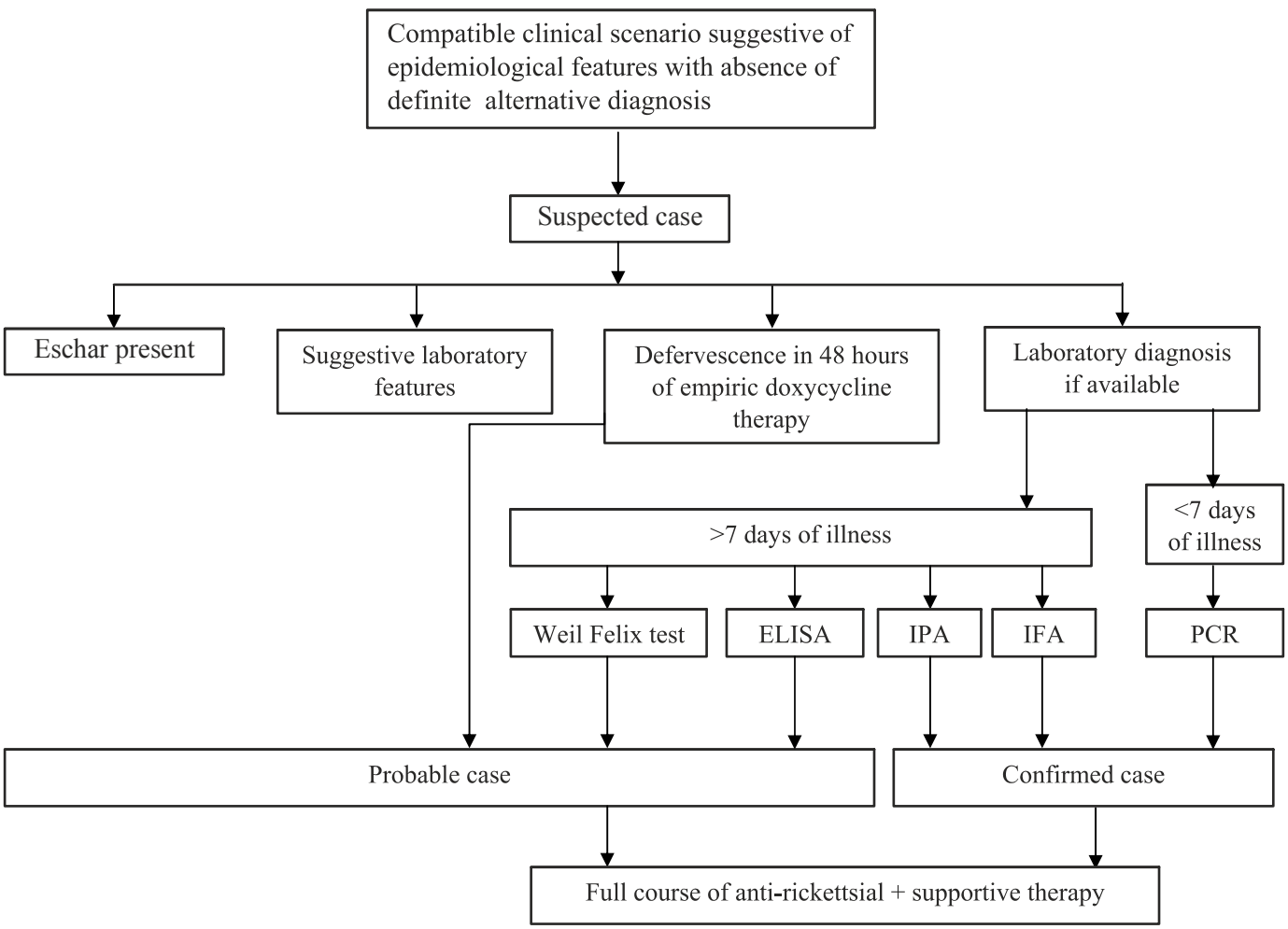
Indirect Immunoperoxidase Assay (IPA) gives result similar to that of IFA but comes with the same disadvantages.

Polymerase chain reaction (PCR) applied to blood of the patient can make a diagnosis in a good number of patients. Other samples like Eschar, CSF can also be tested using PCR for scrub typhus. PCR has good sensitivity and specificity in spite of the patient having received antibiotic therapy.

Histopathological examination of eschar shows lymphohistiocytic vasculitis which is the hallmark of scrub typhus. There are focal areas of cutaneous necrosis surrounded by a zone of vasculitis with perivascular collection of lymphocytes and macrophages. Culture of the organism is available only in selected centres due to specialized needs and rigorous quality control and safety measures.

Management[12,13]

Prompt diagnosis and initiation of treatment is essential as delayed initiation of the management is associated with the poor outcomes. Management should be started even if laboratory reports are inclusive or awaited and should not be stopped if results are negative but clinical suspicion is very high in endemic region. Commonly used drugs are doxycycline, chloramphenicol, tetracycline, azithromycin and rifampicin. Doxycycline is the time tested drug and the drug of the choice. Doxycycline is not



ELISA: Enzyme-linked Immunosorbent assay, IPA: Immunoperoxidase assay, IFA: Immunoflorescent assay, PCR: Polymerase chain reaction.

Fig.2. Management algorithm for rickettsial infections[12]

associated with tooth staining while used in pediatric population. The dosages of different antirickettsial drugs has been summarized in Table II and management algorithm in given in Fig 2.

Prognosis

Disease may be fatal without intervention and prognosis is proportional to how early the treatment was started.[14] Earlier the treatment started better the prognosis. It is also dependent on the complications associated with scrub typhus. Meningoencephalitis, myocarditis and ARDS have poorer prognosis. In general, younger age, male gender, comorbidities like diabetes, cardiovascular disease and glucose 6 phosphate dehydrogenase (G6PD) deficiency are associated with poor outcome. Oxidative stress is one of the pathways of cell injury in rickettsial infection. Those drugs that cause increase in oxidative stress will lead to poor prognosis as seen with sulphonamides.[12]

Prevention

No vaccine is available for prevention of the scrub typhus and also for the post exposure prophylaxis. Research for development of vaccines for scrub typhus during World War II lost momentum due to the development of effective and rapid acting antirickettsial agents. Chemoprophylaxis is recommended by some studies.[15] The main stay of the prevention is avoidance of the mite bite and vector control. Controlling rodents, cutting, burning or bulldozing grass with insecticide sprays are the methods of vector control while personal protection by using long sleeved faint colour cloths (for prompt detection of chiggers/mites), spraying cloths with insecticides and avoidance of going into vector infested areas may prevent tick bite.[12] Prompt detection and removal of mites is also an essential part of prevention, as it needs at least 4-6 hours of attachment before they can transmit infection.

Points to Remember

- ***Scrub typhus caused by O. tsutsugamushi is transmitted by trombiculid mites and its larva, chigger.***
- ***It is characterised by a triad of fever, headache and myalgia.***
- ***Eschar is pathognomonic of scrub typhus but the frequency of finding it is variable to the extent of 50%-80%.***
- ***Drug of choice is doxycycline.***
- ***Prevention is mainly by avoidance of bite of mite as no vaccine or post exposure prophylaxis exist.***

References

1. Browning JS, Raphael M, Klein EF, Coblenz A. Scrub typhus. Amer J Trop Med 1945; 25:481-492.
2. Kelly DJ, Richards AL, Temenak J, Strickman D, Dasch GA. The past and present threat of rickettsial diseases to military medicine and international public health. Clin Infect Dis 2002; 34(Suppl 4): S145-169.
3. Bonell A, Lubell Y, Newton PN, Crump JA, Paris DH. Estimating the burden of scrub typhus: A systematic review. PLoSNegl Trop Dis 2017; 11(9):e0005838.
4. Parmar V. Scrub typhus. In: PG Textbook of Pediatrics. New Delhi: Jaypee Brothers Medical Publishers; 2013; pp1309-1312.
5. Mansueto P, Vitale G, Cascio A, Seidita A, Pepe I, Carroccio A, et al. New Insight into Immunity and Immunopathology of Rickettsial Diseases. Clin Dev Immunol 2012; 2012:1-26.
6. Sonthayanon P, Chierakul W, Wuthiekanun V, Phimda K, Pukrittayakamee S, Day NP, et al. Association of high Orientia tsutsugamushiDNA loads with disease of greater severity in adults with scrub typhus. J Clin Microbiol 2009; 47:430-434.
7. Kulkarni A. Rickettsial infections. In: IAP textbook of infectious diseases. 1st edn. New Delhi: Jaypee Brothers Medical Publishers; 2013; pp376-385.
8. Reller ME Dumler JS. Rickettsial Infection. In: Nelson's Textbook of pediatrics. Robert M Kliegman, Bonita F Stanton, Joseph W St Geme III, Nina F. Schor (Eds), 20th edn. 1st South Asia Edition Read Elseiver India Pvt. Ltd, New Delhi 2015; pp1497-1511.
9. Kim SJ, Chung IK, Chung IS, Song DH, Park SH, Kim HS, et al. The clinical significance of upper gastrointestinal endoscopyin gastrointestinal vasculitis related to scrub typhus. Endoscopy 2000; 32:950-955.
10. Premaratna R, Chandrasena TG, Dassayake AS, Loftis AD, Dasch GA, de Silva HJ. Acute hearing loss due to scrub typhus: a forgotten complication of a re-emerging disease. Clin Infect Dis 2006; 42: e6-8.
11. La Scola B, Raoult D. Laboratory diagnosis of rickettsioses: current approaches to diagnosis of old and new rickettsial diseases. J Clin Microbiol. 1997; 35:2715-2727.
12. Rathi N, Kulkarni A, Yewale V. For Indian Academy of Pediatrics Guidelines on Rickettsial Diseases in Children Committee. IAP guidelines on rickettsial diseases in children. Indian Pediatr 2017; 54(3):223-229.
13. Rahi M, Gupte MD, Bhargava A, Varghese GM, Arora R. DHR-ICMR. Guidelines for Diagnosis and Management of Rickettsial Diseases in India. Indian J Med Res. 2015, 417-422.
14. Taylor AJ, Paris DH, Newton PN. A Systematic Review of Mortality from Untreated Scrub Typhus (Orientia tsutsugamushi). PLoSNegl Trop Dis 2015; 9: e0003971.
15. Andrew R, Bonnin JM, Williams S. Tick typhus in North Queensland. Med J Aust 1946; 2:253-258.

INFECTIOUS DISEASES - II

DENGUE FEVER - NEWER INSIGHTS

***Bhaskar Shenoy**
****Sanjay P Deshpande**

Abstract: *Dengue fever is a self-limiting febrile illness, which usually resolve spontaneously or progress to severe dengue with shock and hemodynamic compromise. Current molecular and gene studies show that NS 1 antigen and antibody dependent enhancement act in concert with complement system and chemokines leading to increased vascular permeability and subsequently multi-organ dysfunction, resulting in morbidity and mortality. Newer insights in entomology give information about the transmission of dengue from vector to host, thereby helping in preventing the disease. However, even with newer insights in prevention and diagnosis, treatment remains largely supportive and morbidity in pediatric population remains high.*

Keywords: *NS 1 antigen, Antibody dependent enhancement, Immuno-pathogenesis, Chemokines, Cytokine.*

Dengue fever caused by dengue virus is a self-limiting acute febrile illness transmitted by mosquitoes to humans. It is characterized by biphasic fever, myalgia or arthralgia, rash, leukopenia and thrombocytopenia. Dengue hemorrhagic fever (DHF) is characterized by abnormalities in hemostasis and leakage of fluid and protein from capillaries, which results in hemodynamic compromise and shock. Both are manifestations of the dengue vascular permeability syndrome with an immune-complex mediated immunopathology.[1] In 2009, the World Health Organization (WHO) defined the spectrum of this disease as, dengue, dengue with warning signs and severe dengue.

The incidence of dengue has grown dramatically around the world in recent decades. The actual numbers of dengue cases are under-reported and many cases are misclassified. One recent estimate indicates 390 million dengue infections per year [95% confidence interval (95% CI) 284-528 million], of which 96 million (67-136 million) manifest clinically (with any severity of disease).[2] Similar studies assessing the prevalence of dengue, estimated 3.9 billion people, in 128 countries, are at risk of infection with dengue viruses.[3] Data from the Ministry of Health and Family welfare, Government of India, shows 89974 cases and 144 deaths, but there are large sub-sections of under reported cases.[4]

Morphology of dengue virus

Dengue virus is an enveloped positive-sense single-stranded RNA virus that produces a spherical particle with a diameter of approximately 500A. Four clearly defined types exist (conventionally named as DEN-1, DEN-2, DEN-3 and DEN-4), as determined by plaque-reduction neutralization tests using antibodies raised by infection of monkeys or fluorescent antibody tests using monoclonal antibodies raised in mice.[5] The four types have distinctive genetic and antigenic structures separable by homotypic antibodies.[6-9] Recovery from infection by one provides lifelong immunity against that particular serotype. However, cross-immunity to the other serotypes after recovery is only partial and temporary. Subsequent infections by other serotypes increase the risk of developing severe dengue.[1]

Vector and transmission

Aedes aegypti, a daytime-biting mosquito, is the principal vector. All four virus types have been recovered from the naturally infected A. aegypti.[10] In most tropical areas, A. aegyptiis highly domesticated and breeds in water stored for drinking, washing or bathing or in any container collecting fresh water. Dengue viruses also have been recovered from naturally infected Aedes albopictus, which breeds outdoors in vegetation.[10,11] Transmission of dengue by A. aegypti may be explosive and involve as much as 70% to 80% of the population. Because A. aegypti has a limited flight range, spread of virus is mainly by movement of infected humans. Dengue viruses replicate in the gut, brain and salivary glands of infected mosquitoes without apparent harm to adult mosquitoes. Mosquitoes are

* Head, Department of Pediatrics and Division of Pediatric Infectious Diseases
** Consultant - Pediatrics and Pediatric Infectious Diseases.
Manipal Hospital, Bengaluru, Karnataka.
email: bshenoy@gmail.com

infectious for a lifetime and for as long as 70 days in experimental circumstances.Because female mosquitoes take repeated blood meals, long-lived female mosquitoes have a greater potential as vectors. A. aegypti preferentially feeds on people and hence is most abundant in and around human habitations. The mosquito breeds in clean water. Breeding sites may be provided by humans who share habitats, as in Thailand, where water is stored in and around homes in large earthenware jars. In contrast, A. aegypti is not abundant in some parts of India because only small amounts of water are brought to homes from village wells for immediate use. Water in flower vases, household offerings, ant traps, coconut husks, tin cans and rubber tyres may supply breeding sites for A. aegypti. In the tropics, outbreaks of dengue generally coincide with the monsoon season. Eggs, which resist desiccation, are deposited inside water containers above the water line. Temperature is important in controlling viral transmission. Evidence indicates that the extrinsic incubation period shortens with increasing mean temperatures; the mosquito biting rates increase with increased temperature and relative humidity.[11]

Clinical manifestations

In children, clinical manifestations of both primary and secondary dengue infections are varied. They often have leukopenia, pharyngeal injection, maculo-papular rash, petechiae, facial flush, liver enlargement and cold extremities with primary or secondary dengue infections. Published data suggests that primary infections with dengue virus types 2 and 4 are largely inapparent. By contrast, primary infections with dengue virus types 1 and 3 in children more often result in mild to moderate febrile disease, sometimes accompanied by low-grade vascular permeability. Epistaxis, petechiae and purpuric lesions are uncommon manifestations but may occur at any stage of the disease. In classic dengue fever (seen most frequently in adults), after an incubation period of 2 to 7 days, patients experience a sudden onset of fever, which rapidly rises to 39.5°C to 41.4°C (103°F”106°F) and usually is accompanied by frontal or retro-orbital headache. A transient, macular, generalized rash that blanches under pressure may be seen during the first 24 to 48 hours of fever. The pulse rate may be slow in proportion to the degree of fever. Myalgia or bone pain occurs soon after onset and increases in severity. During the second to sixth day of fever, nausea and vomiting are likely to occur. One or 2 days after defervescence, a generalized morbilliform, maculopapular rash appears, with sparing of the palms and soles. It disappears in 1 to 5 days. In some cases, edema of the palms and soles may be noted. About the time of appearance of this morbilliform rash, the body temperature, which has fallen to normal, may become elevated slightly and establish the biphasic temperature curve.[11]

Dengue vascular permeability syndrome

The dengue vascular permeability syndrome (DVPS) is the core pathophysiologic phenomenon in DHF/DSS and severe dengue. In infants and children, progression of the illness is characteristic. A relatively mild first phase (febrile phase) with an abrupt onset of fever, malaise, vomiting, headache, anorexia and cough may be followed after 2 to 5 days by acute mid epigastric abdominal pain and lassitude. In this second phase (critical phase), the patient usually has cold and clammy extremities, a warm trunk, flushed face, diaphoresis and anuria. Patients are lethargic or restless and irritable and complain of epigastric pain. Frequently, scattered petechiae appear on the forehead and extremities, spontaneous ecchymoses may develop and easy bruisability and bleeding at sites of venipuncture are common findings. Circumoral and peripheral cyanosis may occur. There is slow venous filling time. Respirations are rapid and often labored. The pulse is weak, rapid, and thready and the heart sounds are faint. Systolic pressure may remain normal or even elevated (because of compensatory sympathetic activity) and the patient appears deceptively well, retaining full consciousness.When hypotension ensues, the pulse pressure becomes narrow (<20 mm Hg) and later systolic and diastolic pressures fall rapidly.

The liver may be enlarged become palpable. Chest radiographs may show unilateral (right) or bilateral pleural effusions. Ultrasonographic evidence of plasma leakage

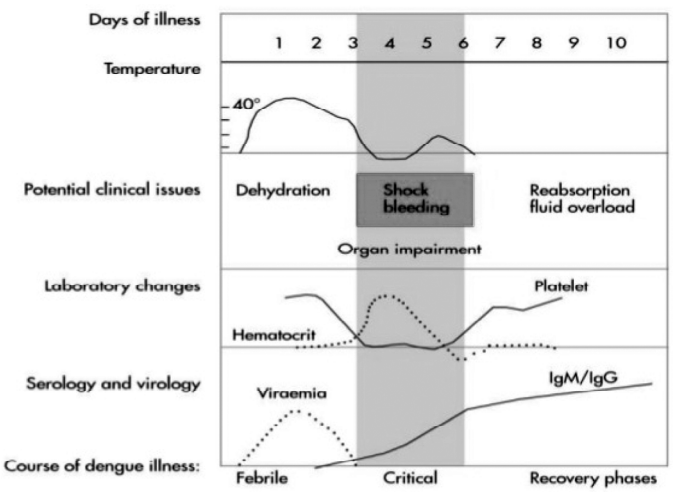


Fig.1. Course of dengue illness

(Source: WHO, 2009. Dengue: guidelines of diagnosis, treatment, prevention and control – new edition. Geneva: WHO.p25)

may be detected in some cases within 3 days after the fever onset. Other findings such as thickening of the gallbladder wall, post-vesicular edema and ascites are detected less frequently and resolve more rapidly than pleural effusions. Up to 10% of patients may have gross ecchymosis or GI bleeding. During the transition from the febrile to the critical phase, it is crucial for the clinician to be aware of warning signs of impending vascular permeability which are persistent vomiting, increasingly severe abdominal pain, rising hematocrit and falling platelet count. After a 24- or 36-hour period of crisis, convalescence is fairly rapid in children who recover. The temperature may return to normal before or during the stage of shock (Fig.1).[11]

It should be noted that DVPS occurs regularly in infants in countries where multiple dengue viruses are hyper-endemic. These babies are born to mothers with two or more lifetime dengue infections but do not occur when mothers have experienced only a single dengue infection before pregnancy. Infants, predominantly aged 5 to 10 months, experience physiologically the same dengue vascular permeability syndrome as older children, except that they are more difficult to diagnose and treat and their case-fatality rates are higher.[11] The case definition for dengue is given in Table I.

Immuno-pathogenesis

Epidemiologic, clinical and virologic studies of Dengue Hemorrhagic Fever (DHF)/ Dengue Shock Syndrome (DSS) in humans have shown a significant association between DVPS and dengue virus infection in the presence of circulating dengue antibody, whether it is passively acquired from the mother or actively acquired from previous infection. Risk for developing vascular permeability syndrome is inversely correlated with age; the youngest children are at highest intrinsic risk. In humans, circulating antibody appears to have two biologic activities namely neutralization of virus and enhancement of infection.[11] In published literature from Thailand and Vietnam, DHF/DSS developed in infants during dengue virus type 2 infection only when maternal neutralizing antibody had catabolized to low titer and infection- enhancing antibodies were left in circulation.[11] Similarly, in a prospective study of dengue virus infection in Thai children, DHF/DSS occurred in children who had

Table I. Definition for dengue

Classification	Features
Probable Dengue	The patient lives in or travels to dengue-endemic area and has a fever and two of the following: • Nausea, vomiting • Rash • Aches and pains • Positive tourniquet test • Leucopenia • Any "warning sign"
Dengue with warning signs	• Abdominal pain or tenderness • Persistent vomiting • Clinical fluid accumulation • Mucosal bleed • Lethargy, restlessness • Liver enlargement >2 cm • Laboratory increase in HCT concurrent with rapid decrease in platelet count
Severe dengue	• Severe plasma leakage • Shock (DSS) • Fluid accumulation with respiratory distress • Severe bleeding (as evaluated by clinician) • Severe organ involvement • Liver AST or ALT $\geq$1000 • CNS-impaired consciousness • Heart and other organs

circulating enhancing antibodies from a previous single dengue virus infection, but it did not occur in children whose first infection left them with low levels of cross-reactive dengue virus type 2 neutralizing antibody at the time of the second dengue virus infection.[11] Published data suggests that heterotypic protective immunity delays a clinically second severe dengue infections to at least 2 or more years after the first infection.[11] Furthermore, monkeys infected initially with dengue viruses 1, 3, or 4 and then with dengue virus 2 had higher viremia than when the same virus was inoculated into susceptible animals. A similar phenomenon was observed in monkeys given diluted human polyclonal dengue antibodies and then challenged with dengue 2 virus. This phenomenon, in vivo is described as antibody-dependent enhancement (ADE) of dengue infection, provides an explanatory hypothesis of the immune-pathogenesis of dengue in humans.[11]

Published studies by Wang, et al have discovered that patients with DHF/DSS respond to infection by producing IgG's with enhanced affinity for the activating Fc receptor IIIA due to afucosylated Fc glycans and IgG1 subclass.[12] The reactive non-neutralizing IgG (RNNIg) enriched for afucosylated IgG1 triggered platelet reduction in vivo and was a significant risk factor for thrombocytopenia and concluded that anti-DENV IgG's with enhanced affinity for FcγRIIIA could mediate ADE of dengue, which is distinct from ADE of infection. However, these assays are for research purpose and not yet commercially available, thereby putting clinical diagnosis of severe dengue as the most valuable tool.[12]

Studies have shown that nonstructural protein 1 (NS1) of the dengue viruses are viral toxins that contribute to dengue pathogenesis by mechanisms similar to those of bacterial endotoxins in the toxic shock syndrome. The NS1 activates the toll-like receptor 4 (TLR4) on primary human myeloid cells, resulting in increased production of chemokines and pro-inflammatory cytokines as a byproduct of this interaction. In both in vitro and in vivo models, it activates TLR4 on human and mouse endothelial cells, resulting in loss of endothelial integrity and increased vascular permeability. In earlier studies, NS1 was shown to activate complement by the alternative pathway and to target liver cells promoting intracellular dengue virus infection and it was detected as a complex with thrombin in acute-phase blood of dengue patients.[11] Available studies and literature suggest that the direct role and toxicity of DENV NS1 provide a single causal mechanism for the dengue vascular permeability syndrome, reconciling severe disease in infants born to dengue-immune mothers to that of older individuals experiencing a second dengue infection. It is still not clear why peak vascular permeability is delayed until defervescence rather correlating with peak NS1 blood levels observed earlier in disease. It has long been suggested that the cellular immune response targeting dengue-infected cells triggers DVPS. But the failure of cortisone to prevent DVPS argues against a direct cytopathic role for cytokines and chemokines. It has been suggested that as dengue-infected target cells are disrupted by cytotoxic T cells, a final pathogenic bolus of DENV NS1 is released.[11]

Laboratory diagnosis

Laboratory diagnosis of dengue is established directly by detection of viral components in serum or indirectly by serology. The sensitivity of each approach is influenced by the duration of the patient's illness. During the febrile phase, detection of viral nucleic acid in serum by means of reverse-transcriptase polymerase-chain reaction (RT-PCR) assay or detection of the virus expressed soluble nonstructural protein 1 (NS1) by enzyme-linked immunosorbent assay (ELISA) or the lateral-flow rapid test is sufficient for a confirmatory diagnosis. For primary infections in persons who have not been infected previously, the diagnostic sensitivity of NS1 detection in the febrile phase can exceed 90% and antigenemia may persist for several days after the resolution of fever.[11] The sensitivity of NS1 detection in the febrile phase is lower in secondary infections (60 to 80%), reflecting an anamnestic serologic response due to a previous dengue virus or related flavivirus infection. Serologic diagnosis of dengue relies on the detection of high levels of serum IgM that bind dengue virus antigens in an ELISA or a lateral-flow rapid test; IgM can be detected as early as 4 days after the onset of fever. IgM sero-conversion between paired samples is considered a confirmatory finding, whereas detection of IgM in a single specimen obtained from a patient with a clinical syndrome that is consistent with dengue is widely used to establish a presumptive diagnosis. The titer of rise in levels of IgM however does not predict severity of disease. Commercially available IgM tests with acceptable performance characteristics have recently been identified. Serologic diagnosis of dengue can be confounded if the patient has very recently been infected or vaccinated with an antigenically related flavivirus (yellow fever or Japanese encephalitis). In addition, patients with secondary infections mount rapid anamnestic antibody responses in which dengue virus–reactive IgG may predominate over IgM. In clinical settings where methods of molecular detection (e.g., RTPCR) are not available, investigation for elevated levels of dengue virus–reactive IgM or soluble NS1 in serum is a pragmatic diagnostic approach in a patient in whom dengue is suspected.[11]

Newer tools for diagnosis

During the course of dengue fever, there is a window period during which both NS1 antigen and IgM antibody may be negative and also biochemical or hematological clues pointing towards other differential diagnoses are absent too. This time frame poses a state of "Diagnostic Dilemma" where the clinicians are at a crossroads, as the outcomes of dengue fever rely on an early diagnosis and optimal fluid resuscitation. Hence, there is a need to research other biomarkers that can help differentiate dengue as a cause of febrile illness and even attempt to predict severity during this critical and narrow window period.

In a meta-analysis by Soo, et al which evaluated several studies on biomarkers and narrowed down on certain biomarkers such as IL-7, IL-8, IL-10, TGF-b and VEGFR2 that could be used as potential early laboratory biomarkers in the differentiation between dengue fever and severe dengue and to monitor the effectiveness of treatment.[13] However the hurdles of lab infrastructure for performance of these sophisticated tests and their reporting must be overcome in future research to reduce variables that affect the results and to confirm the findings.

A study carried out by Wathanee, et al in children with confirmed dengue fever evaluated the importance of serum ferritin and concluded that the use of serum ferritin as a tool to predict progression to severe dengue (level $\geq$1200 ng/ml) as early as on day four of the illness and continuing into the convalescent stage.[14] Similar data by Van de Weg Cam, et al provided evidence that ferritin can be used as a biomarker to discriminate between dengue and other febrile illnesses and findings of high levels of ferritin in patients with dengue is indicative of highly active disease resulting in immune activation and coagulation disturbances.[15]

Management

Currently, no effective antiviral agents to treat dengue infection are available and treatment remains supportive and symptomatic, with particular emphasis on careful fluid management. Patients with only dengue fever who are able to tolerate oral fluids may remain at home with instructions to return to the hospital immediately when warning signs develop. Development of any warning sign indicates the need for hospitalization and close observation, with judicious use of parenteral fluids in patients with inadequate oral intake or a rapidly increasing hematocrit. If the patient worsens and dengue shock syndrome ensues, then prompt fluid resuscitation to restore plasma volume is imperative, followed by ongoing fluid therapy to support the circulation at a level just sufficient to maintain critical organ perfusion. Blood transfusion can be lifesaving for patients with severe bleeding that compromises cardiovascular function. Platelet concentrates, fresh-frozen plasma and cryoprecipitate may also be needed depending on the coagulation profile. There is no evidence from available literature to date that prophylactic platelet transfusions are of any value in patients who do not have clinically significant bleeding, even when thrombocytopenia is profound.[11]

Newer modalities of treatment

Although the cornerstone of severe dengue is optimum fluid managementalong with adjunctive supportive treatment (blood products, inotropes, mechanical ventilation), published literature has promised some new therapeutic options. Of worthy to mention, is intravenous anti-D globulin. Published data from an RCT from Philippines in 2007 studied the response in adults and children with dengue hemorrhagic fever and concluded that beneficial effects were shown in terms of improvement of thrombocytopenia following anti-D globulin.[16] Similar RCTs from India showed that administration of anti-D globulin resulted in an increase in platelet count as well as a reduction in bleeding[17] However, both these studies had their own limitations demanding the need for further research into its therapeutic potential.

IVIG too somewhat shares a similar background story. There is only one RCT from the Philippines in 2007, which reviewed the effect of IVIG on thrombocytopenia in dengue infection and concluded that no difference exists in platelet counts were seen in the two groups.[18] Hence, at present insufficient evidence regarding the role of anti-D globulin and IVIG in the prevention or treatment of bleeding in dengue infection and there is a place for further research on these therapeutic options.[19]

Prevention is better than cure: Dengue vaccines[20]

Although there are several dengue vaccine candidates in clinical development, 2 live attenuated (recombinant) tetravalent vaccines are currently under evaluation in phase III trials.

The first licensed dengue vaccine, CYD-TDV (Dengvaxia®), is a live attenuated, recombinant tetravalent vaccine, which employs the attenuated yellow fever virus 17D strain as the replicative platform. It is licensed for use in individuals aged 9-45 years in dengue-endemic countries (Mexico, Philippines, and Brazil in December 2015 and in El Salvador, Costa Rica, Paraguay, Guatemala, Peru, Indonesia, Thailand and Singapore in 2016). The vaccination schedule consists of 3 injections of

0.5 ml, administered subcutaneously at 6-month intervals. Pooled efficacies in trial population aged 2-16 years vaccine efficacy against symptomatic virologically confirmed dengue of any severity was 60.3% (95% CI: 55.7-64.5). Vaccine efficacy was higher in the older age groups, with 65.6% (95% CI: 60.7-69.9) for those aged 9-16 years, versus 44.6% (95% CI: 31.6-55.0) for those younger than 2-8 years.

Current recommendations by WHO[20]

The live attenuated dengue vaccine CYD-TDV has been shown in clinical trials to be efficacious and safe in dengue seropositive individuals. Virus infection in the past carries an increased risk of severe dengue in (dengue) sero-negative individuals and countries should consider introduction of the vaccine only if the minimization of risk among seronegative population can be assured and recommends that countries considering CYD-TDV as a part of their dengue control programme, mandating a pre-vaccination screening tool forevidence of a past dengue infection (based on an antibody test, or on a documented laboratory confirmed dengue infection in the past). If a pre-vaccination screening is not possible, vaccination without individual screening can be considered in areas with recent documentation of sero-prevalence rates of at least 80% by age 9 years.

Conclusion

Scientific knowledge of immune-pathogenesis of dengue fever and its complications has led to the understanding of the complex interplay between host immunity and the virus morphology. Despite the progress made in understanding the molecular dynamics, treatment still remains largely supportive. Vaccines would play a crucial role in preventing dengue after carefully weighing cost and benefit ratio, as a part of the immunization program in the near future.

Points to Remember

- ***Dengue is an acute febrile illness caused by 4 types of dengue viruses.***
- ***Host immunity and prior dengue infection influence adverse outcomes.***
- ***Supportive treatment is still the cornerstone of dengue management.***

References

1. Halstead SB. Pathogenesis of Dengue: Dawn of a New Era. F1000Res. 2015; 4. pii: F1000 Faculty Rev-1353. Accessed on 5th July, 2019.
2. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, et.al. The global distribution and burden of dengue. Nature 2013; 496(7446):504-507.
3. Brady OJ, Gething PW, Bhatt S, Messina JP, Brownstein JS, Hoen AG, et al. Refining the global spatial limits of dengue virus transmission by evidence-based consensus. PLoSNegl Trop Dis. 2012; 6:e1760. doi:10.1371/journal.pntd.0001760. Accessed on 15th June, 2019.
4. https://nvbdcp.gov.in/index4.php? lang=1&level=0&linkid=431&lid=3715. Accessed on 25th November 2018. Accessed on 20th June, 2019.
5. Wang E, Ni H, Xu R, Barrett AD, Watowich SJ, Gubler DJ, et al. Evolutionary relationships of endemic/epidemic and sylvatic dengue viruses. J Virol 2000; 74(7):3227-3234
6. Russell PK, Nisalak A, Sukhavachana P, Vivona S. A plaque reduction test for dengue virus neutralization antibodies. J Immunol 1967; 99(2):285-290.
7. DeMadrid AT, Porterfield JS. The flaviviruses (group B arboviruses): A crossneutralization study. J Gen Virol 1974; 23:91-96.
8. He RT, Innis BL, Nisalak A, Usawattanakul W, Wang S, Kalayanarooj S, et al. Antibodies that block virus attachment to vero cells are a major component of the human neutralizing antibody response against dengue virus type 2. J Med Virol 1995; 45:451-461.
9. Katzelnick LC, Fonville JM, Gromowski GD, Bustos Arriaga J, Green A, James SL, et al. Dengue viruses cluster antigenically but not as discrete serotypes. Science 2015; 349(6254): 1338-1343.
10. Halstead SB. Mosquito-borne haemorrhagic fevers of South and South-East Asia. Bull World Health Organ 1966; 35:3-15.
11. Halstead SB. Dengue, Dengue Hemorrhagic Fever, and Severe Dengue. In: Halstead SB. Feigin And Cherry's Textbook Of Pediatric Infectious Diseases, 19th edn, Philadelphia: Elsevier 2019; pp1661-1671.
12. Wang TT, Sewatanon J, Memoli MJ, Wrammert J, Bournazos S, Bhaumik SK, et al. IgG antibodies to dengue enhanced for FcãRIIIA binding determine disease severity. Science 2017; 355(6323):395–398. doi:10.1126/science.aai8128
13. Soo KM, Khalid B, Ching SM, Tham CL, Basir R, Chee HY. Meta-analysis of biomarkers for severe dengue infections. Peer J 2017; 5:e3589. doi: 10.7717/peerj.3589. eCollection 2017.
14. Chaiyaratana W, Chuansumrit A, Atamasirikul K, Tangnararatchakit K. Serum ferritin levels in children with dengue infection. Southeast Asian J Trop Med Public Health. 2008; 39(5):832-836.
15. Van de Weg CAM, Huits RMHG, Pannuti CS, Brouns RM, van den Berg RWA, et al. (2014) Hyperferritinaemia in Dengue Virus Infected Patients Is Associated with Immune

Activation and Coagulation Disturbances. PLoSNegl Trop Dis 8(10): e3214. doi:10.1371/journal.pntd.0003214. Accessed on 12th July, 2019.

16. de Castro RA1, de Castro JA, Barez MY, Frias MV, Dixit J, Genereux M. Thrombocytopenia associated with dengue hemorrhagic fever responds to intravenous administration of anti-D (RH0-D) immune globulin. Am J Trop Med Hyg 2007; 76(4):737-742.
17. Pannu AK, Bhalla A, Singhal M, Suri V, Shafiq N, Varma S. Safety and efficacy of a single dose of anti-D (WinRho®) in severe thrombocytopenia secondary to dengue virus infection. Indian J Crit Care Med 2017; 21(2):80-84.
18. Dimaano EM, Saito M, Honda S, Miranda EA, Alonzo MT, Valerio MD, et al. Lack of efficacy of high-dose intravenous immunoglobulin treatment of severe thrombocytopenia in patients with secondary dengue virus infection. Am J Trop Med Hyg 2007; 77(6):1135-1138.
19. Senaka Rajapakse, Nipun Lakshitha de Silva, Praveen Weeratunga, Chaturaka Rodrigo, Sumadhya Deepika Fernando, Prophylactic and therapeutic interventions for bleeding in dengue: a systematic review, Transactions of The Royal Society of Tropical Medicine and Hygiene, Volume 111, Issue 10, October 2017, Pages 433–439, https://doi.org/10.1093/trstmh/trx079 Accessed on 17th July, 2019.
20. Dengue vaccine: WHO position paper – September 2018. https://www.ncbi.nlm.nih.gov/pubmed/30424888. Accessed on 17th July, 2019.

CLIPPINGS

Serum miR-204 is an early biomarker of type 1 diabetes-associated pancreatic beta-cell loss. American Journal of Physiology-Endocrinology and Metabolism.

Beta cells in the pancreas produce insulin. Beta cell death is a key feature of Type 1 diabetes, and that loss starts long before diagnosis. However, there has been no straightforward way to measure that early loss. Researchers have now identified an early biomarker of Type 1 diabetes associated beta-cell loss in humans-microRNA-204, or miR-204. Shalev and colleagues report that miR-204, which is highly enriched in human beta cells, is released by dying beta cells. After that release, it becomes detectable in circulating blood. Measurements using human blood samples showed that serum miR-204 was elevated in children and adults with early Type 1 diabetes, and in people with autoantibodies who are at risk for Type 1 diabetes, but it was not elevated in Type 2 diabetes or another autoimmune disease. Furthermore, serum miR-204 levels were inversely correlated with remaining beta-cell function in recent-onset Type 1 diabetes. The authors conclude the following from the study. Having a non-invasive, straightforward method sensitive enough to detect early beta-cell loss—especially prior to the diagnosis of Type 1 diabetes—is critical in order to allow for any therapeutic intervention to be started as early as possible in the disease process and ideally before the majority of beta cells has been destroyed.

Xu G, Thielen LA, Chen J, Grayson TB, Grimes T, Bridges Jr SL, et al. Serum miR-204 is an early biomarker of type 1 diabetes-associated pancreatic beta-cell loss. American Journal of Physiology-Endocrinology and Metabolism. 2019 Aug 13. DOI: 10.1152/ajpendo.00122.2019.

NEWS AND NOTES

50TH ANNUAL CONFERENCE OF INDIA SOCIETY OF NEPHROLOGY

Date: 21st – 24th November, 2019

Conference Secretariat

Deparment of Nephrology, PGIMER, Chandigarh

Ph: 91-172-2756735, Fax: 91-172-2744401

Email: info@isncon2019.com,

www.meetingsnmore.com

INFECTIOUS DISEASES - II

FUNGAL INFECTIONS IN CHILDREN – REVIEW AND PRACTICE

***Revathi Raj**
****Ramya Uppuluri***

Abstract: *Fungal infections are not uncommon in children and a high index of suspicion is required to make an early diagnosis particularly of an underlying primary immune deficiency disorder. In children undergoing chemotherapy and hematopoietic stem cell transplantation, fungal infections pose a huge challenge and adequate prophylaxis and prompt therapy prevents morbidity and mortality. Fungal infections can be classified as probable, possible and proven infections. With the advent of newer antifungal agents, knowledge of medications used in young children and their side effects are of utmost importance. Early diagnosis and effective management result in optimal outcomes.*

Keywords: *Fungal infections, Antifungal agents, Immunocompromised*

Invasive fungal disease (IFD) is now on the rise and is seen in premature infants, prolonged intensive care unit (ICU) stay, post-operative children who had extensive abdominal surgery or corrective heart surgery and an increasing number of children with autoimmune conditions treated with immunomodulatory agents.[1,2] Children undergoing chemotherapy for malignancies particularly acute leukemia and those undergoing hematopoietic and solid organ transplant are at an increased risk of invasive fungal infections.[3] Fungal spores are often present in the air or soil and hence, fungal infections usually begin in the lungs or on the skin. Fungal infections are rarely serious unless the immune system is weakened, usually by drugs or medical disorders which make them spread albeit slowly.

* Senior Consultant

** Consultant,
Department of Pediatric Hematology, Oncology,
Blood and Marrow Transplant,
Apollo Hospitals,
Chennai.

email : revaraj@yahoo.com

Types of fungal infections

It is essential for a practicing pediatrician to recognize the pathogen and the host interactions to arrive at an early diagnosis. Table I illustrates the association between particular conditions and their propensity for a particular species of fungi resulting in disease.

Diagnosis

The European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group definitions have helped advance clinical and epidemiological research and serve as a useful model for defining fungal infections (Table II).[4]

The diagnosis of fungal infections could be made from culture of blood, urine or sterile body fluids. Increasingly, non-invasive screening in the form of serum beta D-glucan and aspergillus galactomannan have been included in the armamentarium. An abundant cell wall polysaccharide, (1-3)-β-D-glucan (BDG) is found in most fungi, with the exception of the cryptococci. In invasive fungal disease, an optical density value of above 0.5 is taken as a cut off to prompt investigations to confirm the diagnosis. There are false positive and negative values and the maximum value of antigen-based tests is seen in immunocompromised children. Increasingly the use of imaging including HRCT chest has become the additional modality in the rapid diagnosis of invasive fungal disease.

Fungal infections and febrile neutropenia

In 2017, the guidelines for the management of fever and neutropenia in children with cancer and hematopoietic stem cell transplantation (HSCT) recipients was published.[3] Invasive fungal diseases (IFD) were found to be more common in children undergoing chemotherapy for acute myeloid leukemia, relapsed leukemia, those with prolonged neutropenia, on prolonged corticosteroids and those undergoing allogenic HSCT. The recommendations state that any child with febrile neutropenia for more than 96 hours should be considered for antifungal therapy. No specific biomarkers have been recommended to be confirmatory and only HRCT chest is to be performed.

Table I. Correlation of fungal species with host factors

Organism and source	Host
Yeasts	
Candida species – Gastrointestinal tract of the patient	Preterm babies, ICU stay, prolonged steroid use, broad spectrum antibiotics, post chemotherapy, post hematopoietic or solid organ transplantation
Cryptococcus neoformans - Inhalation	Advanced HIV infection
Spores	
Aspergillus species - Inhalation	Immunocompromised child – Primary immune deficiency disorders, post chemotherapy or organ transplantation
Mucormycoses - Inhalation	Poorly controlled diabetes
Fusarium species – Breached skin or mucosal surface	Immunocompromised child – Post high dose chemotherapy or transplantation

Table II. Definitions for fungal infections[4]

Proven	Histological or culture-based evidence of fungi
Probable	Host factors, clinical and mycological criterion are present
Possible	Host factor and clinical criterion are present, mycological criterion absent

In children with high risk for IFD with more than 96 hours of fever and neutropenia unresponsive to antibacterial agents, empirical echinocandins namely caspofungin or liposomal amphotericin B are recommended. No empirical antifungal is recommended for those at low risk for IFD.

Practical issues

Fungal infections in immunocompetent children are rare but need a high index of suspicion for early diagnosis. Candida species are now increasingly non albicans such as glabrata and these are resistant to azoles but the addition of echinocandins or amphotericin can save lives.[5,6] Candida auris is now a multidrug resistant infection resulting in mortality in intensive care and oncology units. Early removal of central venous catheters are essential to control infection due to candida. Candida parapsilosis infections are associated with hyperalimentation solutions, prosthetic devices and indwelling catheters, as well as the nosocomial spread of disease through the hands of health care workers. Candida parapsilosis is resistant to azoles and echinocandins and need to be treated with amphotericin.[7] The mode of action of different antifungals is given in Table III.

Infections due to spores such as aspergillus increase in the presence of construction work in hospitals. Adequate precautions should be taken to protect immunocompromised patients in this situation. The angiotropic properties of aspergillus enables them to

Table III. Antifungals and their mechanisms of action (MOA)

Class of antifungal and MOA	Generic drugs available	Drug specifications
Azoles - Inhibit cell membrane synthesis	Fluconazole, itraconazole, voriconazole, posaconazole	Fluconazole– candida, Rest – good aspergillus cover, mucor and fusarium
Echinocandins - Inhibit cell wall synthesis	Mycafungin, Caspofungin, Anadulafungin	Candida species Prophylaxis for aspergillus
Amphotericin B - Inhibit cell membrane synthesis	Amphotericin B Liposomal amphotericin B	Broad spectrum – candida, aspergillus, mucor, fusarium

invade the vascular wall and proliferate within the lumen of blood vessels. The most characteristic feature of mucor is invasion of blood vessel by hyphae resulting in hemorrhage thrombosis, infarction and necrosis of tissues. Children with these infections may not exhibit any clinical signs except for a dry cough or sinus tenderness and early imaging will help arrive at a diagnosis.[8]

Prophylaxis for fungal infections is only indicated in immunocompromised children as rampant use of fluconazole could result in the emergence of drug resistant candida species. Risk based recommendations and guidelines need to be tailored to local hospital pathogens and their sensitivity pattern with inputs from infection control team. Combination of antifungal agents needs to be used judiciously as there are several drug interactions. Echinocandin such as caspofungin can be used in combination with an azole such as voriconazole effectively. However, a combination of amphotericin and voriconazole can reduce both drug levels and need to be used with drug monitoring.

Voriconazole can be targeted using therapeutic drug monitoring and it takes about 4 to 7 days to reach therapeutic levels.[9,10] Voriconazole and posaconazole need to be taken with a fatty meal and intravenous preparations may cause visual disturbances and nephrotoxicity. Concomitant use of proton pump inhibitors with oral azoles needs to be avoided. Echinocandins have the least drug interactions and anidulafungin can be used in the presence of liver dysfunction.[11,12] Amphotericin B in its liposomal formulation is prepared in 5% dextrose and administered over 4 to 6 hours. Tubular leak of potassium and magnesium is the most important side effect and this needs to be monitored and replaced.[13]

Conclusion

The diagnosis and treatment of fungal infections has been made easier with guidelines, advanced imaging and effective antifungal agents. The most important step is for the clinician to understand the host factors and predict the risk of fungal infection and treat before the onset of invasive fungal disease.

Points to Remember

- ***Fungal infections are more common in an immunocompromised host.***
- ***Systemic antibiotics, mucositis and prolonged steroid use predispose to candida sepsis.***
- ***Invasive aspergillus infection can be diagnosed with a combination of serum markers namely beta D glucan, serum galactomannan and high-resolution computed tomography chest.***
- ***Antifungal agents like azoles, echinocandins and amphotericin are safe to use in newborn and children with frequent monitoring for side effects.***
- ***Early removal of central venous line is essential for prevention of candida infection.***

References

1. Dornbusch HJ, Manzoni P, Roilides E, Walsh TJ, Groll AH. Invasive fungal infections in children. Pediatr Infect Dis J 2009; 28(8):734-737.
2. Luise ER, William JS., Aspergillus. In: Robert MK, Bonita FS, Joseph WS, Nina FS, Richard EB. Nelson Textbook of Paediatrics. 19th edn. Philadelphia: saunders Elseiver; 2011: pp1058-1062.
3. Lehrnbecher T, Robinson P, Fisher B, Alexander S, Ammann RA, Beauchemin M, et al. Guideline for the Management of Fever and Neutropenia in Children With Cancer and Hematopoietic Stem-Cell Transplantation Recipients: 2017 Update. J Clin Oncol 2017; 35(18): 2082-2094.
4. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis 2008; 46(12):1813-1821.
5. King J, Pana ZD, Lehrnbecher T, Steinbach WJ, Warris A. Recognition and Clinical Presentation of Invasive Fungal Disease in Neonates and Children. J Pediatr Infect Dis Soc 2017; 6(suppl_1):S12-S21.
6. Ong CW, Chen SC, Clark JE, Halliday CL, Kidd SE, Marriott DJ. Diagnosis, management and prevention of Candida auris in hospitals: Position statement of the Australasian Society for Infectious Diseases. Intern Med J 2019 Aug 19. doi: 10.1111/imj.14612. Accessed on 4th September 2019.
7. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical Practice Guideline forthe Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis 2016; 62(4):e1-50.
8. Patterson TF, Thompson GR 3rd, Denning DW, Fishman JA, Hadley S, Herbrecht R, et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis 2016; 63(4):e1-e60.

9. Ruiz J, Gordon M, Villarreal E, Peruccioni M, Marqués MR, Poveda-Andrés JL, et al. Impact of voriconazole plasma concentrations on treatment response in critically ill patients. J Clin Pharm Ther 2019; 44(4):572-578.

10. Lempers VJ, Meuwese E, Mavinkurve-Groothuis AM, Henriet S, van der Sluis IM, Hanff LM, et al. Impact of dose adaptations following voriconazole therapeutic drug monitoring in pediatric patients. Med Mycol 2019 Feb 13. doi: 10.1093/mmy/myz006.

11. Verma A, Auzinger G, Kantecki M, Campling J, Spurden D, Percival F et al. Safety and Efficacy of Anidulafungin for Fungal Infection in Patients With Liver Dysfunction or Multiorgan Failure. Open Forum Infect Dis 2016; 4(1):ofw241.

12. Vekeman F, Weiss L, Aram J, Ionescu-Ittu R, Moosavi S, Xiao Y, et al. Retrospective cohort study comparing the risk of severe hepatotoxicity in hospitalized patients treated with echinocandins for invasive candidiasis in the presence of confounding by indication. BMC Infect Dis 2018; 18(1):438.

13. Kobayashi R, Keino D, Hori D, Sano H, Suzuki D, Kishimoto K, et al. Analysis of Hypokalemia as a Side Effect of Liposomal Amphotericin in Pediatric Patients. Pediatr Infect Dis J 2018; 37(5):447-450.

CLIPPINGS

Phenotypic variability and disparities in treatment and outcomes of childhood arthritis throughout the world: an observational cohort study

In this multinational, cross-sectional, observational cohort study, international paediatric rheumatologists from specialised centres were asked to enrol children with a diagnosis of juvenile idiopathic arthritis, according to International League of Associations for Rheumatology criteria, who were seen consecutively for a period of 6 months. Each patient underwent retrospective and cross-sectional assessments, including measures of disease activity and damage and questionnaires on the wellbeing and quality of life of the children. The collected data across eight geographical areas, association between disease activity and damage and a country's gross domestic product (GDP) with a multiple logistic regression analysis was qualitatively compared.

Between April 4, 2011, and Nov 21, 2016, 9081 patients were enrolled at 130 centres in 49 countries, grouped into eight geographical areas. Systemic arthritis (125 [33·0%] of 379 patients) and enthesitis-related arthritis (113 [29·8%] of 379) were more common in southeast Asia, whereas oligoarthritis was more prevalent in southern Europe (1360 [56·7%] of 2400) and rheumatoid factor-negative polyarthritis was more frequent in North America (165 [31·5%] of 523) than in the other areas. Prevalence of uveitis was highest in northern Europe (161 [19·1%] of 845 patients) and southern Europe (450 [18·8%] of 2400) and lowest in Latin America (54 [6·4%] of 849), Africa and Middle East (71 [5·9%] of 1209), and southeast Asia (19 [5·0%] of 379). Median age at disease onset was lower in southern Europe (3·5 years, IQR 1·9–7·3) than in other regions. Biological, disease-modifying antirheumatic drugs were prescribed more frequently in northern Europe and North America than in other geographical settings. Patients living in countries with lower GDP had greater disease activity and damage than those living in wealthier countries. Damage was associated with referral delay.

This study documents a variability in prevalence of disease phenotypes and disparities in therapeutic choices and outcomes across geographical areas and wealth status of countries. The greater disease burden in lower-resource settings highlights the need for public health efforts aimed at improving equity in access to effective treatments and care for juvenile idiopathic arthritis.

Consolaro A, Giancane G, Alongi A, van Dijkhuizen EH, Aggarwal A, Al-Mayouf SM, Bovis F, De Inocencio J, Demirkaya E, Flato B, Foell D. Phenotypic variability and disparities in treatment and outcomes of childhood arthritis throughout the world: an observational cohort study. The Lancet Child & Adolescent Health. 2019 Apr 1;3(4):255-63.

INFECTIOUS DISEASES - II

UPDATES IN PEDIATRIC HUMAN IMMUNODEFICIENCY VIRUS INFECTION

*Ira Shah
**Akanksha Jaiswal
***Srushti Gandhi

Abstract: *Human immunodeficiency virus has now evolved from a fatal condition to that of a chronic manageable disease. With newer advances both in antiretroviral drugs and diagnostics, human immunodeficiency virus treatment has become simplified and available to all those who are infected. The recent protocol of prevention of parent to child transmission has simplified therapy as well as holds promise of <2% transmission of human immunodeficiency virus thus almost decreasing new cases of pediatric human immunodeficiency virus. Every pediatrician should have the basic knowledge of retroviral therapy and the current developments. This article gives a review of all the recent advances in pediatric human immunodeficiency virus.*

Keywords: *Human immunodeficiency virus, Diagnosis, Infants, Children, Treatment, Prevention of parent to child transmission, Antiretroviral therapy.*

Epidemiology

India ranks 3rd amongst the world's largest human immunodeficiency virus (HIV) communities. The prevalence of HIV in India in 2015 was 0.2% which has remained almost constant as per 2017 UNAIDS data with almost 21,10,000 people being HIV infected.[1] Of these, 6.47% are children below 15 years of age. About 1,07,000 HIV infected people including 57,230 children are receiving antiretroviral therapy (ART) as per the December 2016 estimation.[2]

* Professor and Head
** Clinical Associate
*** Senior Medical Officer,
Pediatric HIV Clinic,
Department of Pediatric Infectious Diseases,
B.J.Wadia Hospital for Children,
Mumbai.
email: irashah@pediatriconcall.com

There are two main types of HIV – HIV-1 is most common and HIV-2 is relatively uncommon and less infectious. There are four strains or groups of HIV-1 which are M, N, O and P. and M is the 'major' group responsible for many global HIV epidemics. Other three groups are uncommon. There are nine genetically distinct subtypes within groups M which are A, B, C, D, F, G, H, J and K.[3]

Updates in investigations

Updates in screening for HIV[4]

The Guidelines of UNAIDS issued in April 2019 is given in Box 1.

Box 1. Guidelines on screening 2019

- All pregnant women should be tested as early as possible during each pregnancy.
- Partners of pregnant women should undergo HIV testing if their HIV status is not known.
- A third-trimester HIV re-testing is advocated in places where it is not routinely done.
- In patients with maternal non-B subtype virus or Group O infections, specific assays that detect HIV non-B subtype viruses or Group O virus are now recommended.
- Infants born to HIV infected mothers, but are non-breastfed and have no clinical or virologic evidence of HIV infection, may continue to have maternal HIV antibodies up to the age of 24 months. These children are called late seroreverters. Their HIV status should be tested at 24 months to prevent false positive results.

Diagnostic tests that are approved for testing of HIV

Food and Drug Administration (FDA)-approved diagnostic tests include:[5-9]

- Antigen/antibody combination immunoassays, which detect HIV-1/2 antibodies as well as HIV-1 p24 antigen. These assays are recommended for initial screening. However, p24 antigen from HIV-1 non-B strains, HIV-1 non-M strains and HIV-2 strains may not be detected.

- HIV-1/2 immunoassays (third-generation antibody tests) are alternatives for initial testing.
- HIV-1/HIV-2 antibody differentiation immunoassay, which differentiates HIV-1 antibodies from HIV-2 antibodies is recommended for detection of HIV-2 infection.
- HIV-1 qualitative PCR may be necessary to diagnose acute HIV infection or for perinatally acquired HIV.
- HIV-1 Western blot are useful as confirmatory tests where screening tests are positive.
- Real-time HIV RNA PCR assays and the qualitative diagnostic RNA assay are now available for detection of non-subtype B HIV infection.

Virologic testing for newborns at risk of perinatal HIV transmission

As per USAIDS,[10-15] virologic testing at birth is considered for newborns born to HIV infected women who did not receive antiretroviral (ARV) drugs adequately or had an inadequate viral suppression. Testing HIV exposed infants at the time of birth only identifies 20% to 58% of infants with HIV infection. As per National AIDS Control Organization (NACO),[4,16,17] early infant diagnosis (EID) by virological testing should be done at 6 weeks of age with a repeat testing at 6 months, 12 months and 6 weeks after cessation of breastfeeds. Confirmation of HIV status of all babies should be done at 18 months using all 3 antibody (Rapid) tests.

Updates in antiretroviral drugs[4,18,19]

Antiretrovirals are a group of drugs that are used in the treatment of children living with HIV to decrease the viral burden. These drugs fall into 3 major classes – Nucleoside and nucleotide Analogue Reverse Transcriptase Inhibitors (NRTIs), Non-nucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs) and Protease Inhibitors (PIs) along with pharmacokinetic enhancers. Newer classes of drugs are now approved for treatment of HIV in children such as entry and fusion inhibitors, integrase strand transfer inhibitors (INSTIs) (Table I).

Nucleoside reverse transcriptase inhibitors (NRTIs)

Tenofovir alafenamide (TAF): It is a new NRTI similar to Tenofovir disoproxil fumerate (TDF). TAF has lesser bone and renal toxicity than TDF, but equal antiviral efficacy as TDF. Due to their toxicity, stavudine and didanosine are no longer recommended for use in children.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Etravirine: It is a second line NNRTI used in children above 6 years of age and is considered a 'second generation' NNRTI, in part because it retains activity against HIV-1 isolates which are resistant to other NNRTIs. The other 2nd generation NNRTI is rilpivirine which is only approved for use in adults.

Table I. Recently approved antiretrovirals

Drug class	Recently approved drugs
Nucleoside and nucleotide Analogue Reverse Transcriptase Inhibitors (NRTIs)	Tenofovir alafenamide (TAF)
Non-nucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)	Etravirine (for children above 6 years of age), rilpivirine (approved only for adults)
Protease Inhibitors (PIs)	Ritonavir (RTV), co-formulated lopinavir/ritonavir, atazanavir, fosamprenavir, darunavir and tipranavir
Entry inhibitors	Maraviroc - CCR5 co-receptor antagonist (approved for use by children more than 2 years of age), Enfurvirtide (T-20) (used only in children over 6 years)
Integrase strand transfer inhibitors (INSTIs)	Raltegravir, dolutegravir, elvitegravir and bictegravir
Post-Attachment Inhibitors	Ibalizumab
Pharmacokinetic Enhancers	Cobicistat (not recommended in children less than 18 years of age)

Protease Inhibitors (PIs)[4]

They are active against both HIV-1 and HIV-2. Low-dose ritonavir (RTV), a potent PI, acts as a potent inhibitor of the cytochrome P450 3A4 (CYP3A4) isoenzyme, thereby inhibiting the metabolism of other PIs. It has been used in low doses combined with another PI as a "pharmacokinetic booster," increasing drug exposure by prolonging the second drug's half-life. Boosted PI-based regimens are commonly used in treatment of adults, but adequate pediatric data are only available for co-formulated lopinavir/ritonavir in children older than 2 weeks of age and for atazanavir, fosamprenavir, darunavir and tipranavir with low-dose ritonavir in children age above 6 years.

Entry inhibitors[20,21]

These agents inhibit viral binding or fusion to host target cells. Enfurvirtide (T-20) is currently used and is to be used only in children over 6 years of age. It is to be administered subcutaneously, twice daily. It prevents virus-cell fusion. It is used as part of salvage regime in patients who have multiple ART failures.

Chemokine co-receptor type 5 (CCR5) antagonist:[22-24] Maraviroc blocks the chemokine CCR5 coreceptor on the CD4 cell surface thereby preventing HIV from entering the cell. This was the first antiretroviral drug to be developed that does not actually target the virus itself. This drug is approved for use by children more than 2 years of age. Maraviroc is effective in combination with other ART in patients with multi-drug-resistant HIV-1. However, it is necessary to check for CCR5 or CXCR4 virus tropism before starting the drug. CCR5 antagonists will be inactive against CXCR4-tropic virus and mixed/dual tropic HIV virus. There are considerable interactions with both PI and NNRTI classes, requiring alteration in maraviroc dosing depending on other drugs in the regimen.

Integrase strand transfer inhibitors (INSTIs)[25-28]

They block the integrase enzyme thereby preventing incorporation of viral DNA into human genome. Raltegravir, dolutegravir, elvitegravir and bictegravir are integrase strand-transfer inhibitors (INSTIs). These drugs have been found to be useful in the treatment of patients with multi-drug-resistant HIV-1. Raltegravir is FDA-approved for the treatment of HIV-infected full term neonates, infants and children. Raltegravir has a favorable safety profile and lacks significant drug interactions. FDA has recently approved dolutegravir for children above 30kg body weight. The drug has a very favorable safety profile and can be dosed once daily in treatment of INSTI-naive patients.

There appears to be increased risk of neural tube defects in infants born to women who were receiving dolutegravir (DTG) at the time of conception. Thus dolutegravir is not recommended for use in pregnant women during the first trimester and in non-pregnant women who are trying to conceive.

Post-attachment inhibitor[29]

Ibalizumab (IBA), is a CD4 post-attachment inhibitor, and has been recently approved for treatment of multi-drug resistant (MDR) HIV infection.

Pharmacokinetic enhancers[30]

Cobicistat: It is recommended for use in adolescents and adults as a pharmacokinetic enhancer (boosting agent) of selected protease inhibitors (PIs) and the integrase inhibitor elvitegravir. It is not recommended in children <18 years of age.

Updates in antiretroviral therapy (ART)

At present, highly active combination regimens including at least three drugs are recommended. These regimens have shown increased survival, fall in the opportunistic infections, improved growth and neurocognition and improved quality of life in children. The current guidelines for starting ART have been simplified. As per WHO July 2017 update on HIV treatment and care, ART should be initiated in everyone infected with HIV at any/all CD4 cell count, regardless of WHO clinical stage.[31,32] NACO has adopted WHO guidelines to TREAT ALL people with HIV with ART regardless of CD4 count, clinical stage and age or population.[33] Dual NRTIs backbone regimen includes, zidovudine with lamivudine or emtricitabine combination due to favorable safety profile and extensive experience and abacavir plus lamivudine or emtricitabine for children aged ≥3 months. Tenofovir alafenamide and emtricitabine as fixed dose combination tablet along with NNRTI (single tablet) is indicated in children ≥25kg weight or ≥6 years with estimated creatine clearance (CrCl) ≥30 ml/min.[34] Tenofovir disoproxil fumarate with lamivudine or emtricitabine combination is FDA approved for use in children ≥2 years. However, risk of decreased bone mineral density versus benefits should be considered.[35] The preferred ART regimen in HIV infected children according to the World Health Organization (WHO) November 2015 consolidated guidelines is depicted in Table II.[36]

Table II. Preferred and alternative first-line regimens for children

Age group	Preferred first-line regimens	Alternative first-line regimens
<3 years	ABC (or AZT)+ 3TC + LPV /r	ABC (or AZT) + 3TC + NVP
3 years to <10 years	ABC + 3TC + EFV	ABC + 3TC + NVP, AZT +3TC +EFV (or NVP), TDF + 3TC(or FTC)+EFV (or NVP)
Adolescents	TDF + 3TC (or FTC) + EFV	AZT +3TC +EFV (or NVP), TDF or ABC + 3TC or FTC + DTG* and EFV_{400}* or NVP

ABC = abacavir, AZT= zidovudine, 3TC= lamivudine, LPV/r= lopinavir-ritonavir, NVP= nevirapine, EFV= efavirenz, FTC= emtricitabine, TDF= tenofovir, DTG= dolutegravir, EFV_{400}= efavirenz at lower dose (400mg/day)

**Safety profile and efficacy data on use of DTG and EFV_{400} in people with HIV/TB co-infection and children <12 years are not yet available*

Table III. Dose and duration of nevirapine (NVP) prophylaxis in infants[38]

Birth weight (kg)*	Daily NVP dose in mg	NVP dose in ml**	NVP dose in ml**
Less than 2 kg	2 mg/kg Once a day	0.2 ml/kg Once a day	Up to six weeks, irrespective of whether the baby is exclusively breastfed or exclusively replacement fed. The duration may be extended to 12 weeks if the mother had not received ART for at least 24 weeks,including women initiated on ART during labour and if she is breastfeeding the child.
2–2.5 kg	10 mg Once a day	1 ml Once a day	
More than 2.5 kg	15 mg Once a day	1.5 ml Once a day	

*** Infant NVP: Give first dose of NVP (within 6 to 12 hours of delivery and continue daily for 6 weeks; *Formulation: 10 mg Nevirapine in 1ml suspension.*

Response to ART

By one month of starting an effective ART regimen in children, there is a substantial drop in the plasma HIV viral load and the CD4 count starts to rise. Infants, with an initial viral load of between 10^5-10^7 copies/mL can take longer to become undetectable. As per new WHO recommendations,[2] routine viral load testing is encouraged at 6 months followed by 12 months after initiating ART and if the patient is stable on ART and then every year thereafter. Stable on ART means ART for more than or at least one year, no present illness/pregnancy, good undersanding of lifelong adherence and evidence of treatment success which is two consecutive viral load measuring below 1000 copies/mL. WHO recommends measurement of the CD4 cell count 6 monthly until stable on ART, following which CD4 cell count monitoring can be withheld in patients who are virally suppressed and stable on ART.[4]

Antiretroviral management and feeding of newborns with perinatal HIV exposure or perinatal HIV

As per NACO prevention of parent to child transmission (PPTCT) guidelines,[37] HIV exposed infant should be started on postpartum ARV prophylaxis for minimum of 6 weeks (Table III). They may be given exclusive breastfeeds for 6 months and continued breastfeeds along with complementary feeds from 6 months to 1 year. For babies who are HIV infected and are on ART, breastfeeding up to 2 years is recommended. Only when breastfeeding is contraindicated or cannot be done (maternal death, severe maternal illness) or the mother does not want to feed the child (at her own risk), exclusive replacement feeding may be considered. AFASS (A – Affordable F – Feasible A – Acceptable S – Sustainable S – Safe) criteria must be fulfilled to give exclusive replacement feeding. During the first six months, mixed feeding should not be done under any circumstance. Mixed feeding refers to breast feeds and replacement feeds simultaneously in the first 6 months as it can lead to mucosal abrasions in the gut of the baby, which can facilitate HIV virus entry through these abrasions. Co-trimoxazole prophylaxis should be started from 6 weeks of age.

Conclusion

There is a wide range of antiretroviral drugs and various ART regimens available for treatment of children infected with HIV, even with extensive drug resistance. Extensive research is being done in the field of HIV and the screening, diagnosis and management of HIV keeps getting updated based on latest evidence. It is of utmost importance that the person exposed to, or affected by HIV is referred to a specialist with the most expertise for their management. With good care, a person with HIV can have a near-normal quality of life.

Points to Remember

- ***Infants born to HIV infected mothers, may continue to have maternal HIV antibodies up to age 24 months and their HIV status should be tested at 24 months to prevent false positive results.***
- ***Apart from NRTI, NNRTI and PI, there are newer classes of drugs such as entry and fusion inhibitors, integrase strand transfer inhibitors (INSTIs).***
- ***As per WHO, ART should be initiated in everyone infected with HIV at any CD4 cell count, regardless of clinical stage.***
- ***Routine viral load testing is encouraged at 6 months followed by 12 months after initiating ART and if stable every year thereafter.***
- ***As per NACO PPTCT guidelines, HIV exposed infant should be started on postpartum ARV prophylaxis for minimum of 6 weeks.***
- ***Exclusive breastfeeding is recommended for 6 months and continued breastfeeds along with complementary feeds from 6 months to 1 year.***
- ***Early infant diagnosis (EID) by virological testing should be done at 6 weeks of age with a repeat testing at 6 months, 12 months and 6 weeks after cessation of breastfeeds.***

References

1. UNAIDS. Trends of New HIV Infections. Available at URL: http://aidsinfo.unaids.org/. Accessed in March 2019.
2. NACO. National Guidelines for HIV-1 Viral Load Laboratory Testing. Available at URL:http://naco.gov.in/sites/default/files/National Guidelines For HIV 1 Viral Load LaboratoryTestingApril2018%20%282%29.pdf. Accessed on 29th April 2019.
3. AVERT Global information and education on HIV and AIDS. HIV strains and types. Available at https://www.avert.org/professionals/hiv-science/types-strains. Accessed on 11th July, 2019.
4. UNAIDS. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. Available at URL: https://aidsinfo.nih.gov/guidelines/html/2/pediatric-arv/45/whats-new-in-the-guidelines. Accessed on 29th April, 2019.
5. Havens PL, Mofenson LM. American Academy of Pediatrics Committee on Pediatric AIDS. Evaluation and management of the infant exposed to HIV-1 in the United States. Pediatrics 2009; 123:175-187.
6. Hegazi A, Forsyth S, Prime K, Bashh Adolescent Special Interest Group (ASIG). Testing the children of HIV-infected parents: 6 years on from 'don't forget the children'. Sex Transm Infect 2015; 91:76-77.
7. AIDS info. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Accessed on 29th April 2019.
8. Branson BM, Owen SM, Wesolowski LG, Bennett B, Werner BG, Wroblewski KE, et al. Laboratory testing for the diagnosis of HIV infection: updated recommendations. Centers for Disease Control and Prevention. 2014. Available at: https://stacks.cdc.gov/view/cdc/23447. Accessed on 7th April 2019.
9. World Health Organisation (WHO). Mother-to-child transmission of HIV. Available at URL: https://www.who.int/hiv/topics/mtct/en/. Accessed on 29th April, 2019.
10. Lilian RR, Kalk E, Technau KG, Sherman GG. Birth diagnosis of HIV infection on infants to reduce infant mortality and monitor for elimination of mother-to-child transmission. Pediatr Infect Dis J 2013; 32:1080-1085.
11. Jourdain G, Mary JY, Coeur SL, Ngo-Giang-Huong N, Yuthavisuthi P, Limtrakul A, et al. Risk factors for in utero or intrapartum mother-to-child transmission of human immunodeficiency virus type 1 in Thailand. J Infect Dis 2007; 196:1629-1636.
12. Tubiana R, Le Chenadec J, Rouzioux C, Mandelbrot L, Hamrene K, Dollfus C, et al. Factors associated with mother-to-child transmission of HIV-1 despite a maternal viral load <500 copies/mL at delivery: a case-control study nested in the French perinatal cohort (EPF-ANRS CO1). Clin Infect Dis 2010; 50:585-596.
13. Katz IT, Shapiro DE, Tuomala R. Factors associated with lack of viral suppression at delivery. Ann Intern Med 2015; 162:874-875.
14. Momplaisir FM, Brady KA, Fekete T, Thompson DR, Diez Roux A, Yehia BR. Time of HIV diagnosis and engagement in prenatal care impact virologic outcomes of pregnant women with HIV. PLoS One 2015; 10:e0132262.
15. Mandelbrot L, Tubiana R, Le Chenadec J, Dollfus C, Faye A, Pannier E, et al. No perinatal HIV-1 transmission from women with effective antiretroviral therapy starting before conception. Clin Infect Dis 2015; 61:1715-1725.

16. Burgard M, Blanche S, Jasseron C, Descamps P, Allemon MC, Ciraru-Vigneron N, et al. Performance of HIV-1 DNA or HIV-1 RNA tests for early diagnosis of perinatal HIV-1 infection during anti-retroviral prophylaxis. J Pediatr 2012; 160:60-66 e61.
17. Lilian RR, Johnson LF, Moolla H, Sherman GG. A mathematical model evaluating the timing of early diagnostic testing in HIV-exposed infants in South Africa. J Acquir Immune Defic Syndr 2014; 67:341-348.
18. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Second edition. 2016. Available at URL: https://www.who.int/hiv/pub/arv/arv-2016/en/. Accessed on 29th April, 2019.
19. WHO. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV. Available at URL: https://www.who.int/hiv/pub/guidelines/ARV2018update/en/. Accessed on 29th April, 2019.
20. Wiznia A, Church J, Emmanuel P, Eppes S, Rowell L, Evans C, et al. Safety and efficacy of enfuvirtide for 48 weeks as part of an optimized antiretroviral regimen in pediatric human immunodeficiency virus 1-infected patients. Pediatr Infect Dis J 2007; 26:799-805.
21. Zhang X, Lin T, Bertasso A, Evans C, Dorr A, Kolis SJ, Salgo M, et al. Population pharmacokinetics of enfuvirtide in HIV-1-infected pediatric patients over 48 weeks of treatment. J Clin Pharmacol 2007; 47:510-517.
22. Maraviroc [package insert]. Food and Drug Administration. 2016. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208984_022128s017lbl.pdf. Accessed on 29th April, 2019.
23. Agwu AL, Yao TJ, Eshleman SH, Patel K, Huang W, Burchett SK, et al. Phenotypic co-receptor tropism in perinatally HIV-infected youth failing antiretroviral rherapy. Pediatr Infect Dis J 2016; 35:777-781.
24. Raffi F, Jaeger H, Quiros-Roldan E, Albrecht H, Belonosova E, Gatell JM, et al. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. Lancet Infect Dis 2013; 13:927-935.
25. Molina JM, Clotet B, van Lunzen J, Lazzarin A, Cavassini M, Henry K, et al. Once-daily dolutegravir is superior to once-daily darunavir/ritonavir in treatment-naive HIV-1-positive individuals: 96 week results from FLAMINGO. J Int AIDS Soc 2014; 17(4 Suppl 3):19490.
26. Viani RM, Alvero C, Fenton T, Acosta EP, Hazra R, Townley E, et al. Safety, Pharmacokinetics and efficacy of dolutegravir in treatment-experienced HIV-1 infected adolescents: 48-week results from IMPAACT P1093. Pediatr Infect Dis J 2015; 34:1207-1213.
27. Wiznia A, Alvero C, Fenton T, George K, Townley E, Hazra R, et al. IMPAACT 1093: Dolutegravir in 6- to 12-Year-Old HIV-Infected Children: 48- Week Results. Presented at: 23rd Conference on Retroviruses and Opportunistic Infections 2016. Boston, MA.
28. Walmsley S, Baumgarten A, Berenguer J, Felizarta F, Florence E, Khuong-Josses MA, et al. Dolutegravir plus abacavir/lamivudine for the treatment of HIV-1 infection in antiretroviral therapy-naive patients: week 96 and week 144 results from the SINGLE randomized clinical trial. J Acquir Immune Defic Syndr 2015; 70:515-519.
29. Emu B, Fessel J, Schrader S, Kumar P, Richmond G, Win S, et al. Phase 3 Study of Ibalizumab for Multidrug-Resistant HIV-1; N Engl J Med 2018; 379:645-654.
30. Aids Info. Cobicistat. Available at URL: https://aidsinfo.nih.gov/drugs/536/cobicistat/0/patient. Accessed on 29th April, 2019
31. WHO. What's new in treatment monitoring: viral load and cd4 testing. Available at URL: https://www.who.int/hiv/pub/arv/treatment-monitoring-info-2017/en/. Accessed 31st March 2019.
32. WHO. TRANSITION TO NEW ANTIRETROVIRALS IN HIV PROGRAMMES. Available at URL: https://www.who.int/hiv/pub/toolkits/transition-to-new-arv/en/. Accessed on 29th April 2019.
33. World Health Organisation. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV; 2015: Available at: https://apps.who.int/iris/bitstream/handle/10665/186275/9789241509565_eng.pdf?sequence=1. Accessed on 29th April, 2019.
34. Arribas JR, Thompson M, Sax PE, Haas B, McDonald C, Wohl DA, et al. Brief report: randomized, double-blind comparison of tenofovir alafenamide (TAF) vs tenofovir disoproxil fumarate (TDF), each coformulated with elvitegravir, cobicistat, and emtricitabine (E/C/F) for initial HIV-1 treatment: week 144 results. J Acquir Immune Defic Syndr 2017; 75:211-218.
35. Hill A, Hughes SL, Gotham D, Pozniak AL. Tenofovir alafenamide versus tenofovir disoproxil fumarate: is there a true difference in efficacy and safety? J Virus Erad 2018; 4:72-79.
36. World Health Organisation. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: what's new. 2015. Available at: https://www.who.int/hiv/pub/arv/15249_HIV Treatement and Care_PolicybriefforWEB.pdfAccessed on 29th April, 2019.
37. NACO. Prevention of Parent to Child Transmission. Available at URL: http://naco.gov.in/prevention-parent-child-transmissionpptct. Accessed on 29th April, 2019.
38. UNAIDS. Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV: Available at: https://aidsinfo.nih.gov/guidelines/html/3/perinatal/187/antiretroviral-management-of-newborns-with-perinatal-hiv-exposure-or-perinatal-hiv. Accessed on 29th April, 2019.

INFECTIOUS DISEASES - II

RE-EMERGING INFECTIONS

***Monjori Mitra**
****Rohit Banerjee**
*****Mallar Mukherjee**
*****Sumita Kundu**
*****Barnali Das**

Abstract: *Despite effective and extensive vaccination, infectious diseases such as pertussis, diphtheria, syphilis and Hansen's disease are on the rise since the last few decades in the United States with outbreaks being reported in many other countries like Australia, Brazil, United Kingdom and Chile in the last decade. While certain infections such as syphilis have plausible reason for the resurgence explained by increases in high-risk sexual behavior among people from all socio-demographic backgrounds, re-emergence of infections like Hansen's disease is due to high level of migration from endemic zones, secondary drug resistance or irrational use of antibiotics. Continuous monitoring of antigenic changes in the bacteria and evolution of resistance to antibiotics along with regular surveillance on the duration of immunity achieved by the vaccine is necessary.*

The re-emergence could also be due to changes in the transmission patterns and epidemiology of infections like pertussis and possible waning of vaccine induced immunity in adults as seen by the growing trend of cases amongst adults and adolescents. Some of the steps which can be taken to control pertussis are ensuring high ontime vaccine coverage of above 90% all over the globe particularly for the primary vaccination schedule and first booster doses. It is better to protect the newborn by immunisation of pregnant mothers and healthcare workers and by cocooning. Three major measures to counter the resurgence of diphtheria are high immunization coverage nearly 90% of target groups (including children at 5 years and adults), prompt diagnosis and management of diphtheria cases, and rapid identification of close contacts and their proper management to prevent secondary cases. Surveillance must be strengthened to identify new outbreaks of infection especially syphilis, thereby enabling a rapid response for treatment of infected individuals and their contacts and to determine which intervention strategies are working and warrant expansion.

Keywords: *Pertussis, Syphilis, Hansen's disease, Diphtheria, Re-emergence, Vaccines, Antigenic changes.*

Re-emergence of pertussis

Pertussis, also called whooping cough, is a highly infectious and contagious disease affecting the human respiratory tract and is caused mainly by Bordetella *pertussis* and less frequently by Bordetella para pertussis. In recent years there is emergence of Bordetella holmessi as a causative agent of whooping cough in Barcelona, Spain where the prevalence had doubled from 3.9% in 2015 to 8.8% in 2016 raising concerns regarding the re-emergence of pertussis and the effectiveness of the current pertussis vaccine.[1]

In the last decade there was a shift in transmission of the disease which was observed in highly vaccinated population from school age children to adults, adolescents and children under 1 year of age.[1] Pertussis became a reportable disease in 1922 and is transmitted by airborne droplets from an infected host. Currently two types of vaccines namely the whole cell and the acellular pertussis vaccines are used all over the world to achieve primary immunisation against pertussis.

Despite effective and extensive vaccination, pertussis is on the rise in the last 20 years in United States with outbreaks being reported in many other countries like Australia, Brazil, United Kingdom and Chile in the last decade.

In 2010, a total of 9156 pertussis cases were reported to the California department of public health which was the highest number of cases ever reported since 1947 when 9394 cases were reported.[2,3] CDC reported 7867 confirmed cases around the world in 2000 as compared to only 1010 cases reported in 1976. The re-emergence could be due to

* Professor
** Associate Professor
*** Assistant Professor
Institute of Child Health, Kolkata.
email: rohitbannerji@gmail.com

the changes in the transmission patterns, epidemiology of pertussis and possible waning of vaccine induced immunity in the adults as seen by the growing trend of cases amongst adults and adolescents. In recent years, adults and adolescents account for over 50% of new cases of pertussis reported and are directly responsible for the transmission to infants and young children. This has led to increased incidence of pertussis with the highest age specific case fatality ratio of 0.77% in infants below one year of age with the maximum pertussis deaths occurring among infants below 2 months of age who were too young to be fully vaccinated.[4]

Furthermore, there are differences reported, depending on the types of vaccines which are used. Whole cell vaccines developed during the 1940s with severe forms of reactogenicity leading to reluctance of the acceptance of the vaccine led to the development of a more highly purified acellular vaccine during the 1970s. Acellular vaccines have been found to be less effective than some of the highly effective whole cell vaccines and induce a protection of shorter duration than that provided by whole cell vaccines.[1] In spite of these immunological differences, there have also been increased cases reported from countries like Brazil and Chile which use the whole cell vaccine suggesting that the vaccine factor may not be the most important reason for its resurgence. Temporal changes of the circulating strains of the bacteria have also been implicated for the resurgence, in that, there has been isolation of strains producing increased amounts of pertussis toxin and some that are unable to produce pertactin.[1,4] Certain authors have attributed this change to vaccine pressure and a consequence of adaptation to the human host.[1]

The emergence of more sensitive diagnostic tests like Real Time PCR (RT-PCR) and increased awareness amongst health care workers could also be one of the reasons for the reported rise in the incidence of this disease.[1]

Some of the steps which can be taken to control pertussis are ensuring high ontime vaccine coverage of above 90% all over the globe particularly for the primary vaccination schedule and first booster doses. Focus on the newborn by immunisation of pregnant women, healthcare workers, immunization of neonates as early as birth and cocooning. Cocooning is a strategy already adopted by many developing nations whereby all household members and close contacts are immunised to protect the unimmunised newborn from pertussis. Booster immunisation of adults and adolescents could bring down the incidence of pertussis in young infants.

Continuous monitoring for antigenic changes in the bacteria and evolution of resistance to antibiotics along with regular surveillance on the duration of immunity achieved by the vaccine is necessary. Newer vaccine approaches are under trial e.g. Vaccines with new antigens, adjuvanted vaccines, live attenuated pertussis vaccines which look very promising for the future. Last but not the least, increased investigations coupled with more extensive research are needed for an even better understanding of the basics of pertussis infection, immunity and disease.

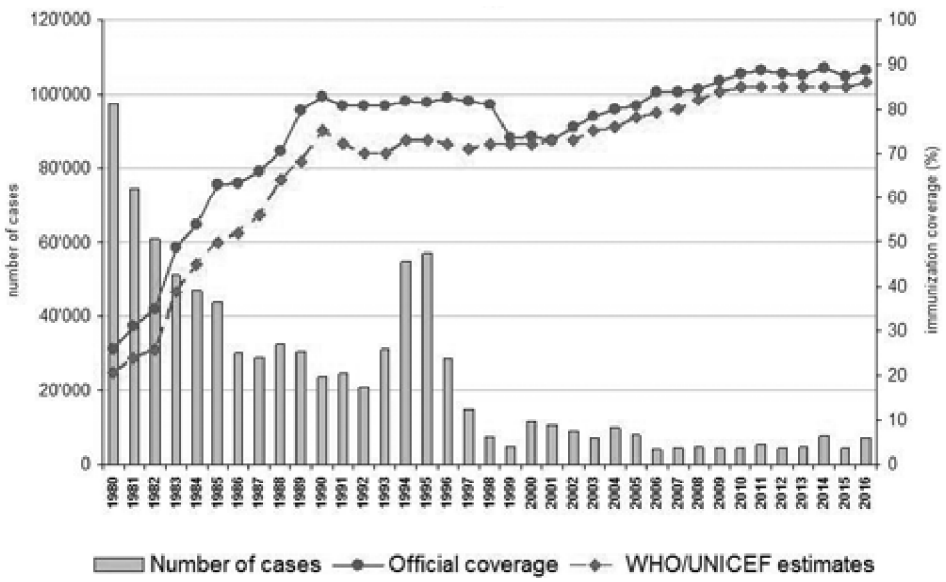


Fig.1. Distribution of the reported diphtheria cases and DTP3 coverage 1980-2016 (Top curve shows official coverage and bottom curve represents WHO UNICEF estimates)

(Source: WHO IVB database, 2017 - data as of 19 July, 2017)

Resurgence of diphtheria

Diphtheria had become a disease of the past following its inclusion in the universal immunization and expanded immunization program of the WHO except for a few scattered cases. But in continents like Russia and Eastern Europe where childhood immunization was interrupted, cluster of cases have been found to occur afresh, especially in adults in the last couple of years. These are the same reasons along with lack of adult booster dose, as well as lack of proper surveillance, the prime reasons behind resurgence of diphtheria in India too.[5] In developing countries with warm climates, it was cutaneous diphtheria which was found to circulate silently without producing symptoms or risks of classic diphtheria.[6] Cutaneous diphtheria however does not meet the WHO case definition[7] and so it has not been reported as case of diphtheria and hence overlooked. WHO in 2017 has shown the world wide distribution of the reported diphtheria cases and DTP3 coverage from 1980 to 2016 (Fig.1). It has been seen observed over the years, with increased DPT coverage, the incidence of diphtheria has decreased but the recent reemergence of sporadic cases are of concern.

Review of the Epidemiology of Diphtheria (2000-2016) by Kristie E. N. Clarke (US Centre for Disease Control and Prevention) reported that diphtheria cases declined from almost 10,000 per year (2000-2004) to 5288 per year (2005-2009) after which it has remained almost the same.[8] The South-East Asian region is the primary driver of global diphtheria incidence since 2005. Out of the 9 countries with a clear outbreak from 2005- 2015 (defined as at least 2 years of reported case counts of 30 cases), it has been found that 6 countries (67%) followed a 3 dose schedule of vaccination of DPT, 2 countries followed a 3+1 schedule, and 1 country (Brazil) followed a 3 dose + 2 schedule.

Meanwhile, cases reported from the European and African regions have been found to be decreased. Among countries with the top 10 case counts since the year 2000, India has the largest number of reported cases, with Indonesia and Nepal being the other contributors. Nigeria also has missing diphtheria data on the joint reporting form for 11 years from 2000- 2016, despite published cases in the literature for these years.[9] Three other countries had large outbreaks during this time period-Madagascar, Papua New Guinea (with average DTP3 coverage of 72% and 61%, respectively, prior to their outbreaks) and Nepal (90% DTP3 coverage). All these three countries however recommended 3 dose primary schedule without booster dose.

Vaccination schedules and DTP3 coverage for the 10 countries reporting the most cases of diphtheria in 2011-2015 (Table I). Developing countries report 80 to 90% of the worldwide cases of diphtheria.[10] In India, diphtheria cases accounted for 19-84% of the total global burden

Table I. Vaccination schedules and DTP3 coverage for the 10 countries reporting the most cases of diphtheria in 2011-2015

Country	Reported diphtheria cases (2011-2015)	Vaccination schedule	Age at last booster	Mean DPT3 coverage (2011-2015)
India	18350	3dose+2	5	84%
Indonesia	3203	3dose+4	8	82%
Madagascar	1633	3 dose	_	72%
Nepal	1440	3dose	_	91%
Iran	513	3dose+2	6	99%
Lao PDR	344	3dose	_	84%
Pakistan	321	3dose	_	72%
Sudan	222	3dose	_	93%
Myanmar	180	3dose	_	79%
Thailand	157	3dose+2	4	99%

between 1998 and 2008. The cause behind this resurgence was probably decreased childhood immunization, increased susceptibility among adults and high population movement.[9] A shift in the age of presentation has been observed from preschool to school age children as also in adults.[11] There was also altered clinical picture due to rural quackery, reluctance of the people to get immunized because of certain myths, different branches of medicine which discourage vaccination, improper cold chain maintenance and lastly due to lack of availability of anti-diphtheric serum (ADS) and medications. Some reports have shown that vaccine acceptance was an issue noticed in certain sections of the community in north Kerala in the year 2015 outbreak. Disease occurrence in the immunized individuals highlighted the defect in the whole process of immunization. There was a significant drop out between the 1st and 3rd dose of OPV/DPT in different parts of India, but there was hardly any provision to trace the vaccine drop outs.

Worldwide resurgence of syphilis

Syphilis is a multisystem disease with mucocutaneous lesions caused by spirochete Treponema pallidum. Acquired syphilis presents early and late. The early stage can be primary syphilis, secondary syphilis and early latent syphilis. The late stage can be late latent and tertiary syphilis, cardiovascular and neurosyphilis. Syphilis is the second most common infectious cause of stillbirth worldwide and an important preventable contributor to infant morbidity and mortality.[12]

According to the most recent estimation of the WHO, approximately 17.7 million individuals 15-49 years of age globally had syphilis in 2012, with an estimated 5.6 million new cases every year.[13] The estimated prevalence and incidence of syphilis varied substantially by region or country, with the highest prevalence in Africa and >60% of new cases occurring in low and middle income countries (LMIC) from 1.00 (0.89–1.23) million in 2012 to 0.99 (0.81–1.41) million in 2016 (Fig.2). In LMICs, heterosexual spread remains problematic in some high-risk sub-populations, such as female sex workers (FSWs) and their male clients. A recent study of FSWs in Johannesburg, South Africa, showed that 21% of participating women had past or current infection and 3% had active infection.

Males having sex with male (MSM) accounted for 75% of all primary and secondary syphilis cases and in 2015, that was (309 per 100,000) 221-times the rate for women (1.4 per 100,000) and 106 times the rate for heterosexual men (2.9 per 100,000) (Fig.3).[14] In 2017,

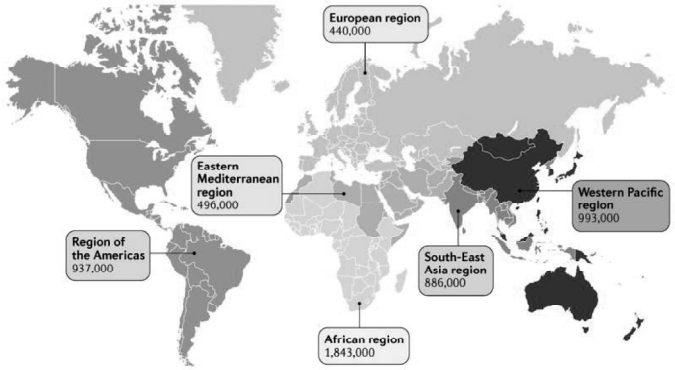


Fig.2. Incidence of syphilis worldwide

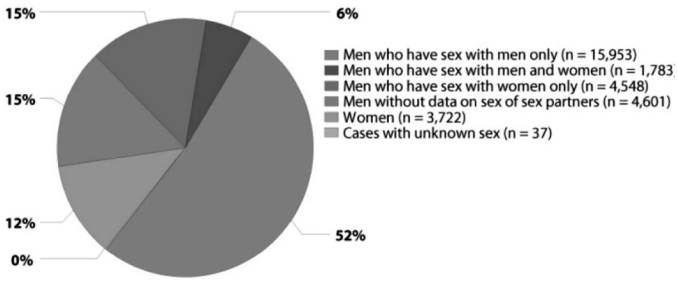


Fig.3. Primary and Secondary syphilis-Distribution of cases by Sex and Sexual Behaviour, US, 2017

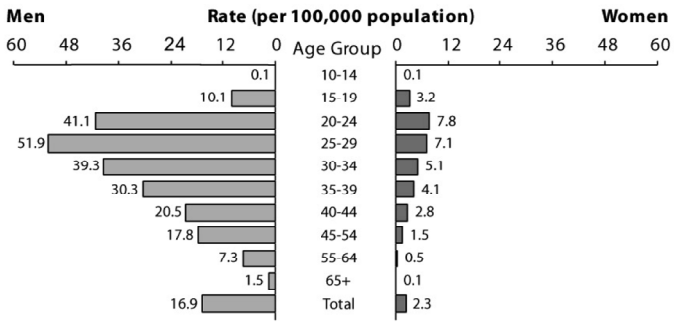


Fig.4. Primary and secondary Syphilis-Cases by age group and sex, US, 2017

a total of 30,644 cases of primary and secondary (P&S) syphilis were reported in the United States, yielding a rate of 9.5 cases per 100,000 populations (Fig.4). This rate represents a 10.5% increase compared with 2016 and a 72.7% increase compared with 2013. Of 30,644 reported primary and secondary syphilis cases in 2017, 17,736 (57.9%) were among MSM, including 15,953 (52.1%) cases among men who had sex with men only and 1,783 (5.8%) cases among men who had sex with both men and women. In Canada, compared with reported cases in the general male population, the incidence of syphilis was more than 300-times greater among HIV-positive MSM.[15]

Studies in emerging economies, such as China, indicate that syphilis is increasing among 'mobile men with money.[16] The most dramatic change in reported cases of syphilis in recent decades occurred in China.[17] Although syphilis was nearly eliminated in China during the early 1960s, cases began to rise in the 1980s. In 2013, 444,952 cases of syphilis were reported with a rate of almost 33 cases per 100,000 populations.

Epidemiology of congenital syphilis (CS)

According to WHO, the estimated number of pregnant women with probable active syphilis fell from 1.36 million in 2008 to 930,000 in 2012; the number of adverse birth outcomes (ABO) fell from 520,905 in 2008 to 351,000 in 2012. Between 2012 and 2016, the increase in total number of pregnancies combined with the stable maternal syphilis prevalence resulted in a slight decrease in the number of pregnant women with active syphilis (Table II).[18] Prevalence was also stable within most regions, except for non-significant increases in the Region of the Americas from 0.64% to 0.86% and in the Region of the Eastern Mediterranean from 0.69% to 0.77% and a non-significant decrease in the South-East Asian Region from 0.32% to 0.21%.

The estimated total number of CS cases globally fell from 748,000 in 2012 to 661,000 in 2016, and the CS cases per 100,000 live births fell from 539 to 473; (Table II). The majority of cases of CS were in the African Region-which accounted for 62% and 61% of total CS cases in

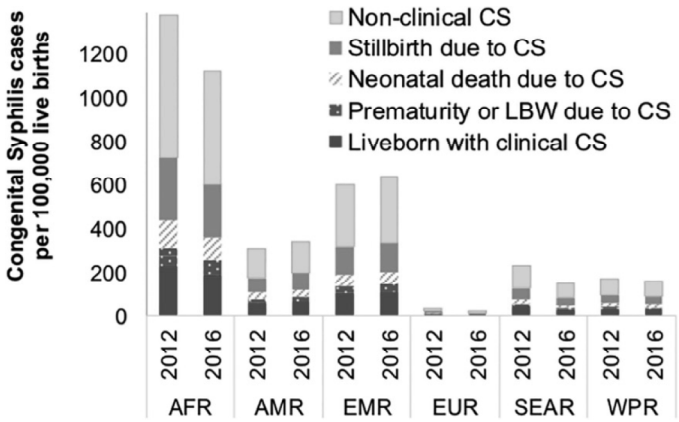


Fig.5. Distribution of CS case rates per 100,000 live births, by type, WHO region and calendar year.

AFR = WHO African Region; AMR = WHO Region of the Americas; EMR = WHO Eastern Mediterranean region; EUR = WHO European Region; SEAR = WHO South-East Asia Region; WPR = WHO Western Pacific Region, Pacific Region

2012 and 2016, respectively (Fig.5). The largest decline in terms of absolute numbers was in the African Region (65,000) but the greatest proportionate decline was in the South-East Asia Region (42% drop). Early fetal deaths or stillbirths accounted for 143,000 of the estimated 355,000 global ABOs in 2016. Clinical disease in infants accounted for another 109,000, neonatal deaths for 14,000 and prematurity/LBW for 41,000.

Table II. Estimated maternal and congenital syphilis and ABO cases and associated ANC service coverage, by WHO region

Region	Year	Pregnancies	Maternal syphilis prevalence	Pregnant women with active syphilis	ANC1 coverage	Syphilis screening coverage	Treatment coverage, mothers in ANC	Estimated ABO cases	Estimated non-clinical / non-ABO CS cases	Estimated total CS cases	Estimated CS case rate / 100,000 live births
African region	2012	35,055,000	1.62%	569,000	80%	35%	69%	247,000	222,000	469,000	1,377
	2016	37,150,000	1.52%	564,000	83%	47%	76%	216,000	188,000	404,000	1,119
Region of the Americas	2012	15,364,000	0.64%	98,000	97%	74%	84%	26,000	21,000	47,000	307
	2016	15,253,000	0.86%	131,000	97%	82%	88%	30,000	21,000	51,000	339
Eastern Mediterranean Region	2012	17,866,000	0.69%	124,000	78%	44%	82%	55,000	49,000	104,000	597
	2016	18,251,000	0.77%	140,000	78%	53%	85%	60,000	53,000	113,000	635
European Region	2012	11,449,000	0.11%	13,000	97%	90%	90%	1,930	1,470	3,400	30
	2016	11,289,000	0.10%	11,000	97%	94%	94%	1,260	940	2,200	19
South-East Asia Region	2012	37,889,000	0.32%	122,000	77%	59%	69%	46,000	39,000	85,000	231
	2016	36,987,000	0.21%	78,000	87%	65%	71%	28,000	25,000	53,000	145
Western Pacific Region	2012	24,802,000	0.28%	70,000	94%	81%	67%	22,000	19,000	41,000	165
	2016	24,297,000	0.26%	64,000	96%	84%	72%	20,000	18,000	38,000	156
World	**2012**	**142,425,000**	**0.70%**	**996,000**	**85%**	**59%**	**74%**	**397,000**	**352,000**	**749,000**	**540**
	2016	**143,227,000**	**0.69%**	**988,000**	**88%**	**66%**	**78%**	**355,000**	**306,000**	**661,000**	**473**

Indian Scenario

A study conducted in South India showed that the prevalence of syphilis increased from 35 (1.91%) cases in 2013 to145 (2.78%) cases in 2017. The gender-wise distribution was analyzed in 414 cases. There were 246 males and 85 females, male-to-female ratio is (3.2:1) and 30 transgender. Of 246 males, 104 were MSM and 32 had bisexual behaviors. Syphilis has shown a rising trend in a tertiary care center in North India, in 2015. A total of 103,960 pregnant women with probable active syphilis were estimated to occur in India, resulting in an estimated 53,187 adverse outcomes during the year 2012 alone. Further, it was observed that, despite 90% of pregnant women having attended at least one ANC visit, more than 90% of women were not screened for syphilis and only half of all seropositive women were treated.

Reason behind resurgence

A plausible reason for the resurgence of primary and secondary syphilis may be explained by increases in high-risk sexual behavior among people from all sociodemographic backgrounds. Also, the use of nitrate inhalants and other drugs, and an increased inclination to ignore messages promoting safe sex are thought to increase the risk. For example, a study that examined the use of methamphetamine, among MSM, reported an increase in the risk of syphilis acquisition.[19,20] Recently, the internet and social media have emerged as an important avenue for engaging sexual partners. Benzathine penicillin, the only recommended treatment to prevent mother-to-child transmission was noted to be in acute shortage in 39(41%) out of 95 countries according to a study conducted by the WHO during the time period of 2014-2016.

Resurgence of Hansen's disease (HD)

Hansen's disease is a chronic infectious disease caused by a very slow growing intracellular bacillus, Mycobacterium leprae. Early diagnosis and treatment can prevent but cannot reverse disability and the affected individual becomes no longer contagious as the treatment is started.

Although there is decrease in prevalence since the mid-1980s to elimination levels, new cases are emerging, indicating hidden cases with continued transmission. The global prevalence by 2016 was 171,948 (0.23/10,000), a decrease from that in 2015. The new cases in the year, however, were 214,783, a marginal increase compared to 2015. These figures are based on the reports of 143 countries. But reports are deficient from several countries as 17 from the African region, 24 from the Americas and 2 from the Southeast Asian region.[21]

In India, prevalence rate of 57.8/10,000 in 1983, has decreased to less than 1/10,000 by 2005 and even further came down to 0.66/10,000 by 2016 with use of MDT. All the states achieved national elimination target by 2005 except Chhattisgarh and the UT of Dadra and Nagar Haveli. By the end of March 2016, 551 districts (82.36%), out of 669 reached the target prevalence of <1/10,000.[22]

Despite the above successes, India accounts for 60% of new cases reported globally each year and are among the 22 "global priority countries" that contribute 95% of world numbers of leprosy. In the year 2007, new cases detected in India were 137,685 and nine years later in 2016, the number remained almost the same at 135,485, a significant increase over the 127,326 new cases detected in 2015. This increase in new cases is due to new strategy of Case Detection Campaign (LCDC), which resulted in the detection of 34,000 new cases in 2016 from highly endemic pockets, which accounted for 25% of annual new cases. Of the total new cases detected, almost 50% were multibacillary leprosy and the child rate was about 8.7%, which was similar to the previous year's figures, both indicating continued transmission. The LCDC also resulted in increasing the number of districts with a prevalence of >1/10,000 in the country.

National leprosy eradication program (NLEP) annual reports of the last 4 years have consistently observed that the four states/UTs (Orissa, Chandigarh, Delhi, and Lakshadweep), which achieved elimination earlier in 2011–2012, have shown a prevalence of >1 per 10,000 population. In addition, although the average national child leprosy rate is approximately 9%, the proportion of child cases was more than 10% of new cases detected in eleven states/UTs of India, with 6 of them (Tamil Nadu, Punjab, Dadra & Nagar haveli, Bihar, Mizoram and Arunachal Pradesh) showing very high rates ranging from 14% to 23%. Incubation period is around 5-20 years and symptoms are not detectable initially. Later, when detectable they are very nonspecific and easily misdiagnosed as vitiligo, fungal infections, other mycobacterial infections, allergic reactions, mucocutaneous leishmaniasis and syphilis or as diabetes or rheumatoid arthritis. Due to variable immune response, manifestations may be too mild to be detected. Migration of affected individuals to the area with relatively few cases imposes a great risk of transmitting the infection as general practitioners and even dermatologists may not be keen on recognizing the disease in early stages and services for treatment may not be readily available.

So, the disease should be suspected more often when foreign-born patients present with chronic dermatitis with peripheral nerve involvement.[23]

Genome-wide association study showed that six genes CCDC122 (13q14), C13orf31 (13q14), NOD2 (16q12), TNFSF15 (9q32), HLA-DR (6p21) and RIPK2 (8q21) of innate immune system may be associated with disease susceptibility. Other genes involved are PARK2/PACRG (6q25-q27) and NRAMP1 (2q35) TAP1, TAP2 and TNFá (6p21).[24] These may provide early diagnostic markers. Another step is development of a lateral flow test. It detects antibodies to the bacilli specific phenolic glycolipid I (PGL-I) antigen before symptoms appear. But this test is only for multibacillary cases and whether this test can detect family contacts is not yet known. Factors like under-nutrition, starvation and overcrowding causes transmission in endemic zones. These may result from the stigma, disability and depression after the diagnosis due to lack of employment or access to resources. Hunting of armadillo is another risk factor.

In India, there is increased number of relapses (536 in 2016 and 459 in 2015) due to secondary drug resistance. In 2016, India reported the largest number of retreatment cases of 6701 and cure rates are 95.4% and 91.9% for paucibacillary and multibacillary cases respectively.

Decreased treatment duration and rifampicin, ofloxacin, minocycline (ROM) therapy may lead to relapse. The latter is due to inadequate funds in many countries. Guidelines of "fixed duration therapy" (FDT) especially for all types of multibacillary leprosy is urgently needed. Use of chemoprophylaxis is another concern in "Global leprosy control strategy" as risk is ten times higher in household contacts and three to five times in neighbour and social contacts. Single dose rifampicin reduces the risk by 57% during first 2 years after administration with minimal risk of developing resistance to M. tuberculosis if there is no active TB. A study is going on in Dadra and Nagar Haveli to assess the feasibility and acceptance of this same. NLEP has also decided to start it in districts where leprosy case detection campaign (LCDC) is ongoing.[25]

Besides chemoprophylaxis, Mycobacterium Indicus Prani (MiP) vaccine introduced by NLEP in 2016 has both immuno-therapeutic and immune-prophylactic effects in multibacillary leprosy. It reduces bacillary load, improves histopathology, completely clears granuloma, reduces reactions and neuritis and reduces the duration of therapy. BCG vaccine has also been reported to impart protection against HD in different populations. The National Sample Survey (2010–2011) and surveys by other Indian leprosy institutes depicted a gap between the number of reported and actual cases. The Director General for leprosy of India in August 2016 pointed to four alarming trends. One, pockets of high endemicity with ongoing transmission. Two, hidden cases in the community revealed by ICMR. Three, the new case detection rate has remained almost the same since 2005 and finally increasing disability rates in new cases due to delayed diagnosis.

In 2016, WHO has also launched "Global Leprosy Strategy 2016-2020: Accelerating towards a leprosy-free world" with the targets of zero disabilities among new pediatric patients, a grade-2 disability rate of less than 1 case per 1 million people, zero countries with legislation allowing discrimination on basis of leprosy. The strategy is based on three core pillars: Strengthening government ownership, coordination and partnership, stop leprosy and its complications, stop discrimination and promote inclusion.

Points to Remember

- ***Steps to control pertussis are immunisation of pregnant mothers and healthcare workers, and cocooning besides ensuring a high on-time vaccine coverage of above 90%.***
- ***Diptheria resurgence can be tackled by atleast three major measures - high immunization coverage nearly 90%, prompt diagnosis and management of cases and rapid identification of close contacts.***
- ***Surveillance must be strengthened to identify new outbreaks / re-emergence of infections.***

References

1. Mir-Cros A, Codina G, Martín-Gómez MT, Fàbrega A, Fàbrega A, Martínez X, et al. Emergence of Bordetella holmesii as a Causative Agent of Whooping Cough, Barcelona, Spain. Emerg Infect Dis 2017; 23(11):1856-1859.
2. Winter K, Harriman K, Zipprich J, Schechter R, Talarico J, Watt J, et al. California pertussis epidemic, 2010. J Pediatr 2012; 161:1091-1096.
3. Queenan AM, Cassiday PK, Evangelista A. Pertactin-negative variants of Bordetella pertussis in the United States. N Engl J Med 2013; 368:583-584.
4. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine from the Advisory Committee on Immunization Practices, 2010. Centers for Disease Control and Prevention. MMWR Morb. Mortal. Wkly Rep 2011; 60(1):13-15.

5. Phalkey RK, Bhosale RV, Joshi AP, Wakchoure SS, Tambe MP, Awate P, et al. Preventing the preventable through effective surveillance: the case of diphtheria in a rural district of Maharashtra, India. BMC Public Health 2013; 13:317.
6. Scheifele DW, Ochnio JJ. Diphtheria Update. World Health Organization: Geneva, 2009
7. Organization WH. WHO–recommended standards for surveillance of selected vaccine-preventable diseases. In. Geneva, 2014; pp10-12.
8. Clarke KE. Review of the epidemiology of diphtheria 2000-2016. Geneva: World Health Organization 2017.
9. Sadoh AE, Oladokun RE. Re-emergence of diphtheria and pertussis: Implications for Nigeria. Vaccine 2012; 30(50): 7221-7228.
10. Dandinarasaiah M, Vikram BK, Krishnamurthy N, Chetan AC, Jain A. Diphtheria Re-emergence: Problems Faced by Developing Countries. Indian Journal of Otolaryngology and Head & Neck Surgery. 2013; 65:pp314-318.
11. Bhagat S, Grover S S, Gupta N, Roy R D, Khare S. Persistence of Corynebacterium diphtheriae in Delhi & National Capital Region (NCR). Indian J Med Res 2015; 142:459-461.
12. World Health Organization Prevalence and incidence of selected sexually transmitted infections Chlamydia trachomatis, Neisseria gonorrhoeae, syphilis and Trichomonas vaginalis: methods and results used by WHO to generate 2005 estimates. 2011.
13. Black V, Williams BG, Maseko V, Radebe F, Rees HV, Lewis DA. Field evaluation of Standard Diagnostics' Bioline HIV/Syphilis Duo test among female sex workers in Johannesburg, South Africa. Sex Transm Infect 2016; 92:495-498.
14. de Voux A, Kidd S, Grey JA, Rosenberg ES, Gift TL, Weinstock H, et al. State-Specific Rates of Primary and Secondary Syphilis Among Men Who Have Sex with Men - United States, 2015. MMWR Morb Mortal Wkly Rep 2017; 66:349-354.
15. Burchell AN, Allen VG, Gardner SL, Moravan V, Tan DH, Grewal R, et al. High incidence of diagnosis with syphilis co-infection among men who have sex with men in an HIV cohort in Ontario, Canada. BMC Infect Dis. 2015; 15: 356.
16. Chen XS, Yin YP, Wang QQ, Wang BX. Historical perspective of syphilis in the past 60 years in China: eliminated, forgotten, on the return. Chin Med J (Engl) 2013; 126(14):2774–2779.
17. Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance 2015; Department of Health and Human Services: Atlanta, GA, USA, 2016. Available online: https://www.cdc.gov/std/stats15/std-surveillance-2015-print.pdf (accessed on 10 November 2016).
18. Korenromp EL, Rowley J, Alonso M, Mello MB, Wijesooriya NS, Mahiane SG, Ishikawa N, Le LV, Newman-Owiredu M, Nagelkerke N, Newman L. Global burden of maternal and congenital syphilis and associated adverse birth outcomes-Estimates for 2016 and progress since 2012. PloS one. 2019 Feb 27;14(2):e0211720.
19. Willeford WG, Bachmann LH. Syphilis ascendant: A brief history and modern trends. Trop. Dis Travel Med Vaccines 2016; 2:20.
20. WHO. Weekly Epidemiological Record No. 35. 2017 Sep 1; 92:501-520.
21. NLEP Annual Report 2015-2016. Central Leprosy Division, Directorate General of Health Services, Ministry of Health and Family Welfare Government of India, Nirman Bhavan, New Delhi.
22. Boggild AK, Keystone JS, Kain K. Leprosy: a primer for Canadian physicians. CMAJ 2004; 170:71-78.
23. Scollard D, Adams LB, Gillis TP, Krahenbuhl JL, Truman RW, Williams DL. The continuing challenges of leprosy. Clin Microbiol Rev 2006; 19:338-381. doi:10.1128/CMR.19.2.338-381.2006.
24. Sharma P, Mukherjee R, Talwar GP, Sarathchandra KG, Walia R, Parida SK, et al. Immunoprophylactic effects of the anti-leprosy Mw vaccine in household contacts of leprosy patients: Clinical field trials with a follow up of 8-10 years. Lepr Rev 2005; 76:127-143.
25. Global leprosy strategy 2016–2020: Accelerating towards a leprosy-free world. New Delhi, World Health Organization, Regional Office for South-East Asia. 2016.

NEWS AND NOTES

XXXIX NATIONAL CONFERENCE OF NNF-NEOCON 2019

Organised by: NNF Telengana state in association with National Neonatology Forum, India

Date: 12th - 15th December, 2019, Venue: HICC, Hyderabad

Conference Secretariat

Dr.Dinesh K Chirla

Chief Organising Secretary - NEOCON 2019,

Phone: 9100064670, 9701443111, Email: secretariat@neocon2019.com, Website: www.neocon2019.com

INFECTIOUS DISEASES - II

ACUTE VIRAL RESPIRATORY ILLNESSES

*Sasidaran Kandasamy
**Viswateja Chitturi
***Balaji Sridharan

Abstract: *Acute respiratory illness by viruses is a major cause of morbidity and mortality in children. A systematic approach is necessary to diagnose, treat and control the disease and also to prevent inadvertent use of antibiotics. This review article discusses the epidemiology, clinical features, management and prevention of viral respiratory illnesses among children in developing countries with particular emphasis on influenza and respiratory syncytial virus.*

Keywords: *Acute respiratory illness, Influenza, Respiratory syncytial virus*

Acute respiratory infections (ARI) is one of the major causes of morbidity and mortality in developing countries like India, especially in children below 5 years of age. Most of them have a viral etiology. Rhinovirus followed by respiratory syncytial virus (RSV) is the most common cause of viral infections in children. Epidemiology, clinical features, diagnosis and management of common viral respiratory tract infections are covered with emphasis on influenza and RSV.

Etiology

RNA viruses

1. Respiratory syncytial virus: RSV is the most common cause of bronchiolitis and viral pneumonia in infants and children below 2 years of age.

2. Influenza A, B, and C: Influenza A is an important cause of morbidity and mortality worldwide. Influenza A is responsible for previous pandemics. Two subtypes which are more important are the avian flu (H5N1) and swine flu (H1N1) because of recent epidemics.

3. Rhinovirus: More than 170 serotypes have been identified. Pneumonia caused by rhinovirus is seen in young children and in those with chronic pulmonary disease.

4. Parainfluenza virus (PIV): Four types of para-influenza viruses are present, types1, 2, 3, 4. Para-influenza viruses may infect both upper and lower respiratory tract, but are predominantly associated with croup**,** bronchiolitis and pneumonia.

5. Human metapneumovirus (hMPV): It is a newly emerging RNA virus, causing serious lower respiratory tract illness in children.

6. Coronavirus: Severe acute respiratory syndrome (SARS) was caused by a corona virus that most likely originated from the Chinese horseshoe bat. Middle east respiratory syndrome (MERS) is also caused by a corona virus which had an initial mortality rate of 30%.

7. Human bocavirus 1,2,3,4 – Bronchiolitis and pertussis-like illness are most often seen in infection by Bocavirus. Human bocavirus 2, 3 and 4 are primarily enteric viruses.

DNA viruses

Adenovirus: It causes upper respiratory tract infection like pharyngitis and coryza and lower respiratory tract infections including bronchiolitis and pneumonia. Adenovirus is mostly associated with disseminated disease, unlike other viruses.

Other DNA viruses like cytomegalovirus (CMV), varicella-zoster virus (VZV) and RNA virus like enterovirus are also responsible for respiratory tract infections both in developed and in developing countries, but are of less significance.

Epidemiology

ARI, mainly of lower respiratory tract is the leading cause of death among children under five years of age in developing countries.[1-3] It results in approximately 1.9 million deaths in children per year, of which 20% are

* Head, Advanced Pediatric Critical Care Center,
** Critical Care Fellow,
*** Research Associate,
Department of Pediatrics,
Mehta Multi-Speciality Hospitals India Pvt. Ltd.,
Chennai.
email: sasidarpgi@gmail.com

estimated to be occurring in India.[4, 5] In a recent estimate of acute lower respiratory infection associated mortality, pneumonia was responsible for 28% of all deaths among 1-59 months, making it the single most important killer in this age group in India.[6] ARI accounts for 30%-50% of the total pediatric outpatient visits and 20%-30% of the pediatric admissions.[7] The causative agents include mainly viruses, (up to 60%).[8,9] Rhinoviruses accounts for 25 to 30%; RSV, parainfluenza and influenza viruses, hMPV and adenoviruses are seen in 25 to 35%; corona viruses are seen in 10% and unidentified viruses for the remainder.[10] Para-influenza viruses account for 50% of croup cases, 15% of bronchiolitis and pneumonia. Corona viruses received attention during the SARS outbreak (caused by SARS-CoV) and was responsible for more than 800 deaths worldwide. Another novel corona virus, identified as MERS-CoV was responsible for 700 deaths worldwide (~35% mortality rate) till 2017.[11] Viral co-infections occur in 20% of the illnesses. There is no consensus on the effect of co-infection on disease severity.

Retrospective analysis from our single tertiary care centre in Chennai, India showed that 248 children were admitted with viral respiratory infections during the period from October 2016 to January 2018. Viral PCR was positive in 110 children (Table I).

Most of the viral infections occur before 5 years of age and they occur predominantly in seasonal epidemics. The incubation period ranges from 1-6 days for almost all viruses. Transmission is mainly by direct contact or exposure to the infected secretions involving droplets, aerosols or contaminated surfaces. Feco-oral transmission can occur with adenovirus. Epidemiology of influenza and RSV are discussed separately.

Table I. PCR positive viral respiratory infections in PICU (n 110)*

Viral PCR	Number of Cases	Percentage (%)
RSV B	42	38.3
H1N1	21	19.2
Rhinovirus	10	9.1
PIV2	9	8.1
PIV3	9	8.1
hMPV	6	5.5
RSV A	4	3.6
Influenza B	4	3.6
Adenovirus	2	1.8
PIV1	2	1.8
H3N2	1	0.9

**Unpublished data*

Influenza

Influenza is an acute viral respiratory illness caused by influenza A, B or C.

Epidemiology: In the 20th century, three pandemics 1918, 1957 and 1968 were all caused by different strains of influenza.[12] In 21st century, the recent pandemic announced in 2009 was because of influenza A (H1N1) virus pdm2009.[13] According to a recent estimate, 2,91,243-6,45,832 influenza-associated respiratory deaths occur annually worldwide.[14] As per integrated disease surveillance programme (IDSP) in 2018, a total of 15,266 cases were reported in India, with 1,113 deaths. In 2019 till 9th June, 25,958 cases were reported, with 1061 deaths. Two peaks of influenza activity were noticed in the recent years. One peak was during February to April and the other was between August and October. Clustering of cases is noticed more during summer months in north India and during winter months in south India and eastern India.[15] The infection spreads through respiratory droplets. Incubation period ranges from 12-72 hours.

Virus morphology: Influenza viruses are single stranded RNA viruses, which belong to the family Orthomyxoviridae.There are 4 types-Influenza A, B, C, D. Types A and B can cause seasonal epidemics while C results in sporadic infections. Infuenza D viruses primarily affect cattle and are not known to infect or cause illness in people. Influenza occurs in outbreaks because of its remarkable ability to mutate, as there are periodic changes in antigenic properties of the enveloped glycoprotein, hemagglutinin and neuraminidase.

Antigenic shift and drift: Antigenic shifts are sudden major phenotypic changes that occur through reassortment of viral gene when two or more strains of influenza affect the same host or by direct adaptation of animal virus to human host. Antigenic shifts are major changes which are responsible for global pandemics since 1900. These occur in influenza A viruses.

Antigenic drifts occur due to the point mutations in the gene segments that code for hemagglutinin and neuraminidase. This phenomenon occurs in both influenza A and B.

Table II. Uncomplicated influenza infection - Clinical features

Respiratory manifestations	Non-respiratory manifestations
Rhinorrhea	Fever, chills
Cough	Malaise
Nasal congestion	Nausea and vomiting
Sore throat or throat congestion	Diarrhoea, abdominal pain
Pleuritic chest pain	Myalgia, arthralgia

Clinical features: Children affected from influenza present with varied manifestations ranging from asymptomatic infection to severe respiratory distress, systemic illness, etc. The respiratory and non-respiratory features are given in Table II. Abdominal pain, diarrhea, vomiting are noted in some children affected with influenza A (H1N1) compared to other viruses.

Apart from these clinical manifestations, complications can occur in children infected with influenza virus (Table III).[16] Otitis media, sepsis like syndrome, multi-organ dysfunction, ARDS, encephalopathy and/or encephalitis are some of the important complications seen in influenza infection.

Diagnosis: One should have a high index of suspicion in child presenting with fever, malaise and respiratory symptoms especially during epidemics. But clinical manifestations alone are not sufficient to distinguish from other viruses like RSV, adenovirus, etc. Confirmation of influenza infection should be done wherever resources are available. Many diagnostic tests are available for the detection of influenza like 1) Rapid diagnostic tests, 2) RT-PCR, 3) Viral culture, etc (Table IV).

For confirmation of diagnosis, nasopharyngeal swab, nasal swab, throat swab, ET secretions or BAL are collected and tested for influenza virus preferably before anti-viral therapy. Sensitivity of the rapid diagnostic tests is 70%, while the specificity is 95%. So, there are high chances of false negative results. Negative tests do not rule out influenza. Therefore if there is a high suspicion of infection based on clinical features and complications, early empiric therapy should be started regardless of the tests (RT-PCR or Viral culture) performed for confirmation.

Treatment: Influenza virus will respond to anti-viral therapy. Three classes of antiviral drugs are available for the treatment of influenza infection (Table V).

1. Neuraminidase inhibitor - Oseltamivir, zanamivir, peramivir.
2. Cap-dependent endonuclease inhibitor - bolaxavir
3. Adamantanes - oral amantadine, rimantidine.

Decision to treat should be based on the clinical features and epidemiological characters. Confirmation of influenza virus infection by diagnostic testing is not required to prescribe antiviral medication. Empirical treatment should not be delayed waiting for test result especially in the high-risk groups. Antiviral treatment is clinically most beneficial when started as soon as possible.[12]

Oseltamivir and inhaled zanamivir are commonly used drugs in the treatment of influenza. Oral oseltamivir is used to treat children as young as 2 weeks. It can be used to treat term and pre-term newborn also. The dosing recommendations of the drugs are discussed in Table V and VI. Oral bolaxavir is approved by US FDA in 2018, in children above 12 years of age. Third class of anti-virals (adamantanes) is not recommended now in view of resistance.

Table III. Complications and manifestations of influenza in children[16]

Age group	Complication/manifestation
Infants and pre-school children	Fever without respiratory complications, "sepsis-like syndrome", otitis media, parotitis, bronchiolitis, croup, reactive airway disease, pneumonia, myocarditis, pericarditis, rhabdomyolysisfebrile seizures, encephalopathy and/or encephalitis, invasive bacterial co-infection, reye syndrome (with aspirin exposure) sudden death, exacerbation of chronic disease
School going children	Otitis media, parotitis, bronchitis, sinusitis, reactive airway disease, pneumonia, myocarditis, pericarditis, myositis, rhabdomyolysis, encephalopathy and/or encephalitis, Reye syndrome, toxic shock syndrome, exacerbation of chronic disease.

RT-PCR – Reverse Transcription Polymerase Chain Reaction; RNA – Ribonucleic Acid

Table IV. Influenza diagnostic tests in respiratory specimens

Test category	Method	Influenza virus detected
Molecular assay (including RT-PCR)	Nucleic acid amplification	Influenza A and B viral RNA
Direct/Indirect immunofluorescence	Antigen detection	Influenza A and B antigens
Rapid influenza diagnostic test	Antigen detection	Influenza A and B antigens
Viral Culture	Viral isolation	Influenza A and B

Table V. Oseltamivir for influenza infection

Weight (Kg)	Treatment (Dosing for 5 days)	Prophylaxis (Dosing for 10 days)
2 weeks to <1 year of age*		
Any weight	3 mg /kg twice daily (3mg/kg once daily for babies less than 2 weeks of age)	3 mg/kg Once daily from 3 months age
1 to 12 years of age (based on body weight)		
15 kg or less	30 mg twice daily	30 mg Once daily
15.1 kg to 23 kg	45 mg twice daily	45 mg Once daily
23.1 kg to 40 kg	60 mg twice daily	60 mg Once daily
40.1 kg or more	75 mg twice daily	75 mg Once daily

**Govt of India, Ministry of Health Recommendation: For infants: <3 months 12 mg BD for 5 days; 3-5 months 20 mg BD for 5 days 6-11 months; 25 mg BD for 5 days*

Table VI. Influenza treatment - Other antivirals

Medication	Treatment dosing
Inhaled zanamivir	
Children (≥7-year-old for treatment)	10 mg (two 5 mginhalations) twice daily
Intravenous peramivir	
Children (2-12 year)	One 12 mg/kg dose, up to 600 mg maximum,
Children (13-17 year)	One 600 mg dose
Oral bolaxavir	
2-11 year	Not recommended
12-17 year, 40 to <80 kg	One 40 mg dose
12-17 year, >80 kg	One 80 mg dose

CDC recommends treatment especially to 3 groups, 1) Hospitalised children, 2) Patients at high risk of developing influenza infection, 3) Complicated illness. It recommends 5 days of oseltamivir and zanamivir, twice daily regimen and single dose of peramivir and bolaxavir for uncomplicated influenza. In severe illnesses or in high risk group patients, 10 days of antiviral therapy should be considered.

Other supportive management like hydration, oxygen support, high flow nasal cannula (HFNC), mechanical ventilation, treatment of super added bacterial infections should be given as per patient requirement.

Adjunctive therapies: Corticosteroids are not recommended for the treatment of adults or children with seasonal influenza, influenza-associated pneumonia, ARDS, unless clinically indicated for other reasons. Immunoglobulin preparations such as IVIG are not routinely recommended.

Respiratory syncytial virus

Respiratory syncytial virus is the most common cause of bronchiolitis and viral pneumonia in children below 2 years of age. It is a single stranded RNA virus, belongs to the family pneumoviridae. RSV contains two subgroups, RSV A and B, based on G glycoprotein, a surface protein that helps in the attachment of the virus to host cells.

Epidemiology: RSV is one of the important respiratory viruses that occur worldwide. In both temperate and tropical climate, its occurrence is seen during winter months. It occurs predominantly in children below 2 years, especially in infants below 6 months of age. The hospitalization rate for RSV infection in otherwise healthy infants is typically 0.5-4%. RSV plays a causative role in an estimated 40%-75% of cases of hospitalized bronchiolitis, 15%-40% of cases of childhood pneumonia and 6%-15% of cases of croup. It is more common in boys than in girls by a ratio of approximately 1.5:1. The incubation period from exposure to first symptom is approximately 3-5 days. Spread of infection occurs through infected droplets, either airborne or conveyed on hands or other fomites that are inoculated in the nasopharynx of a susceptible subject.

Clinical features: RSV may result in both upper respiratory and lower respiratory infection. Fever is not a regular manifestation of RSV infection. Rhinorrhea and cough are the initial symptoms, followed by wheezing. In uncomplicated cases, the disease is self limited. In progressive infections, symptoms worsen and signs of respiratory distress like tachypnea, nasal flaring, chest retractions, grunting and cyanosis develop. Signs of severe life threatening illness include central cyanosis, respiratory rate>70/min, apneic spells, severe hyperexpanded chest, silent chest on auscultation.

Diagnosis: Bronchiolitis is predominantly a clinical diagnosis. CBC may show leukocytosis with or without mononuclear predominance. The definitive diagnosis of RSV infection is based on the detection of live virus in respiratory secretions by cell culture. The detection of viral RNA by RT-PCR or detection of viral antigens in the clinical setting is strongly supportive of infection. Nasopharyngeal, throat swabs, nasopharyngeal wash are usually preferred. Chest X-ray (CXR) will show hyperexpansion of lung fields, peribronchial thickening and interstitial infiltrates.

Treatment: It is mainly supportive and symptomatic. Most children can be managed at home as this is a self limited disease.

Oxygenation: Supplemental oxygen should be started to maintain SpO_2 above 92% if hypoxemic. HFNC /CPAP are better tolerated and may even prevent the need for mechanical ventilation. However, invasive ventilation is directly preferred in children with hemodynamic instability, apnea and loss of airway protective reflexes.

Hydration: The child is started on feeds based on clinical condition, either through direct oral feeds, nasogastric or naso-duodenal feeds. IV fluids are preferred in case of severe respiratory distress.

Interventions which can be given a trial: Inhaled bronchodilators - can be tried with salbutamol or adrenaline nebulisation. Further doses are given only if documented evidence of improvement is noticed. Nebulised hypertonic saline has been documented to augment airway clearance and reduce the duration of hospital stay. But it cannot be recommended in all cases of bronchiolitis. Dexamethasone 0.6mg/kg/dose OD in combination with nebulised epinephrine can be used in severe bronchiolitis.

Interventions which are not effective: Oral bronchodilators, systemic corticosteroids / inhaled corticosteroids, chest physiotherapy, antibiotics, steam or cool mist inhalation are not routinely recommended as there is no evidence suggestive of clinical improvement on using the above measures.

Antivirals: Ribavirin administered through inhaled or oral form is continued for 3-5 days. In some trials it showed some beneficial effect on the reduction of hospitalization and mechanical ventilation. However, subsequent studies has not shown any benefit for its use. Use of this drug is recommended based on clinician judgement and experience.

Chemoprophylaxis: Chemoprophylaxis with palivizumab for high risk infants like chronic lung disease of prematurity, congenital heart disease, immunodeficiency and prematurity etc., during RSV season is recommended. It does prevent about half of the expected hospitalizations.[17]

Other viruses

Apart from influenza and RSV, other viruses like parainfluenza virus, adenovirus, human metapneumovirus, rhinovirus, corona virus etc. pose significant public health problem worldwide and in India. They infect both upper respiratory and lower respiratory tract which results in varied manifestations and complications.

Clinical features: They are similar in most of the respiratory viruses and it is difficult to identify the organism based on the features alone. Viral infection may manifest either with upper respiratory or lower respiratory symptoms based on the site of infection. Extra-pulmonary features like ocular, gastrointestinal, urinary, nervous system features, etc. are usually seen in adenoviral infection (Table VII).

Table VII. Extra-pulmonary features of adenovirus infection

Organ involved	Clinical feature
Skin	Exanthematous rash
Ocular	Conjunctivitis acute follicular conjunctivitis epidemic keratoconjunctivitis
Nervous	Aseptic meningitis, meningoencephalitis, encephalitis
Gastrointestinal	DiarrhoeaHepatitis
Urinary	Hemorrhagic cystitis
Disseminated disease	Multi-organ dysfunction syndrome (MODS)

Most of the viral illnesses initially present with rhinorrhea, cough, especially brassy cough in croup and wheezing. But some infections may progress gradually, leading to tachypnea, tachycardia, signs of respiratory distress like nasal flaring, chest retractions, peripheral and central cyanosis, etc. Involvement of other organs may be seen either due to direct viral infection, immune reaction to infection or hypoxemia leading to MODS.

Diagnosis: Laboratory evaluation may not be required in all children. High risk patients or those presenting with severe disease needs work up to assess disease severity, identify pathogen and to identify complications. The diagnostic accuracy has improved when laboratory evaluation is combined with chest x-ray, history and physical examination.[18-20]

Complete blood count: Leukocytosis or leukopenia with or without lymphopenia, is predominantly seen in corona virus infection. Elevated transaminases are mostly seen in infection with corona virus and adenoviral infection.

Chest-Xray: Radiographic findings of viral pneumonia are variable and overlapping. Two types of radiologic aspects can be observed: (a) insidious course of pneumonia and (b) rapidly progressive virulent pneumonia. In insidious course, CXR shows 4- to 10-mm, poorly defined nodules, patchy areas of peribronchial ground-glass opacity and consolidation with hyperinflation. In virulent pneumonia, the chest radiographs show unilateral (Fig.1) or bilateral patchy opacities, ground-glass opacity or poorly defined centrilobular nodules and bilateral hyperinflation. CXR in croup shows steeple sign (Fig.2).

Fig.1. Antero-posterior CXR depicting viral pneumonia caused by Rhinovirus in a 11-year-old girl

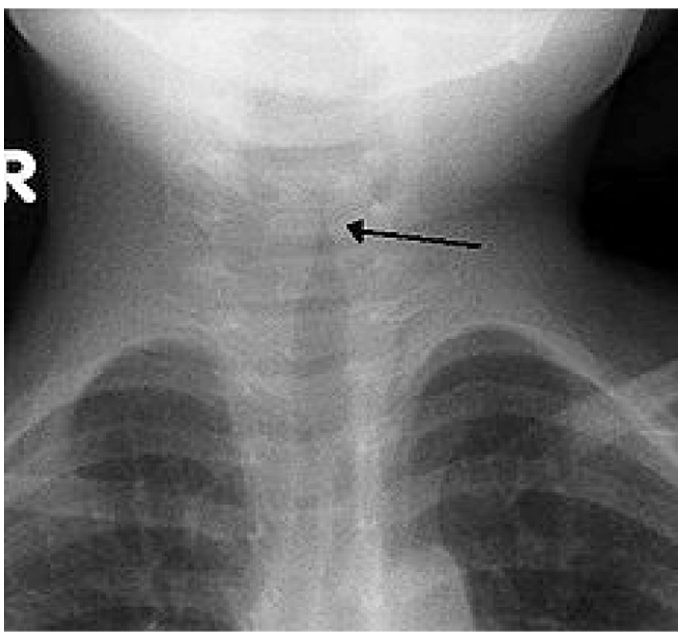


Fig.2. Antero-posterior CXR showing steeple sign in a child with croup

Chest CT scan: CT scan has revolutionized the diagnosis of viral pneumonia. Thin section CT scan can show parenchymal defects and aid in diagnosis, especially if CXR is normal.

Viral isolation: Detection of the infecting agent does not alter treatment, but it will reduce the inappropriate use of antibiotics in common respiratory infections. Identifying the viral pathogen can be done by 4 methods - virus culture, serology, immunoflorescence / antigen detection and

Table VIII. Severity assessment of croup - Westley severity score

Feature	0	1	2	3	4	5
Chest wall retraction	None	Mild	Moderate	Severe		
Stridor	None	With agitation	At rest			
Cyanosis	None				With agitation	At rest
LOC	Normal					Disoriented
Air entry	Normal	Decreased	Markedly decreased			

LOC – Level of consciousness

Table IX. Treatment recommendations of croup based on severity score

Severity	Treatment
Mild (<2)	Corticosteroids - Dexamethasone @0.6mg/kg-single dose and IM
Moderate (3-7)	Corticosteroids-Observe for 4 hours, if needed – hospitalisation followed by treatment like severe croup
Severe (>8)	Corticosteroids + Nebulised epinephrine (0.5 ml/kg/dose with maximum of 5 ml)

nucleic acid / PCR-based tests. Viral culture is gold standard, but labour sensitive and takes prolonged time to identify the organism. Serology and cultures are not used routinely now. RT-PCR is used by most centres for identification of the organism, as it helps in etiological diagnosis with clinically relevant timing. These tests are commonly performed on respiratory secretions, throat swab, nasopharyngeal swabs, BAL secretions, etc.

Treatment: The main treatment of viral respiratory illnesses are supportive. Treatment of croup depends mostly on the severity of the illness, which is determined by Westley severity score (Table VIII). Treatment of croup is mainly based on the severity of the illness (Table IX).

Oxygen support: The main supportive measure required in acute viral infection is to maintain oxygenation. O_2 may be provided by nasal cannula, non-invasive airway, or mechanical ventilation. Oxygenation support is mainly decided by the clinical condition of the child. In mild cases, the child will settle with simple flow O_2. In respiratory distress, the child may require high flow nasal cannula support. In cases of respiratory failure or no improvement with non invasive ventilation, the child is provided with mechanical ventilation support.

Hydration: Maintaining adequate hydration status is either via supervised oral intake, tube feeds or intravenous fluids, depending on the condition of the child.

Antiviral therapy: Specific antiviral therapy is approved for influenza and RSV infection. Antiviral therapy against other viruses' are also available, but still needs further evidence for approval. They are used in severe respiratory illnesses. A summary of antivirals used for treatment and prophylaxis (in high risk group) is given in Table X.

Table X. Antiviral and prophylactic medications used for viral infections

Viral agent	Treatment	Prophylaxis
Influenza	Oseltamivir Zanamivir Peramivir	Influenza vaccine, Chemoprophylaxis with zanamivir or oseltamivir
RSV	Ribavirin	RSV immunoglobulin Palivizumab
Parainfluenza	Ribavirin	Not available
Adenovirus	Ribavirin	Not available
Cytomegalovirus	Ganciclovir Foscarnet	Intravenous immunoglobulin
Corona virus	Cidofovir	Not available.
Rhinovirus	Ribavirin	Not available.

Management of concomitant bacterial infection

Secondary bacterial infections are an important cause of mortality and morbidity in viral infections. It has been observed that most of the mortality during the 1917-1918 influenza pandemic was secondary to superadded bacterial pneumonias.[18-20]

Points to Remember

- ***Influenza infection in children may lead to asymptomatic illness to severe respiratory distress. Empirical oseltamivir should be started immediately in epidemics, if suspicion of influenza is present.***
- ***RSV is the most common viral illness in infants, especially below 6 months of age. Palivizumab can be used in high risk group who get exposed to the virus.***
- ***Oxygen and hydration are the only evidence-based therapies approved for bronchiolitis.***
- ***Treatment with anti virals should not be withheld, based on rapid diagnostic tests alone as there are chances of false negative results.***
- ***More epidemiological studies are needed in developing countries, so that it can help in framing guidelines, following preventive measures and framing vaccination policies.***

References

1. Campbell H. Acute respiratory infection: a global challenge. Arch Dis Child1995; 73(4):281.
2. Victora CG, Fenn B, Bryce J, Kirkwood BR. Co-coverage of preventive interventions and implications for child-survival strategies: evidence from national surveys. The Lancet 2005; 366(9495):1460-1466.
3. Wardlaw TM, Johansson EW, Hodge MJ. Pneumonia: The forgotten killer of children: The UNICEF/WHO. 2006.
4. Reddaiah V, Kapoor SK. Acute respiratory infections in rural underfives. Indian J Pediatr 1988; 55(3):424-426.
5. Williams BG, Gouws E, Boschi-Pinto C, Bryce J, Dye C. Estimates of world-wide distribution of child deaths from acute respiratory infections. Lancet Infect Dis 2002; 2(1):25-32.
6. Collaborators MDS. Causes of neonatal and child mortality in India: a nationally representative mortality survey. The Lancet 2010; 376(9755):1853-1860.
7. Selvaraj K, Chinnakali P, Majumdar A, Krishnan IS. Acute respiratory infections among under-5 children in India: A situational analysis. J Nat Sci Biol Med 2014; 5(1):15.
8. Bicer S, Giray T, Çöl D, Erdað GÇ, Vitrinel A, Gürol Y, et al. Virological and clinical characterizations of respiratory infections in hospitalized children. Ital J Pediatr 2013; 39(1):22.
9. Bhuyan GS, Hossain MA, Sarker SK, Rahat A, Islam MT, Haque TN, et al. Bacterial and viral pathogen spectra of acute respiratory infections in under-5 children in hospital settings in Dhaka city. PLoS One 2017; 12(3):e0174488.
10. Simoes EA, Cherian T, Chow J, Shahid-Salles SA, Laxminarayan R, John TJ. Acute respiratory infections in children. Disease Control Priorities in Developing Countries 2nd edn: The International Bank for Reconstruction and Development/The World Bank; 2006; pp483-497.
11. Donnelly CA, Malik MR, Elkholy A, Cauchemez S, Van Kerkhove MD. Worldwide reduction in MERS cases and deaths since 2016. Emerg Infect Dis 2019 Sep. https://doi.org/10.3201/eid2509.190143.
12. Narain JP, Bhatia R. Influenza A (H1N1): responding to a pandemic threat. Indian J Med Res 2009; 129(5):465-468.
13. Control CfD, Prevention. Outbreak of swine-origin influenza A (H1N1) virus infection-Mexico, March-April 2009. Morb Mortal Wkly Rep. 2009; 58(17):467.
14. Iuliano AD, Roguski KM, Chang HH, Muscatello DJ, Palekar R, Tempia S, et al. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. The Lancet 2018; 391(10127):1285-1300.
15. States/Uts to Central Surveillance Unit, Integrated Disease Surveillance Programme, CDC, Delhi Dated 10.06.2019, Time: 05.30 PM.
16. Uyeki TM, Bernstein HH, Bradley JS, Englund JA, File Jr TM, Fry AM, et al. Clinical practice guidelines by the Infectious Diseases Society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza. Clin Infect Dis. 2019; 68(6):e1-e47.
17. James E. Crowe Jr, Respiratory syncytial virus, chapter 287, Nelson Textbook of Paediatrics, 21st edn, Elsevier, 2019.
18. Cha MJ, Chung MJ, Kim K, Lee KS, Kim TJ, Kim TS. Clinical implication of radiographic scores in acute Middle East respiratory syndrome coronavirus pneumonia: Report from a single tertiary-referral center of South Korea. Eur J Radiol 2018; 107:196-202.
19. Zhang D, Mao H, Lou X, Pan J, Yan H, Tang H, et al. Clinical evaluation of a panel of multiplex quantitative real-time reverse transcription polymerase chain reaction assays for the detection of 16 respiratory viruses associated with community-acquired pneumonia. Arch Virol 2018; 163(10):2855-2860.
20. Yýldýrým D, Özdoðru DS, Þeflek B, Cimentepe M, Bayearam Ý, Yarkýn F. Detection of influenza virus infections by molecular and immunofluorescence methods. Mikrobiyol Bul 2017; 51(4):370-377.

INFECTIOUS DISEASES - II

INFECTION CONTROL IN HOSPITAL PRACTICE

Digant D Shastri

Abstract: *Healthcare associated infections are a major cause of morbidity and mortality posing challenge to the treating clinicians. Considering this along with prolonged stay and the cost of medicare, efforts should be made to make the hospitals as safe as possible by preventing such infections. Proper adherence to infection control by healthcare providers is a highly effective strategy in reducing hospital acquired infections. Measures of infection control include observing hand hygiene, identifying patients at risk of nosocomial infections and following standard precautions to reduce transmission. Environmental factors and architectural layout of both inpatient and outpatient areas also needs to be taken care to control spread of infection.*

Keywords: *Hospital acquired infection, Infection control, Hand hygiene*

Healthcare associated infection (HAI) is one of the most common complications of health care management. It is a serious health hazard as it leads to increased patients' morbidity and mortality, prolonged hospital stay and the costs associated with treatment. Effective infection prevention and control are vital to provide high quality health care for patients and a safe working environment for healthcare personnel. It is important to minimize the risk of spread of infection to patients and staff in hospital by implementing good infection control programme. The modes of spread of infection are given in Fig.1.

Environment

A clean environment plays an important role in the prevention of healthcare associated infections (HAI). Many factors, including the design of patient care areas, operating rooms, air quality, water supply and the laundry can significantly influence the transmission of HAI.

* Senior Consultant Pediatrician and CEO, Killol Children Hospital, Surat
email: drdigantshastri@gmail.com

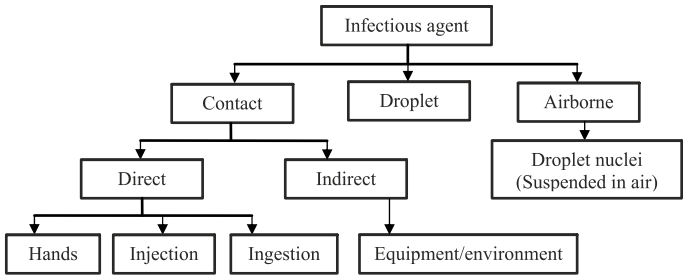


Fig.1. Transmission based infection sources

To minimise the risk of HAI, the following points should be ensured while designing of the facilities[1,2,3] (Box 1).

High risk areas

Ventilation systems should be designed and maintained to minimize microbial contamination. The air conditioning filters should be cleaned periodically and fans that can spread airborne pathogens should be avoided in high-risk areas. High-risk areas such as operating rooms and critical care units also require special ventilation systems. Filtration systems (air handling units) designed to provide clean air should have high efficiency particulate air (HEPA) filters in high-risk areas. Unidirectional laminar airflow systems should be available in appropriate areas in the hospital construction. Ultraclean air (air containing less than 10 CFU/M^3) is valuable in some types of cardiac surgery/neurosurgery/implant surgery theatres and

Box 1. Factors preventing HAI

- Adequate safe water supply
- Adequate floor space for beds
- Adequate interbed space
- Adequate hand washing facilities
- Adequate ventilation for isolation rooms and high-risk areas like operation theatres, transplant units, intensive care areas, etc.
- Adequate isolation facilities for airborne, droplet, contact isolation and protective environment
- Appropriate waste management facilities and practices

transplant units. The general areas, if not air- conditioned, should be well ventilated. In the operation theatres, temperature should be maintained between 20°C and 22°C and humidity between 30% and 60% to prevent bacterial growth.

Waiting area - Design

The waiting area and clinic should be adequately ventilated for good air exchange. For closed waiting rooms, exhaust should be placed to allow air to circulate from inside the clinic to outside. Infection control poster or signage about symptoms of communicable diseases should be placed at reception. Patient with symptoms of communicable diseases should be given appropriate instruction(s) and triage accordingly. Posters with visual alerts for respiratory hygiene / cough etiquette should be displayed as appropriate. Provision for practicing hand hygiene is preferable in waiting area.

In the clinician's chamber

Hand hygiene facilities are necessary inside the doctor's chamber preferably near the examination bed. The wash basin should have a deep sink and should preferably be made of easily washable surfaces like stainless steel. The adjacent walls should have tiles which can be regularly cleaned. Wooden cabinets which are not easily cleanable should be avoided. Paper towels should be available near the sink and a dustbin for disposal of the towels. Disposable paper sheets can be laid on the surface of examination bed / infant weighing scales. If using uncovered examination table, the surface should be cleaned and disinfected daily atleast once and whenever visibly soiled.

Environmental and surface sanitation

Some bacterial species, including C. difficile spores, Vancomycin-resistant enterococci (VRE), Methicillin-resistant Staphylococcus aureus (MRSA) and Acinetobacter species, can survive for 4-5 months or more, on dry surfaces, while norovirus can survive for up to one week. The levels of surface contamination by microorganisms in hospitals are low in comparison to the concentration on patient's skin or in stools. As the infectious dose for many nosocomial pathogens is low, transmission can occur even at low concentrations. For example, the infectious dose for norovirus is thought to be as low as one virus particle. Most patient care areas should be cleaned by wet mopping. Dry sweeping is not recommended. The use of a neutral detergent solution improves the quality of cleaning. Physical (mechanical or manual) cleaning is the most important step in cleaning.

Based on chances of contact, the general surfaces are divided into two groups - those with minimal hand contact (e.g. floors and ceilings) and those with frequent skin contact ('frequently touched' or 'high risk' surfaces). Frequently touched surfaces in patient- care areas should be cleaned using a detergent solution and more frequently than surfaces with minimal hand contact.

Detergent solution is adequate for cleaning general surfaces (e.g. floors, walls), as well as non-patient-care areas (e.g. administrative offices). Damp mopping is preferable to dry mopping for routine cleaning. Walls and blinds in patient-care areas should be cleaned with detergent solution when they are visibly dusty or soiled. Window curtains should be regularly changed in addition to being cleaned when soiled. Sinks and washbasins should be cleaned with a detergent solution.

Cleaning of frequently touched surfaces which are in close proximity to patient can be done with a detergent solution designed for general purpose cleaning but compared to minimal contact surfaces, it should be cleaned more frequently. Door knobs, bedrails, over-bed tables, light switches, table tops and wall areas around the toilet in the patient's room are the frequently touched surfaces and for cleaning these surfaces, the exact choice of detergent will depend on the nature of the surface and the likely degree of contamination.

Cleaning should always precede disinfection as residual debris reduces effectiveness of disinfection. The floor should be cleaned at least three times in 24 hours - ideally. Mop heads are cleaned daily, at the beginning and end of each day. Also the mop head should be dried in sunlight every day. Rubber gloves can be used for staff protection. Housekeeping personnel should wear gloves for potential contact with blood, body fluids, mucous membranes, nonintact skin, or contaminated equipment.

Low level disinfectants (ethyl or isopropyl alcohol (70-90%), sodium hypochlorite (5.25-6.15% household bleach diluted 1:500 provides >100 ppm available chlorine, phenolic germicidal detergent solution, quaternary ammonium germicidal detergent solution) are usually enough for use in outpatient settings. Disinfectants are usually needed when soiled with vomitus/excreta, or on frequently touched surfaces like doorknobs. High level disinfectants are (peracetic acid, hydrogen peroxide, glutaraldehyde, hypochlorous acid, hypochlorite, ortho-phthaldehyde) usually avoided for noncritical equipments like otoscope, weighing scales, etc.

While caring for nebulisation machine, it is preferable to use disposable mask and tubing per patient. The mask and T shaped part should be washed with mild soap and water and dried on clean cloth. Tubings should not be washed or rinsed. The tubing with the mask / T shaped part should be connected and machine run for 10-20 seconds to dry the inside of the nebuliser.

Biomedical waste management

Proper disposal of hospital waste is part of hospital infection prevention measures. Apart from its being a mandatory legal requirement, strict adherence to the Biomedical Waste Management Rules by the Government of India is a duty that should be carried out to protect the health and well-being, not only of the patients and staff of the hospitals, but also of the public at large.Waste management should be conducted in coordination with the infection control team.[4] Few important principles of waste management which can help in infection control in the hospital are given in Box 2.

Hand hygiene

Hands are the most common vehicle for transmission of organisms. Hand hygiene is the single most effective means of preventing the horizontal transmission of infections among hospital patients and health care personnel. Practicing hand hygiene before every patient contact (including between caring for different patients and between different care activities for the same patient) and after any activity or contact that potentially results in hands becoming contaminated (such as removal of gloves) reduces the risk of cross-contamination[5,6] (Fig.2). One can use plain soap, antimicrobial agent, such as an alcoholic hand rub or waterless antiseptic agent.

Health care staff dressing

An open forearm in clinical care is preferred to avoid contamination of clothes. Apron helps to decrease the risk

Box 2. Principles in waste management

- Segregate clinical (infectious) waste from non-clinical waste in dedicated containers
- Transport waste in a dedicated trolley
- Store waste in specified areas with restricted access
- Mark the storage areas with a biohazard symbol
- Ensure that the carts or trolleys used for the transport of segregated waste collection are not used for any other purpose – they should be cleaned regularly

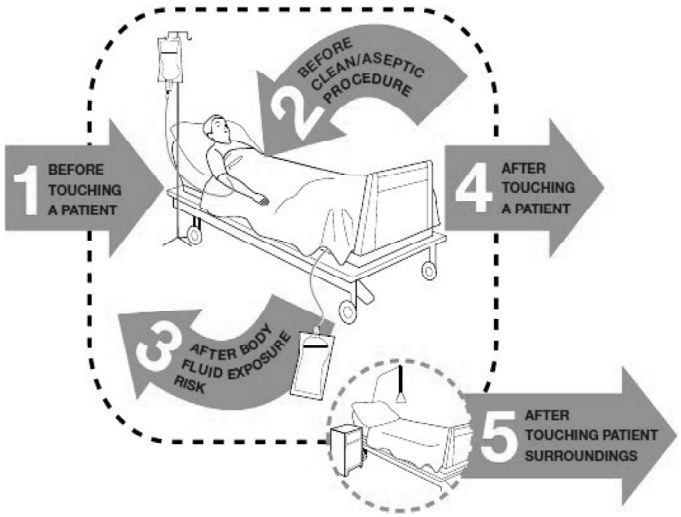


Fig.2. The 5 moments for hand hygiene

(Source: WHO 2009)

of exposure of personal clothes. But the apron should be buttoned. If aprons are not worn, tie should be tucked inside shirt. Coats, sweaters and jackets cannot provide protection as they are seldom washed. One can wear apron over them. Thermals can be worn to protect against cold. Artificial or false nails have been reported to be associated with higher levels of infectious agents, especially Gram-negative bacilli and yeasts, than natural nails. Hence, fingernails should be kept short (e.g. the length of the finger pad) and clean. Artificial fingernails should not be worn.

Hand contamination with infectious agents is increased with ring wearing. The consensus recommendation is to strongly discourage the wearing of watches, rings or other jewellery during health care; however if jewellery must be worn in clinical areas it should be limited to a plain band (e.g. wedding ring) and this should be moved about on the finger during hand hygiene practices. In high-risk settings such as operating suites/ rooms, any jewellery, even a plain band, should not be worn. Each health care facility should develop policies on the wearing of jewellery, artificial fingernails or nail polish by healthcare workers.

Personal protection: Personal protective equipment (PPE) refers to a variety of barriers, used alone or in combination, to protect mucous membranes, airways, skin and clothing from contact with infectious agents (Box 3). Selection of PPE is based on the type of patient interaction, known or possible infectious agents, and/or the likely mode(s) of transmission.

When gloves are worn in combination with other PPE, they are put on last. Removal of aprons and gowns before

Box 3. Personal protective equipments

- Gloves
- Mask
- Gown
- Apron
- Protective eye wear (goggles)
- Shoe covers
- Cap

leaving the patient-care area prevents possible contamination of the environment outside the patient's room. Aprons and gowns should be removed in a manner that prevents contamination of clothing or skin. The outer, 'contaminated', side of the gown is turned inward and rolled into a bundle and then discarded into a designated container for waste or linen to contain contamination.

After use the needles should not be recapped/needles should be disposed in puncture proof closed containers which should be available at the point of care. Overspill of these containers should be avoided. These containers should be out of reach of children. The needles and all sharps are to be collected and disposed in a special container provided by waste management. Clipping, bending or breaking of needles to make them non-usable must not be practised as this may cause accidental inoculation

Immunisation for health care workers[7]

- Hepatitis B

  Three-dose series at 0, 1 and 6 months. Test for hepatitis B surface antibody (anti-HBs) to document immunity 1-2 months after third dose. If anti-HBs is atleast 10 mIU/ml (positive), the patient is immune. No further serologic testing or vaccination is recommended. If anti-HBs is less than 10 mIU/ml (negative), the patient is unprotected from hepatitis B virus (HBV) infection; revaccinate with a three-dose series. Retest anti-HBs, 1-2 months after dose 3. If anti-HBs is negative after six doses of vaccine, patient is a non responder.
- Measles, mumps and rubella: Two doses four weeks apart.
- Tetanus: Booster once every 10 years.
- Meningococcal: One dose to HCW who might contact patients with meningococcal infections.

Box 4. HICC - Policy

- Commitment towards maintenance of surveillance over HAIs.
- Develop a system for identifying, reporting, analyzing, investigating and controlling HAIs.
- Develop and implement preventive and corrective programs in specific situations where infection hazards exist.
- Advice the medical superintendent on matters related to the proper use of antibiotics, develop antibiotic policies and recommend remedial measures when antibiotic resistant strains are detected.
- Review and update hospital infection control policies and procedures from time to time.
- Help to provide employee health education regarding matters related to HAIs.

- Varicella: For HCW who have no serologic proof of immunity, prior vaccination or history of varicella disease (chickenpox). Two doses of varicella vaccine, four weeks apart.
- Influenza: Appropriate dose of vaccine which confers protection from the current circulating epidemic strain must be given, as and when available and recommendations by the Government of India must be followed.

Hospital infection control program

Prevention of HAI in patients is a concern of everyone in the facility and is the responsibility of all individuals and services providing health care. Risk prevention for patients and staff must be supported at the level of senior administration.

The role of the hospital infection control committee (HICC) is to implement the annual infection control programme and policies (Box 4).

HICC should have regular meeting preferably once a month and as often as required. The committee is responsible for establishing and maintaining infection prevention and control, its monitoring, surveillance, reporting, research and education.

Points to Remember

- ***Design of patient care areas, operating rooms, air quality, water supply and the laundry can significantly influence the transmission of HAI.***

- ***In high risk areas, the air handling units designed to provide clean air should have high efficiency particulate air (HEPA) filters.***
- ***Nebulisation machine, preferably use disposable mask and tubing per patient. The mask and T shaped part should be washed with mild soap and water.***
- ***Practicing hand hygiene before every episode of patient contact and after any activity or contact that potentially results in hands becoming contaminated reduces the risk of cross-contamination.***

References

1. Starling B. Postnote July 2005 Number 247 Infection control in healthcare settings. [Last accessed date March 10, 2014]. Available from: http://www.parliamentuk/parliamentary_offices/post/pubs2005.cfm.
2. Australian Government Department of Health and ageing; 2008. [Last accessed date March 10, 2014]. Infection control guidelines for the prevention of transmission of infectious diseases in the health care setting. Available from: http://www.health.gov.au/internet/main/./icg-guidelines-index.htm.
3. Hospital Infection Control Guidelines: Indian Council of Medical Research Antimicrobial Stewardship Program.
4. Guideline for isolation precautions: Preventing transmission of infectious agents in healthcare settings. 2014. Mar 10, Available from: http://www.cdc.gov/hicpac/pdf/isolation/Isolation2007.pdf. [PubMed: 18068815].
5. WHO guidelines on hand hygiene in health care: A summary. 2014. Mar 10, Available from: http: www.whqlibdoc. who.int/hq/2009/WHO_IER_PSP_ 2009.07_eng.pdf.
6. Pittet D. Hand hygiene: Improved standards and practice for hospital care. Curr Opin Infect Dis. 2003; 16:327-35. [PubMed: 12861085].
7. Advisory Committee on Immunization Practices. Recommended adult immunization schedule: United States, 2010. Ann Intern Med. 2010; 152:36–9. [PubMed: 20048270].

CLIPPINGS

Parenteral Antibiotic Therapy Duration in Young Infants With Bacteremic Urinary Tract Infections.

This multicenter retrospective cohort study included infants d”60 days old who had concomitant growth of a pathogen in blood and urine cultures at 11 children’s hospitals between 2011 and 2016. Short-course parenteral antibiotic duration was defined as d”7 days, and long-course parenteral antibiotic duration was defined as >7 days. Propensity scores, calculated using patient characteristics, were used to determine the likelihood of receiving long-course parenteral antibiotics. We conducted inverse probability weighting to achieve covariate balance and applied marginal structural models to the weighted population to examine the association between parenteral antibiotic duration and outcomes (30-day UTI recurrence, 30-day all-cause reutilization and length of stay).Among 115 infants with bacteremic UTI, 58 (50%) infants received short-course parenteral antibiotics. Infants who received long-course parenteral antibiotics were more likely to be ill appearing and have growth of a non–Escherichia coli organism. There was no difference in adjusted 30-day UTI recurrence between the long- and short-course groups (adjusted risk difference: 3%; 95% confidence interval: “5.8 to 12.7) or 30-day all-cause reutilization (risk difference: 3%; 95% confidence interval: “14.5 to 20.6). Young infants with bacteremic UTI who received d”7 days of parenteral antibiotics did not have more frequent recurrent UTIs or hospital reutilization compared with infants who received long-course therapy. Short-course parenteral therapy with early conversion to oral antibiotics may be considered in this population.

Desai S, Aronson PL, Shabanova V, Neuman MI, Balamuth F, Pruitt CM, et al. Parenteral Antibiotic Therapy Duration in Young Infants With Bacteremic Urinary Tract Infections. Pediatrics 2019, 144 (3) e20183844; DOI: 10.1542/peds.2018-3844.

NEWS AND NOTES

GLOBAL CONGRESS ON PEDIATRICS AND NEONATOLOGY

Date: 21st – 22nd October, 2019 Venue: Tokyo, Japan

Email: Pediatrics@inovineconferences.com

Website: pediatrics-conferences.com

DRUG PROFILE

ANTICOAGULANTS IN PEDIATRICS

***Jeeson C Unni**
****Ranjit Baby Joseph**

Abstract: *The incidence of provoked and unprovoked thromboembolism in children is increasing and hence the use of anticoagulants. There are many oral and parenteral anticoagulants in the market. Many of the newer agents are promising but pediatric data on safety and efficacy are scarce. The anticoagulants can be divided into the older multitargeted agents (heparin, low-molecular-weight heparin and warfarin) and the newer targeted agents (argatroban, bivalirudin and fondaparinux). The newer targeted anticoagulants have properties that may make them more attractive for use in specific clinical situations.*

Keywords: *Anticoagulants, Warfarin, Heparin, Lowmolecular weight heparin, Pediatrics*

Thromboembolic disorders in children are relatively rare compared to adults due to the various physiologic protective mechanisms involved.[1] However, the incidence of venous thromboembolism (VTE) in children has seen a significant and steady increase in recent years.[2] This is attributable in large part to technological advances in the management of critically ill children, such as sick neonates, children with congenital heart disease and children with serious and often life-threatening and chronic conditions, such as cancer. Another sizable proportion of the rising incidence is attributable to the widespread use of central venous catheters. It is estimated that 95% of VTEs in children are provoked events with the presence of central venous catheters being the most common risk factor.[3] The first published report of use of warfarin in children was in 1976, although the drug was in use in the pediatric age group since 1962.[4] The currently available anticoagulants may be classified as multitargeted anticoagulants [heparin, low-molecular-weight heparin (LMWH) and warfarin] and the newer targeted anticoagulants (argatroban, bivalirudin and fondaparinux).[5] Newer oral anticoagulants that act via direct thrombin inhibition (Ximelagatran) or direct Factor Xa inhibition (Rivaroxaban) have superior pharmacokinetics than standard agents. Due to lack of pediatric studies, recommendations for use of newer anticoagulants in children are not available.

The mainstay of treatment of acute pediatric thrombosis is anticoagulation with heparins and/or vitamin K antagonists. Only two international, randomized controlled trials of anticoagulation for VTE treatment have been published in children. The Reducing Exsanguination Via In Vivo Expandable Foam (REVIVE) trial was performed to compare Unfractionated Heparin (UFH) with transition to vitamin K antagonists to LMWH in the treatment of VTE in children aged 60 days to 18 years. The study was closed early, but it did show that 9% of subjects had major bleeding and 9% had recurrent thrombosis. The pilot-feasibility phase of the Kids-DOTT trial enrolled a prespecified 100 children with VTE, of which 69 were randomized to 6 weeks versus 3 months of anticoagulant of choice. Rates of symptomatic recurrent VTE and clinically relevant bleeding were 3.3% and 1.4%, respectively. The rest-of-trial phase of Kids-DOTT is ongoing, with nearly 400 children enrolled as of date.[6]

Present guidelines for duration of anticoagulation in pediatric VTE are based largely upon evidence from adult trials and corresponding treatment recommendations in adult VTE. The duration of anticoagulation in pediatric VTE needs to reflect a balance between risks of recurrent VTE and anticoagulant-associated bleeding, as well as quality of life and cost of care. Given the state of current knowledge, many of these factors are as yet unclear and difficult to estimate despite their importance in informing clinical decision-making. It is hoped that the ongoing National Heart Lung Blood Institute(NHLBI)-funded multinational Kids-DOTT (Duration of Therapy for Thrombosis) trial will provide high-quality evidence by which to inform the future standard of care in pediatric VTE treatment.[6]

The major categories of anticoagulants are summarized in Table I.

* Editor-in-chief, IAP Drug Formulary and Lead Consultant - Pediatrics

** Senior Specialist - Pediatrics, Aster Medcity, Kochi.

email: jeeson1955@gmail.com

Table I. Anticoagulant categories

Sl no	Class	Agents
1	Vitamin K antagonists	Warfarin, acenocoumarol, phenprocoumon
2	Indirect thrombin inhibitors	Unfractionated heparin, low molecular weight heparin (enoxaparin, dalteparin, tinzaparin, ardeparin, nadroparin, reviparin)
3	Indirect Factor Xa inhibitors	Fondaparinux, idraparinux
4	Direct thrombin inhibitors	Bivalirudin, argatroban, melagatran, ximelagatran, dabigatran
5	Direct Factor Xainhibitors	Rivaroxaban, apixaban

Vitamin K antagonists

Vitamin K antagonists (VKA) are the most commonly used oral anticoagulants in children of which most frequently used drug is warfarin. Acenocoumarol and phenprocoumon are other two agents which are used in some European and South American countries. These drugs exert their anticoagulant effect by interfering with the cyclic inter conversion of vitamin K and its 2, 3 epoxide. Vitamin K is a cofactor for the post translational carboxylation of glutamate residues of coagulation proteins (factors II, VII, IX and X). In addition to their anticoagulant effect, the VKA inhibit carboxylation of the regulatory anticoagulant proteins C and S and therefore have the potential to exert a procoagulant effect.[7] It takes at least 48 to 72 hours for the anticoagulant effect of VKA; if an immediate effect is required, unfractionated or low molecular weight heparin must be given concomitantly.

Warfarin

The major advantage of warfarin is the oral route of administration. It has high bioavailability and reaches maximal blood concentrations within 90 minutes of oral administration. The drug is highly protein bound (99%) and is metabolized in the liver through the cytochrome P450 system, with a half-life of 42 hours.[8] There are several significant limitations that have led the pediatricians to slowly reduce the use of this agent.[9] Some of them are the need for frequent monitoring due to narrow therapeutic index, availability of tablets as the sole dosage form in most countries, numerous drug and food interactions.[10]

Uses: Warfarin sodium is the drug of choice for the treatment of systemic thromboembolism in children (not neonates) after initial heparinisation. It may also be used occasionally for the treatment of intravascular or intracardiac thrombi. Warfarin sodium is used prophylactically in those with chronic atrial fibrillation, dilated cardiomyopathy, certain forms of reconstructive heart surgery, those with mechanical prosthetic heart valves and some forms of hereditary thrombophilia (e.g. homozygous protein C deficiency).

Dosage:[11] The base-line prothrombin time should be determined but the initial dose should not be delayed whilst awaiting the result. An induction dose is usually given over 4 days. The subsequent maintenance dose depends on the prothrombin time, reported as international normalised ratio (INR) and should be taken at the same time each day.

Neonates and children: 200mcg/kg orally as a single dose on first day, reduced to 100mcg/kg once daily for following 3 days. If INR is <1.4, 200mcg/kg once daily (Max 10mg), If INR is >3, 50mcg/kg once daily (Max 2.5mg) are used and if INR>3.5, the dose is omitted.

The dosing is adjusted according to INR. The usual maintenance 100-300mcg/kg once daily (may need up to 400mcg/kg once daily especially if bottle fed). The therapeutic INR range required is between 2.0 and 3.0. For patients with a mechanical prosthetic valve, a higher INR is recommended, depending on the location and type of the prosthetic valve.

Precautions and side effects: Most common adverse events encountered are bleeding, skin necrosis and osteoporosis.[12,13] Vitamin K, fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC) may be administered to reverse bleeding.

If major bleeding occurs warfarin is stopped; phytomenadione (vitamin K1) is given as slow intravenous injection and then dried prothrombin complex (factors II, VII, IX and X) can be given. If dried prothrombin complex is unavailable, fresh frozen plasma can be given but is less effective; recombinant factor VIIa is not recommended for emergency anticoagulation reversal.

INR >8.0, minor bleeding-stop warfarin; give phytomenadione (vitamin K1) by slow intravenous

injection; repeat dose of phytomenadione if INR is still too high after 24 hours; restart warfarin sodium when INR <5.0.

INR >8.0, no bleeding-stop warfarin; give phytomenadione (vitamin K1) by mouth using the intravenous preparation orally [unlicensed use]; repeat dose of phytomenadione if INR is still too high after 24 hours; restart warfarin sodium when INR <5.0.

INR 5.0-8.0, minor bleeding-stop warfarin; give phytomenadione (vitamin K1) by slow intravenous injection; restart warfarin sodium when INR <5.0.

INR 5.0-8.0, no bleeding-withhold 1 or 2 doses of warfarin sodium and reduce subsequent maintenance dose.[10]

Warfarin has numerous drug interactions in children, mostly with antibiotics and anticonvulsants. Antibiotics reduce intestinal flora, causing excessive PT prolongation in patients adequately controlled on warfarin. On the other hand, valproate, phenytoin and fosphenytoin enhance the risk of hemorrhage through displacement of warfarin from protein binding sites. Hence, dosing adjustments are necessary when those agents are initiated or discontinued and a close monitoring of INR and signs of bleeding are required.[8]

Unfractionated heparin (UFH)

Heparin is a polysaccharide compound derived from porcine intestine and functions as an anticoagulant by potentiating the inhibitory effects of antithrombin on thrombin and factor Xa as its primary anticoagulant effect and factors IXa, XIa and XIIa, as well. It is most often used for the treatment and prevention of thrombosis in critically ill children and is also used to maintain the patency of extracorporeal circuits and venous and arterial catheters. The advantages of heparin include many years of clinical experience, short half-life and easy reversibility with an antidote in overdoses, which are advantageous in the critical care and surgical setting where the risk for bleeding is higher.[14]

Conversely, heparin has a number of significant limitations. One of the most crucial issues involves the laboratory monitoring of heparin, which is challenging on a number of levels. First, there are several different assays used for therapeutic drug monitoring: (1) the activated partial thromboplastin time (aPTT), (2) the anti-factor Xa level and (3) the activated clotting time. Second, the degree to which these assays accurately reflect the degree of anticoagulation is not clear.[15,16] Furthermore, several studies have also demonstrated discrepancies between the aPTT and the anti-Xa assay.[17] There is a high degree of interpatient and even intrapatient variability in dosing, further complicating management.[18] Furthermore, heparin therapy can result in heparin induced thrombocytopenia (HIT), a serious and often under-recognized phenomenon in children, which has the potential to lead to severe consequences in an already vulnerable population of patients. HIT is associated with thrombocytopenia and increased risk of thrombosis despite a reduction in platelet count occurring 5-10 days after heparin exposure. HIT is the result of a complex antigen-antibody interaction and once it is diagnosed the therapeutic intervention is the immediate withdrawal of all heparinoid anticoagulants and substitution with nonheparinoid drugs until the risk of thrombosis is ameliorated.[19] Other disadvantage of UFH is the risk for potential contamination as it is a biological compound.

Dosage: Heparin loading dose is 75 U/kg intravenous (IV) given over 10 min, followed by initial maintenance dose of 25 U/kg/h for infants <1 year old, and 20 U/kg/h for children above 1 year old. Heparin maintenance dose is adjusted to maintain aPTT between 55 and 85 seconds. If aPTT is <50, then another bolus dose is given, whereas if aPTT is between 50 and 95s, the same maintenance dose is continued. If aPTT is between 96 and 120s, thus, heparin must be held for 30 min, whereas if it is >120, therapy must be held for 60 min. aPTT is usually assessed 4 h after heparin loading dose and 4 h after every change in the infusion rate. Once therapeutic levels are achieved, then it must be measured daily.[20]

Adverse effects: The most important adverse effect from heparin use in children is bleeding, yet this risk in children remains unknown. For minor bleeding, discontinuation of heparin infusion is usually sufficient, since heparin has a short half life. For serious bleeding, reversal of heparin effect by protamine sulfate and/or blood product support may be required. The dose of protamine sulfate required to antagonize heparin action is dependent on the total amount of UFH administered. For instance, 1 mg of protamine sulfate is required to neutralize 100 units of heparin. Children who have allergy to fish, or who have previously received protamine may be at risk for hypersensitivity reactions and should be closely monitored.[21] There are few case reports of pediatric UFH-induced osteoporosis. These patients received other concomitant drugs as steroids or high UFH doses for a prolonged period that augment osteoporosis risk.[22] Despite these limitations, heparin is widely used in children, and is still considered the first line therapy for the prevention of thrombosis.

Low molecular weight heparins (LMWH)

Low molecular weight heparins have become the anticoagulant of choice in many pediatric patients for primary prophylaxis and treatment of thromboembolism.[23] The LMWHs are derived from unfractionated heparin and the shorter length of the polysaccharide chains results in distinct properties. First, LMWHs have a more profound effect on factor Xa than on thrombin. Second, LMWHs have more stable pharmacokinetics, resulting in a more predictable dose response and reduced need for monitoring. Last, these agents have a longer half-life, making them particularly useful in the outpatient setting. Additionally these agents do not have much of drugs or diet interaction and also have lower risk of HIT and osteoporosis.[24] Most commonly used LMWHs in neonates and children are enoxaparin, dalteparin, reviparin and tinzaparin. However, most clinical data with respect to LMWH use in pediatric patients are derived from studies that used enoxaparin.[25]

Dosages[11]

Dalteparin

Treatment of thrombotic episodes (By subcutaneous injection).

Neonate: 100 units/kg twice daily.

Child 1 month-11 years: 100 units/kg twice daily

Child 12-17 years: 200 units/kg once daily (max. per dose 18,000 units); reduced to 100 units/kg twice daily, dose reduced if there is increased risk of bleeding

Prophylaxis of thrombotic episodes. (By subcutaneous injection)

Neonate: 100 units/kg once daily.

Child 1 month-11 years: 100 units/kg once daily

Child 12-17 years: 2500-5000 units once daily

Enoxaparin

Treatment of thrombotic episodes (By subcutaneous injection)

Neonate: 1.5-2 mg/kg twice daily

Child 1 month: 1.5 mg/kg twice daily

Child 2 months-17 years: 1 mg/kg twice daily

Prophylaxis of thrombotic episodes (By subcutaneous injection)

Neonate: 750 micrograms/kg twice daily

Child 1 month: 750 micrograms/kg twice daily

Child 2 months–17 years: 500 micrograms/kg twice daily; maximum 40 mg per day

Dose equivalence and conversion: 1 mg equivalent to 100 units

Tinzaparin

Treatment of thrombotic episodes (By subcutaneous injection)

Child 1 month: 275 units/kg once daily

Child 2-11 months: 250 units/kg once daily

Child 1-4 years: 240 units/kg once daily

Child 5-9 years: 200 units/kg once daily

Child 10-17 years: 175 units/kg once daily

Prophylaxis of thrombotic episodes (By subcutaneous injection)

Child: 50 units/kg once daily

Doses of all these LMWHs must be adjusted to achieve an anti Xa activity range of 0.5-1 unit/ml 4-6 hours after injection or a range of 0.5-0.8 unit/ml 2-6 hours after injection.[24] However, routine monitoring of anti- Factor Xa activity is not usually required except in neonates; monitoring may also be necessary in severely ill children and those with renal or hepatic impairment.[11]

Adverse effects: Most reported adverse events were bleeding where a review done by Nowak-Göttl, et al., have reported that in 308 children treated with therapeutic LMWH for venous thrombosis (from six studies), 9 (2.9%) had major bleeding, and 72 (23.4%) had minor bleeding.[26] The use of protamine sulfate will partially reverse the LMWH activity. In addition, temporary hair loss was reported in one out of 13 patients treated with enoxaparin[27] and elevated liver enzymes were reported in 34% of cases with tinzaparin. Multicenter randomized studies are required to determine risk of osteoporosis and HIT in children exposed to LMWH.

Fondaparinux

Fondaparinux is a synthetic, antithrombin-dependent inhibitor of factor Xa with a substantially longer half-life than LMWH. It exerts its anticoagulant activity through a similar mechanism of action as UFH and LMWH. It does not interact with platelets or PF4; hence, it does not initiate pathogenetic HIT cascade observed with UFH or LMWH. For this, fondaparinux is widely admired in the

management of patients who have HIT, although it is not approved for this purpose. Young et al., showed that a dose of 0.1 mg/kg once daily in children above 1-year-old have a comparable pharmacokinetic profile to adult dosing in patients with DVT and HIT, and the major adverse event reported was bleeding.[28]

When applied clinically, several points should be made with reference to using fondaparinux in children. First, unlike in adults, it is recommended that patients have therapeutic drug monitoring using a fondaparinux-based anti-Xa assay. Peak levels should be measured at 3 hours after infusion, targeting a level of 0.5-1 mg/L. In addition, for patients receiving fondaparinux requiring procedures that are, to the extent possible, it should be performed at least 24 hours after the last dose.[5]

Direct thrombin inhibitors (DTI)

This class inhibits thrombin action directly where the effect is independent of AT levels. Furthermore, by reducing the thrombin mediated activation of platelets, these inhibitors also have an antiplatelet effect. These inhibitors are mainly used in acute coronary syndromes with or without percutaneous coronary intervention and HIT.[26] Direct thrombin inhibitors offer several advantages over the standard agents. First, these agents have a low risk of inter-individual variability because they directly bind to thrombin forming inactive complexes and do not require the presence of AT whose levels are not predictable in pediatrics, particularly in critical ill neonates.[29] Second, DTIs have much more predictable pharmacokinetics than heparin because they are not bound to plasma proteins. Third, they have demonstrated significantly lower bleeding risk than heparin in adult patients. Fourth, these agents have better efficacy than the old anticoagulants since they inhibit both clot-bound and circulating thrombin. Finally, the DTI do not cause HIT which is a major limitation for the use of heparin. This class is considered as an alternative to UFH in children with HIT.[30] The most significant limitation is the lack of an available antidote though several studies documented that recombinant activated clotting factor VII can reverse DTI effect.[31] Other constrains include administration by continuous infusion, which is limited by venous access in children and are suitable for hospitalized patients. The major DTIs used are bivalirudin and argatroban in children whereas lepirudin is not used because it increases bleeding risk.[32]

Argatroban

It is the first anticoagulant that gained pediatric labeling in the US for prophylaxis and treatment of thrombosis in patients with HIT.[5] Argatroban is monitored by the aPTT, where the target aPTT time should be 1.5-3 times normal range and checked 2 h after bolus administration. Argatroban is given at 0.75 mcg/kg/min continuous infusion.[33] When introducing coumarins after the acute phase of HIT under argatroban therapy, it should be initiated without a loading dose and argatroban should be continued concomitantly until the INR is in the therapeutic range for 2 days.[34]

Bivalirudin

Bivalirudin, a synthetic oligopeptide analog of hirudin, is a selective reversible DTI. It has a predictable anticoagulation effect, as it does not interact with nonthrombin plasma proteins. It is the drug of choice in patients at risk for hepatic or renal insufficiencies since it is metabolized through intravascular proteolysis. Bivalirudin requires IV continuous infusions since it has a relatively short half-life of 25-34 min with intensive therapeutic monitoring. Pediatric dosing has not yet been added to the bivalirudin labeling in the US; although a pilot study showed the effective and safest dose is 0.125 mg/kg IV bolus followed by 0.125 mg/kg/h continuous infusion.[35]

Dabigatran

Dabigatrane texilate is a prodrug converted to dabigatran in the liver. It is a direct competitive thrombin inhibitor with low bioavailability around 7% that undergoes renal elimination. Peak plasma concentrations are reached quickly within 2 hours after administration with mean t½ around 13 hours. Owing to its predicable anticoagulant effects and lack of drug interactions, coagulation monitoring is not necessary.[36] The safety and effectiveness of dabigatran in pediatric patients have not been established.

Ximelagatran

Ximelagatran is a class of new oral anticoagulants acting by direct thrombin inhibition. It is a prodrug of the active site-directed thrombin inhibitor, melagatran. Ximelagatran has a plasma half-life of 4-5 hours and is administered orally twice daily. The most common side-effect of ximelagatran is a reversible elevation of liver enzymes. One major advantage of ximelagatran is a predictable anticoagulant response enabling fixed-dose administration without routine coagulation monitoring. Ximelagatran has been evaluated for thromboprophylaxis in high-risk orthopedic patients, treatment of venous TE and prevention of cardioembolic events in patients with

nonvalvular atrial fibrillation.[37] There is no data on use of ximelagatran in pediatric patients.

Direct factor Xa inhibitors

In contrast to thrombin inhibitors, factor Xa inhibitors reduce total thrombin generated, thus factor Xa may be a more desirable anticoagulant target.[38] One major concern regarding these new agents is the lack of validated monitoring assays. The development of effective antidotes for these compounds is lagging behind clinical development of the agents.

Rivaroxaban

Rivaroxaban is the first oral DTI, a highly specific inhibitor of factor Xa available for clinical use. This direct inhibitor prevents the formation of the thrombin burst by regulating the coagulation cascade at the point of amplification.[39] It is currently approved for the treatment and long term prophylaxis of deep vein thrombosis (DVT) or pulmonary embolism (PE). It is also approved for the prevention of DVT and PE in adult patients undergoing elective hip or knee replacement surgery and stroke prevention in patients with atrial fibrillation.[40] The comparable safety profile of rivaroxaban to LMWH, high oral bioavailability around 80%, once daily dosing, and limited requirement for monitoring makes this drug an optimal anticoagulant that warrants further investigation in children.[41] There are currently no data on safety and efficacy of rivaroxaban in pediatrics.

Apixaban

Apixaban is a selective oral direct inhibitor of factor Xa. Its bioavailability is about 66% and a t½ of 8-15 hours. Apixabanhas the least renal clearance around 25% as compared with other new oral anticoagulants. In the US, phase I trial for children with central venous catheters is currently enrolling patients.[42]

Points to Remember

- ***All the currently used multi-targeted anticoagulants, heparin, LMWH, and VKAs have significant limitations and will most likely eventually be replaced by a wide variety of targeted anticoagulants.***
- ***Heparin utilization in pediatrics is limited by many factors and the most important ones are heparin induced thrombocytopenia and anaphylaxis. Low molecular weight heparin appears to be an effective and safe alternative treatment.***
- ***Direct thrombin inhibitors (DTI) is a promising class over the other anticoagulants since it offers potential advantages.***
- ***Most of the recommendations regarding the use of newer anticoagulants in children have been extrapolated from the adult literature, with very few randomized trials performed in the pediatric population.***

References

1. Massicotte MP, Dix D, Monagle P, Adams M, Andrew M. Central venous catheter related thrombosis in children: Analysis of the Canadian Registry of Venous Thromboembolic Complications. J Pediatr 1998; 133:770-776.
2. Raffini L, Huang Y, Witmer C, Feudtner C. Dramatic increase in venous thromboembolism in children's hospitals in the United States from 2001-2007. Pediatrics 2009; 124(4):1001-1008.
3. Monagle P, Chan AKC, Goldenberg NA, Ichord RN, Journeycake JM, Nowak-Göttl U, et al. Antithrombotic therapy in neonates and children: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141:e737S-801S.
4. Carpentieri U, Nghiem QX, Harris LC. Clinical experience with an oral anticoagulant in children. Arch Dis Child 1976; 51:445-448.
5. Young G. Anticoagulants in children and adolescents. Hematology Am Soc Hematol Educ Program 2015; 2015:111-116.
6. Tarango C, Schulman S, Betensky M, Goldenberg NA. Duration of anticoagulant therapy in pediatric venous thromboembolism: Current approaches and updates from randomized controlled trials. Expert Rev Hematol 2018; 11(1): 37-44.
7. Hirsh J, Dalen J, Anderson DR, Poller L, Bussey H, Ansell J, et al. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. Chest 2001; 119:8S-21S.
8. Majerus PW, Tollefsen DM. Blood coagulation and anticoagulant, thrombolytic, and antiplatelet drugs. In: Brunton LL, Lazo JS, Parker KL, eds. The Pharmacological Basis of Therapeutics. 11th Edn, United States of America, New York: McGraw Hill 2006; pp1467-1488.
9. Moffett BS, Kim S, Bomgaars LR. Readmissions for warfarin-related bleeding in pediatric patients after hospital discharge. Pediatr Blood Cancer 2013; 60(9):1503-1506.
10. Bonduel MM. Oral anticoagulation therapy in children. Thromb Res 2006; 118:85-94.
11. Joint formulary committee. British National Formulary for Children. BMJ group 2015: 112-118.

12. Gatti L, Carnelli V, Rusconi R, Moia M. Heparin-induced thrombocytopenia and warfarin-induced skin necrosis in a child with severe protein C deficiency: successful treatment with dermatan sulfate and protein C concentrate. J Thromb Haemost 2003; 1:387-388.
13. Cheung AM, Halton J, Dinyari M, Chan A, Shaughnessy S, Webber C, et al. Bone mineral density (BMD) in a cohort of children on long term warfarin therapy. J Thromb Haemost 2001; 78 (suppl 1):1729a.
14. Newall F, Johnston L, Ignjatovic V, Monagle P. Unfractionated heparin therapy in infants and children. Pediatrics 2009; 123:e510-518.
15. Chan AKC, Black L, Ing C, Brandao LR, Williams S. Utility of aPTT in monitoring unfractionated heparin in children. Thromb Res. 2008; 122(1):135-136.
16. Ignatovic V, Summerhayes R, Gan A, Than J, Chan A, Cochrane A, et al. Monitoring unfractionated heparin (UFH) therapy: which anti factor Xa assay is appropriate? Thromb Res 2007; 120(3):347-351.
17. Trucco M, Lehmann CU, Mollenkopf N, Streiff MB, Takemoto CM. Retrospective cohort study comparing activated partial thromboplastin time versus anti-factor Xa activity nomograms for therapeutic unfractionated heparin monitoring in pediatrics. J Thromb Hemost 2015; 13(5):788-794.
18. Sutor AH, Massicotte P, Leaker M, Andrew M. Heparin therapy in pediatric patients. Semin Thromb Hemost 1997; 23(3):303-319.
19. Warkentin TE, Greinacher A, Koster A, Lincoff AM. Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133(6 Suppl):340S-380S.
20. Andrew M, Marzinotto V, Massicotte P, Blanchette V, Ginsberg J, Brill-Edwards P, et al. Heparin therapy in pediatric patients: A prospective cohort study. Pediatr Res 1994; 35:78-83.
21. Monagle P, Michelson AD, Bovill E, Andrew M. Antithrombotic therapy in children. Chest 2001; 119(1 Suppl):344S-370S.
22. Avioli LV. Heparin-induced osteopenia: An appraisal. Adv Exp Med Biol 1975; 52:375-387.
23. Dix D, Andrew M, Marzinotto V, Charpentier K, Bridge S, Monagle P, et al. The use of low molecular weight heparin in pediatric patients: A prospective cohort study. J Pediatr 2000; 136:439-445.
24. Samama MM, Gerotziafas GT. Comparative pharmacokinetics of LMWHs. Semin Thromb Hemost 2000; 26(Suppl) 1:31-38.
25. Trame MN, Mitchell L, Krümpel A, Male C, Hempel G, Nowak-Göttl U. Population pharmacokinetics of enoxaparin in infants, children and adolescents during secondary thromboembolic prophylaxis: A cohort study. J Thromb Haemost 2010; 8:1950-1958.
26. Nowak-Göttl U, Bidlingmaier C, Krümpel A, Göttl L, Kenet G. Pharmacokinetics, efficacy, and safety of LMWHs in venous thrombosis and stroke in neonates, infants and children. Br J Pharmacol 2008; 153:1120-1127.
27. Kuhle S, Massicotte P, Dinyari M, Vegh P, Mitchell D, Marzinotto V, et al. Dose-finding and pharmacokinetics of therapeutic doses of tinzaparin in pediatric patients with thromboembolic events. Thromb Haemost 2005; 94:1164-1171.
28. Young G, Yee DL, O'Brien SH, Khanna R, Barbour A, Nugent DJ. FondaKIDS: a prospective pharmacokinetic and safety study of fondaparinux in children between 1 and 18 years of age. Pediatr Blood Cancer 2011; 57:1049-1054.
29. Bates SM, Weitz JI. The mechanism of action of thrombin inhibitors. J Invasive Cardiol 2000; 12 Suppl F: 27F-32.
30. Potter C, Gill JC, Scott JP, McFarland JG. Heparin-induced thrombocytopenia in a child. J Pediatr 1992; 12(1):135-138.
31. Levi M, Bijsterveld NR, Keller TT. Recombinant factor VIIa as an antidote for anticoagulant treatment. Semin Hematol 2004; 41:65-69.
32. Shantsila E, Lip GYH, Chong BH. Heparin-induced thrombocytopenia. A contemporary clinical approach to diagnosis and management. Chest 2009; 135:1651-1664.
33. Madabushi R, Cox DS, Hossain M, Boyle DA, Patel BR, Young G, et al. Pharmacokinetic and pharmacodynamic basis for effective argatroban dosing in pediatrics. J Clin Pharmacol 2011; 51:19-28.
34. Sheth SB, DiCicco RA, Hursting MJ, Montague T, Jorkasky DK. Interpreting the International Normalized Ratio (INR) in individuals receiving argatroban and warfarin. Thromb Haemost 2001; 85:435-440.
35. Young G, Tarantino MD, Wohrley J, Weber LC, Belvedere M, Nugent DJ. Pilot dose-finding and safety study of bivalirudin in infants <6 months of age with thrombosis. J Thromb Haemost 2007; 5:1654-1659.
36. Blech S, Ebner T, Ludwig-Schwellinger E, Stangier J, Roth W. The metabolism and disposition of the oral direct thrombin inhibitor, dabigatran, in humans. Drug Metab Dispos 2008; 36:386-399.
37. Olsson SB of the Executive Steering Committee of the SPORTIF III Investigators. Stroke prevention and the oral thrombin inhibitor Ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomized controlled trial. Lancet 2003; 362:1691-1698.
38. Turpie AG. Oral, direct factor Xa inhibitors in development for the prevention and treatment of thromboembolic diseases. Arterioscler Thromb Vasc Biol 2007; 27:1238-1247.
39. Eriksson BI, Borris LC, Dahl OE, Haas S, Huisman MV, Kakkar AK, et al. A once-daily, oral, direct Factor Xa

inhibitor, rivaroxaban (BAY 59-7939), for thromboprophylaxis after total hip replacement. Circulation 2006; 114:2374-2381.

40. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011; 365:883-891.
41. Turpie AG, Lassen MR, Davidson BL, Bauer KA, Gent M, Kwong LM, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): A randomised trial. Lancet 2009; 373:1673-1680.
42. Bristol-Myers Squibb. Multiple-Dose Study Apixaban in Pediatric Subjects with an Indwelling Central Venous Catheter. National Institutes of Health; 2011. Available from: http://clinicaltrials.gov/ show/NCT01195727. Last update posted : April 7, 2017. Accessed on 15th Aug. 2019.

CLIPPINGS

Use of Second-line Medications and Treatment Outcomes in Children With Tuberculosis in a Single Center From 2007 to 2018.

This was a retrospective study undertaken in Italy. Children with tuberculosis (TB) referred between 2007 to 2018,were analysed. Authors characterized the treatment of pediatric TB with second-line drugs (SLDs) and factors related to the use of SLDs in children with and without documented drug-resistant forms of tuberculosis (DR-TB). There were 204 children diagnosed with active TB during the study period. Due to confirmed or likely drug resistance, adverse reactions to first-line drugs, involvement of central nervous system, or possible drug resistance that was not confirmed, 42 were treated with SLDs. The authors conclude the following in the article. There have been no reports of death or adverse reactions related to SLDs. In 85.2% of children treated with first-line drugs and 92.9% treated with SLDs, treatment was successful. The only factor linked to DR-TB was < 2 years old, after adjusting for the calendar period. TB at 2 or more sites, extrapulmonary TB or adverse reactions to first-line drugs were factors linked to treatment with SLDs. No variations in age or region of origin were observed. Findings suggested that SLDs have treated a substantial proportion of TB children. A high success rate and a good tolerability profile were related to the use of SLD regimens.

Chiappini E, Matucci T, Lisi C, Petrolini C, Venturini E, Tersigni C, de Martino M, Galli L. Use of Second-line Medications and Treatment Outcomes in Children With Tuberculosis in a Single Center From 2007 to 2018. The Pediatric Infectious Disease Journal. 2019 Aug 6.

Neonatal, infant, and childhood growth following metformin vs insulin treatment for gestational diabetes: A systematic review and meta-analysis.

A systematic review of 28 studies that involved 3,976 mothers who were randomized to metformin or insulin for the treatment of gestational diabetes mellitus (GDM) was done and all studies that reported the weight and growth of their babies in the womb, at birth, or later in childhood were included. Babies whose mothers were treated with metformin weighed on an average 108 grams less at birth than those whose mothers were treated with insulin. They had a lower risk of being born large (>90percentile) for their gestation at delivery. However metformin treated babies were 440 gm heavier by 18-24 months than insulin exposed infants. Metformin treated children had a higher BMI by mid childhood than insulin treated children. The researchers conclude that metformin treatment for gestational diabetes alters the post natal growth trajectory compared to insulin treatment. It is known those infants who are born small and then undergo catch up growth after birth are at increased risk of developing cardiovascular disease and type 2 diabetes later in life. It is important to understand whether this increased risk applies to children whose mothers are treated with metformin during pregnancy.

Tarrt-AdkinsJL, Aiken CE, Ozanne SE. Neonatal, infant, and childhood growth following metformin vs insulin treatment for gestational diabetes: A systematic review and meta-analysis. PLoS Medicine 2019; 16(8):e1002848. doi: 10.1371/journal.pmed.1002848. eCollection 2019 Aug.

GENERAL ARTICLES

SPECIFIC LEARNING DISABILITY - DYSLEXIA

*Sivaprakasam V

Abstract: *Specific learning disability, is a neuro-developmental and biological disorder which refers to ongoing problems in reading or writing or mathematics. Reading difficulty in a child with normal or above normal IQ, is considered as 'dyslexia', writing difficulty as 'dysgraphia' and difficulty in mathematics as 'dyscalculia'. Remedial teaching remains the mainstay of management. Specific learning disability is included in the disability act and children with dyslexia get free remedial teaching and concessions in education by the Government. Early identification of specific learning disability and prompt intervention will result in bright future for these children.*

Keywords: *Learning disability, Dyslexia, Dysgraphia, Dyscalculia, Remedial teaching*

Learning disability in children is increasingly recognized in India. Early identification of learning disability is absolutely vital, as early remediation and intervention has the best chance of favorable outcome. Learning disability affects 5-15% of school children.[1,2,3] The symptoms of dyslexia were first identified by Berkhan in 1881 and the term dyslexia was coined by Rudolf Berlin in 1881.[4]

Specific learning disability (SLD) is a group of neuro-developmental disorder manifesting as persistent difficulty in learning to efficiently read (dyslexia), write (dysgraphia) and perform mathematical calculations (dyscalculia) despite normal intelligence, conventional schooling, intact hearing and vision, adequate motivation and socio-cultural opportunity.[2,5] Any insult to the developing brain, prenatal, natal, postnatal and during infancy may lead to SLD.

* Consultant Pediatrician,
Nataraja Child Development Center &
Nataraja Children's Hospital,
Chidambaram.
email: vsiva_pr@yahoo.co.in

Dyslexia is a disorder in a child, who despite conventional class room experience, fails to attain the language skills, of reading, writing and spelling, commensurate with their intellectual abilities. Learning disability manifests during early school years and it is not attributed to intellectual disabilities or neurological or motor disorders. The difficulties should last for at least six months, to make a diagnosis.

Epidemiology

Eighty percent of SLD is reading disability or dyslexia.[5,6] Around 25% of the children will have ADHD as co-morbid condition which needs medication before remedial teaching. The IQ of the affected kids will be 90-140.[2,6] Definitive diagnosis is usually made at 7-8 years. No detention policy (NDP) in the schooling system leads to delayed identification of learning problems.[7]

Language and its components

Language is a system for human communication and has 5 components (Box 1). Speech is the verbal expression of language. Children with learning disability may have problem with any one or more of the 5 components of language. Core defect in dyslexic children is the lack of phonological awareness which is understanding the relationship between the shape of the letter and sound of the letter.[1,5,6]

Definition of LD as per IAP Guidelines[7]

Learning disabilities (LD) are a heterogeneous group of disorders where the individual unexpectedly fails to competently acquire, retrieve and use information. The academic achievement is lower than expected, based on the child's overall intelligence. LD has been defined as a neurodevelopment disorder of biological origin manifesting in learning difficulties and problems in acquiring academic skills, which are markedly below age level.

DSM.5-Diagnostic criteria-SLD[8]

A. Any one of the following symptoms that have persisted for at least 6 months,

Box 1. Five components of language

Phonology: Phoneme is the smallest linguist unit of speech that signals a different sound (distinct speech sound) e.g. p, b are phonemes (these differentiate the word 'pat' from 'bat').

Morphology: Morpheme is the smallest linguist unit with meaning. It may be prefix, suffix or root word - e.g., unkindness; un- and -ness are the bound morphemes, requiring the root kind to form the word. These are also called affixes as they are attached to the stem. there are two types: Prefix = Un ; Suffix = ness

Syntax: The rule system that governs the structure of a sentence" - e.g. 'Ball hit the man'- 'man, the, ball, hit' have to be structured.

Semantics: The ability to obtain meaning from the words, sentences and other word combinations.

Pragmatics: The use of language in social contexts.

- Inaccurate or slow and effortful word reading.
- Difficulty in understanding the meaning of what is read
- Difficulties with spelling (e.g. may add, omit or substitute letters)
- Difficulties with written expression (e.g. makes multiple grammatical or punctuation errors within sentences
- Difficulties in mastering number sense (Maths)
- Difficulties with mathematical reasoning

B. Two grade low for the age

C. Onset before 7 years

D. Rule out other causes

Various types of SLD are given in Box 2.

Box 2. Types of SLD

Reading	-	Dyslexia
Writing	-	Dysgraphia
Oral (spoken)	-	Dysphasia
Mathematics	-	Dyscalculia
Motor incoordination	-	Dyspraxia

I. Dyslexia - Difficulty in reading

Genetics: Dyslexia is both familial and heritable. There is 40% genetic predisposition for dyslexia. Among dyslexic children 23 to 65% have a parent with dyslexia and 40% among siblings.[9] Linkage study indicates loci in chromosome 2, 3,6,15 and 18. Dyslexia affects both boys and girls equally.[10]

It is caused by deficit in phonological processing.[7] Children with dyslexia read very slowly, word by word, lose place, miss out lines or read the same line again andtherefore need to always keep the finger below the line being read. They hesitate to read aloud, hate reading and refuse to read. These children may try to sound out the individual elements of word, but are often unable to synthesize it into the correct word (e.g. b/e/g and then say bad).[11]

Changes observed in the brain in dyslexic children are identified in PET scan. In normal children a centre will be activated when the child reads (Fig.1). In dyslexic children it is not activated (Fig.2). After remedial teaching for 6 months a new centre will be activated in the frontal lobe (Fig.3). In 10-15% of the children even after remedial teaching no activation is seen (Fig.4).

In normal children, three areas are activated - Broca's area, Wernicke's area and the insula. In dyslexics, only one – Broca's area is activated. Area of activation in the brain during reading as shown in functional MRI in a normal

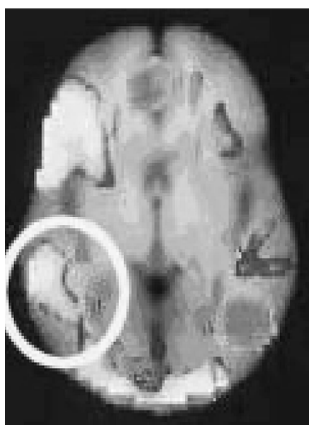


Fig.1.Centre activated when a normal child reads

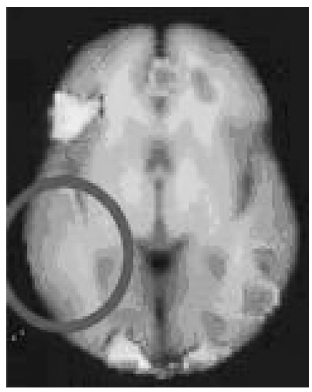


Fig.2.Non-activation in a dyslexic child

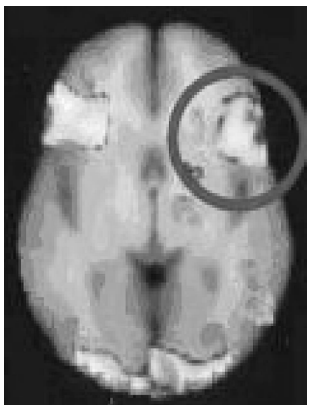


Fig.3. New centre after remedial teaching

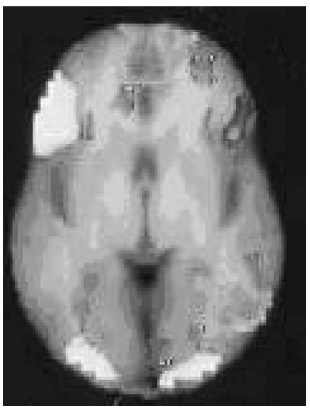


Fig.4. Failure to activate even after teaching

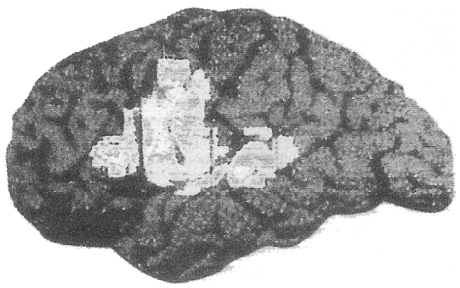


Fig.5.Normal Brain

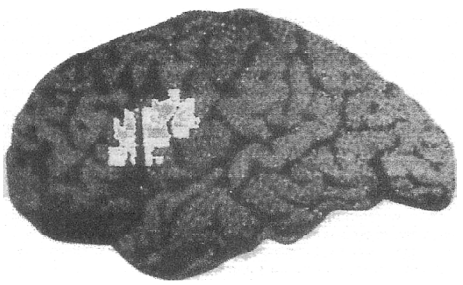


Fig.6.Brain of the child with dyslexia

child and dyslexic child are given in Fig.5 & 6 respectively.[12]

Other presenting features are:

Ignoring punctuation, thus often confusing the meaning of the text.

Confusion with alphabet, shapes and positions (e.g. b as d)[11]

Confusion in words – [e.g. 'was' - as 'saw' (mirror image reading)]

Omission (e.g. 'bet' for 'belt', 'wet' for 'went')

Addition (e.g. 'played' for 'play')

Substitution (e.g. 'house' for 'home')

Mispronunciation of some words such as- 'help' for 'held'

Putting syllables in the wrong order- 'animal' as 'aminal'

They answer well in oral, but fail in written tests. They are unable to tell a story and have difficulty in explaining with examples. Sounds are confused (e.g. 'empty' for 'entry'). These children have poor memory and cannot recall sequence of letters (inefficient visual memory system) with no automatic reading. Concepts are reversed (e.g. 'floor' for 'ceiling').

Reading comprehension

There is difficulty in understanding the meaning of what is read (e.g. may read text accurately but not understand the sequence, relationships, inferences, or deeper meanings of what is read) and poor in reading comprehension. There will be difficulty in reading and understanding questions and if we read out question, the child can answer i.e. understands and learns better if someone reads out the same text to the child.

Co-morbid conditions with dyslexia: Attention deficit hyperactivity disorder (ADHD), conduct disorders - oppositional defiant disorder, anxiety disorders, depression, tic disorders and Tourette's syndrome may be associated with dyslexia.

II. Dysgraphia - Writing disability

It is caused by a range of neurodevelopment weakness including problem with hand writing (fine motor and graphomotor) and visual - spatial perception. Dysgraphia is often multi-factorial, due to impaired letter writing automaticity, finger motor sequencing challenges, organizational and elaborative difficulties and impaired visual word form which makes it difficult to retrieve the visual of words requiring spelling. Here the problem is exclusively in spelling (also called encoding which is ability to use letter sound relationships effectively) in the absence of problem in written expression and it is more indicative of phonological processing deficit i.e. dyslexia.[7,10]

These children will have poor handwriting and the abnormal grip makes writing slow and laborious, notes are incomplete and do not make sense. These children are poor in remembering certain alphabets and unable to copy from board. They show mirror writing with lots of spelling mistakes and grammar mistakes.

Writes letters in the wrong order e.g. Simon as Siomn, what as wtah

Inconsistent errors/sometimes correct spelling - e.g. apple, appel, aple[11]

Reverses letters and words - e.g. b as d, p as q, was as saw (mirror image writing)

Inverts letters - e.g. n-u, m-w, d-q, p-b, f-t

Omits letters - e.g. limp as lip, string as sing

Adds letters - e.g. went as whent, what as whant

Spells the way the word sounds - BUSY as BIZZY

III. Dyscalculia- Difficulty with mathematics

It is a neurological condition characterized by a problem with basic sense of number and quantity and difficulty in retrieving maths facts (arithmetic combinations or calculations), difficulty with language of maths (correctly reading and understanding the text of word problems) and visual- spatial and organizational demands of maths.[7]

They change the shape 6 as 9, position of numbers, 17 as 71 and are poor in number sense. These children lack mastery of basic addition, subtraction, multiplication and division combinations, difficulty in Algebra. They are poor in geometry; subtract bigger number from smaller one, difficulty in carrying over or borrowing sums. They may count from left to right, use fingers for calculations even after 8 years of age.

IV. Dyspraxia

Dyspraxia is now not included in dyslexia. It is considered as a co-morbid condition. It is due to small muscle weakness. These children will have poor posture, awkward clumsy movements, poor handwriting, immature behavior, lack of awareness of potential danger, difficulty writing fast, lack of fluency in reading, poor short term memory, difficulty in buttoning the shirt and tying the shoe lace.

Psychological effects of learning disability in a child

This includes school refusal, school failure, drop out, depression, anxiety, suicidal attempts, intolerance and anger, running away, lack of self confidence, emotional instability, loss of self-esteem, inferiority complex and poor socialization.[2,6,13] By early identification and early intervention in the form of remedial measures these psychological effects can be prevented.

Early pointers for learning disability[1,11]

Though the confirmation of diagnosis of dyslexia can be done at 7 years, we can pick up children by early warning signs as early as 3 years and we can follow up these children till 7 years to confirm the diagnosis of dyslexia.

1. Speech delay; no two words after 18 months
2. Missing of the crawling stage even after 10 months
3. Difficulty in buttoning the shirt even after 7 years
4. Difficulty in tying the shoe lace even after 7 years
5. Difficulty with rhymes
6. Difficulty with puzzle

Even if we are not confirming diagnosis of dyslexia, early stimulation can be started at 3 years by phonics method of teaching, so that, we can reduce the severity of dyslexia.[11]

Diagnosis

When an intelligent child, fails in a class with normal or above normal IQ (100-140),is not performing well in school, dislikes reading, reads slowly, skips words and sentences with reversal tendency, writes slowly with poor hand-writing and lot of spelling and grammar mistakes and is poor in mathematics and algebra. There is a possibility of dyslexia.[7]

Rule out other causes of learning disability[11]

Visual ailments, hearing problems, medical conditions like congestive heart failure, chronic renal failure, hypothyroidism, asthma etc, home atmosphere, school atmosphere, attention deficit hyperactive disorder (ADHD), psychological problems such as anxiety, depression, conduct disorder, oppositional defiant disorder (ODD), Mental retardation, slow learners with IQ-70-89.

Slow learners are those with below average cognitive abilities who are not disabled but struggle to cope up with traditional academic demands of the regular class room.[3] IQ assessment is the only differentiating feature. If IQ 90-140 with the features of learning problem a provisional diagnosis of SLD can be made.[11]

Assessment

Any clinician has to have a high degree of suspicion for diagnosing LD. There are several tools available for screening, diagnosis, and assessment for LD. Guidelines by IAP and DSM-5 criteria are the important tools for diagnosis.

Other tools for diagnosis: Specific Learning Disability Questionnaire (SLD-SQ), used in the studies conducted in India,[14] National Institute of Mental Health and Neuro

sciences (NIMHANS) Index to assess children with SLD,[15] Level 1 - 5-7 years and Level 2 - 8-12 years.

IQ Assessment[7]

Binet-Kamat Test (BKT) Woodcock Johnson Tests of Cognitive Ability (3rd edition; age two and above) or Malin's Intelligence Scale for Indian Children (for children 6 years and above), which is the Indian adaptation of Wechsler Intelligence Scale for Children (WISC).

Achievement: Woodcock Johnson III – tests of Achievement for children; Nelson Denny Reading Test for high school and college students; Cognitive Processing Abilities: Woodcock Johnson Psycho-Educational Battery Revised (Part 1)[7]

Practical approach

All children attending pediatric outpatient clinic, should be asked about their academic performance, whether they love to read or not and their marks. When an intelligent child presents with poor academic performance and persistent low marks in exams with any one of the problems like difficulty in reading, reading slowly, poor hand writing, lot of spelling mistakes and being poor in maths, one need to suspect learning disability. The child should be reviewed again with their notebooks, mark sheets and books. A good history and clinical examination to rule out medical problem, ADHD, intellectual disability (MR) should be done.

How to assess

Reading: Ask to read a simple passage. Note the speed, errors in reading like omission of letters substitution of letters, skipping words or sentences, guess work and mispronunciation.

Comprehension skills:[11] Give one paragraph of reading material and ask him to read out, ask simple questions, and see the answers. If he is not answering read out the paragraph to him and see whether he is able to grasp the main idea and answers all questions.

Writing: Look at the answer papers, and the class note books, for spelling mistakes, poor hand writing, reversal tendency, incomplete answers. Ask him to copy a paragraph and note the speed of writing, irregular hand writing. Give simple dictation words and see the spelling.

Maths: Ask him to identify numbers 1, 2, 3, 4. Give simple addition and subtraction sums.

Send for IQ assessment and academic assessment: IQ test should be done by clinical psychologist. IQ= mental age/chronological age. Dyslexic children will have an IQ of 90-140. Academic assessment needs to be done by LD specialist - where the reading level, writing level and the mathematical level are assessed.

Assessment by child psychiatrist: To rule out any psychological problem which occurs as co-morbid or as an effect of LD.

Final assessment by developmental pediatrician: To rule out any other problem and co morbid conditions, to confirm dyslexia, and to help in planning the individual education plan (IEP) and to guide these children to be certified as dyslexic.

Management

Principles of management[16]

1. Remedial education - Special educator - Educational assessment, Individual educational program (IEP)
2. Occupational therapy - e.g. Handwriting skills
3. Speech and language pathologist intervention
4. Counseling and guidance to family - psychologist/ counselor
5. Treatment of associated problems - General pediatrician, developmental pediatrician, psychiatrist
6. Career counseling - school along with parents

Remedial teaching[2,6,17-19]

When a child is not able to understand in a way they are taught, the way of teaching is changed for the child to understand. It is costly and not affordable by all parents. Remedial teaching 2-3 hours a day for 3 days a week for at least for 6 months is advocated. After academic assessment, they formulate individual education plan. A teacher can handle only 2-3 children at a time. Due to high plasticity of the central nervous system in early years remedial education should be started early when the child is in primary school.[7]

Government programs to help dyslexic children

Sarva Shiksha Abhiyan (SSA): In 2011, Government launched SSA (education for all) that aims to provide useful and relevant education to all children including children with disabilities.[16,20] Inclusive education - Dyslexic children will be getting new method of teaching in the regular classes itself. Training to improve attention concentration, correction of spelling and grammar mistakes will be done in the regular classes. Every school should have resource room.[19]

Resource room: Children will attend regular school and in the evening remedial teaching will be given in the resource room. Remedial teacher, counsellor, social worker, clinical psychologist, occupational therapist will constitute a team.[1,21]

Rashtriya Bal Swasthya Karyakram (RBSK-)[16,22]

Early detection and early intervention of 4 'D's viz. Defects at birth, Deficiencies, Diseases, Development delays including disability and is funded by National Rural Health Mission (NRHM). Medical officer, clinical psychologist, special educator, ooccupational therapist and ssocial worker will constitute a team.[16,22]

District early intervention centre (DEIC)[16,22]

Every district will have a centre to prevent or minimize the effects of selected health conditions. Management of defects at birth, deficiencies, disease and developmental delay including disabilities among children from birth till 18 years will be done.

Government concessions

Government is providing concessions for dyslexic children to compete with normal children in the exams. This includes one hour extra time in public exams. No mark reduction for grammar and spelling mistakes, provision to use calculator in math's exam, exemption from writing one language, permission to have a scribe. In a study, the mean total marks increased by 22% from 41% before to 63% after availing the provisions.[16,23]

Parent education

The problem of dyslexia is neuro developmental and biological. It involves brain circuits. EEG, MRI and CT brain are not needed for diagnosis and management. As it is not a disease or illness, drugs are not needed. Early intervention – remedial teaching works well. Parents should know the weakness like, poor self-esteem and inferiority complex. They should not compare, use rude words, penalise the child and discuss about him in front of others, but always learn how to help him.

Counseling

Parents: They should be explained about dyslexia and their doubts are cleared to bring down their anxiety. One needs to help them to get remedial teaching and need to assure them and guarantee that their children have the potential to do well and be successful in life. The caretakers should be motivated to appreciate their children with SLD and reward them for small achievements too so as to encourage them.

Children: They should be informed about their nature of disability and motivated to overcome the problem by working hard.

Prevention of learning disability

Early stimulation, judicious use of electronic gadgets, more human to human interaction, interaction with the child of same age and playing traditional games are some of the measures to prevent SLD.

Acknowledgement

I thank the dyslexic children and their parents, Dr. MKC Nair, Dr. T.U.Sukumaran, Dr. Sachidananda Kamath, Dr. Jeeson C Unni, Dr. G.Kumaresan, Dr. B.R.Nammalwar and Dr. V.Jayanthini.

Points to Remember

- ***Dyslexic children read slowly word by word, hate reading, have poor hand writing, make grammar and spelling mistakes, with reversal tendency and difficulty with maths.***
- ***Their IQ is normal or above normal and have multiple intelligence.***
- ***Remedial teaching is the main mode of management of these children.***
- ***No drug is needed, unless associated with co morbid condition like ADHD.***

References

1. Karande S, SholapurwalaR, Kulkarni M. Managing Specific Learning Disabilities in schools in India. Indian Pediatr 2011; 48: 515-520.
2. Lagae L. Learning disabilities: definitions, epidemiology, diagnosis, and intervention strategies. Pediatr Clin North Am 2008; 55:1259-1268.
3. Katusic SK, Colligan RC, Barbaresi WJ, Schaid DJ, Jacobsen SJ. Incidence of reading disability in a population based birth cohort, 1976–1982, Rochester, Minn. Mayo Clin Proc 2001; 76:1081-1092.
4. Ambar Chakravarty. Ann Indian Acad Neurol. 2009 Apr-Jun; 12(2): 99–103 doi: 10.4103/0972-2327.53077.
5. Shaywitz SE. Dyslexia. N Engl J Med 1998; 338:307-312.
6. Karande S, Kulkarni M. Specific learning disability: the invisible handicap. Indian Pediatr 2005; 42:315-319.
7. MKC Nair, Prasad C, Unni J, Bhattacharya A, Kamath SS, Dalwai S.Consensus statement of Indian Academy of Pediatrics on evaluation and Management of Learning disability. Indian Pediatr 2017; 54:574-580.
8. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5®). 5th edn, Washington DC, American Psychiatric Publication 2013.

9. Shaywitz SE, Morris R, Shaywitz BA. The Education of Dyslexic Children from Childhood to Young Adulthood. Annu Rev Psychol 2008; 59:451–475.
10. Learning disorders. In: Nelson Textbook of Pediatrics, Eds: Robert M.Kliegman, Bonita F. Stanton, Joseph W. St Geme III, Nina F. Schor. 20th edn, Reed Elsevier India Pvt. Ltd., New Delhi, 2016; pp:192-222.
11. Poor Scholastic performance module (PSPP) IAP president Action Plan 2011 Chapter on early Indicators of Specific Learning Disability, Published by Central IAP.
12. Frith C, Frith U. A biological marker for dyslexia. Nature1996; 382(6586):19-20.
13. Karande S, Kulkarni M. Poor school performance. Indian J Pediatr 2005; 72:961-967.
14. Padhy SK, Goel S, Das SS, Sarkar S, Sharma V, Panigrahi M. Prevalence and patterns of learning disabilities in schoolchildren. Indian J Pediatr 2016; 83:300-306.
15. Kapur M, John A, Rozario J, Oommen A. NIMHANS. Index of Specific Learning Disabilities. Psychological. Assessment of Children in the Clinical Setting. Department of Clinical Psychology, National Institute of Mental Health and Neuro sciences; Bangalore 2002; pp88-126.
16. Learning disorders in office practice. In IAP action plan 2016 - Development for all - Cradle to crayons and beyond. 2016; 69-76.
17. McDonnell ML, McLaughlin MJ, Morison P. Educating one and all: students with disabilities and standards-based reform. Washington DC: National Academy Press; 1997; p204.
18. Dakin KE. Educational assessment and remediation of learning disabilities. Semin Neurol 1991; 11:42-49.
19. Alexander AW, Slinger-Constant AM. Current status of treatments for dyslexia: Critical review. J Child Neurol 2004; 19:744-758.
20. Kainth GS. A mission approach to Sarva Shiksha Abhiyan. Econ Polit Wkly 2006; 41:3288-3291.
21. Lagae L. Learning disabilities: definitions, epidemiology, diagnosis, and intervention strategies. Pediatr Clin North Am 2008; 55:1259-1268.
22. Operational Guidelines on Rashtriya Bal Swasthya Karyakram (RSBK). Ministry of Health and Family Welfare, Government of India. Available from: http://www.pbnrhm.org/docs/rbskguidelines.pdf. Accessed January 13, 2017.
23. Kamala R. Specific learning disabilities in India: Rights, issues and challenges. Indian J Appl Res 2014; 4(5). Available from: https://www.worldwidejournals.com indian-journal-of-applied-research-(IJAR)/file.php?val =May_2014_1398967503_e9548_190.pdf. Accessed January 13, 2017.

NEWS AND NOTES

PUDHUVAI PEDICON 2020

45th Annual Conference of Indian Academy of Pediatrics, Tamilnadu State Chapter

Organised by

IAP Pondicherry-Villupuram & IAP Cuddalore brances

Department of Pediatrics, JIPMER, Puducherry

Date: 13th – 16th August, 2020

Contact details

Dr.Mrs.R.Chidambaram - 9443389991

Dr.N.L.Dhandapani - 8940060026

Dr.V.Tiroumourougane Serane - 8940060026

Email: pudhuvaipedicon@gmail.com

IAP NEOCON 2019

12th National conference of Neonatology Chapter of IAP

Date: 27th – 29th September, 2019

Venue: JW Marriott, Vittal Mallya Road, Bengaluru

Further details contact

Dr.N.Karthik Nagesh

Organising Chairman

Mob: +91 9845047960 / 9886740450

Email: iapneocon2019@gmail.com

SURGERY

EVALUATION AND MANAGEMENT OF CHILDREN WITH DISORDERS OF SEXUAL DEVELOPMENT

Ramesh Babu

Abstract: *The nomenclature, classification, understanding and management of disorders of sexual development (differences of sex development) keep evolving. It is essential to manage them at specialized medical cen-ters involving a multidisciplinary team. Immediately after confirming the diagnosis, the parents should be offered counseling and included in decision making. Sex assignment is dependent on many factors and should be postponed until a complete diagnostic assessment has been performed. Achieving optimal outcomes requires open and transparent dialogue with the family. Delaying the interventions can enable the patient to be involved in the decision process.*

Keywords: *Intersex, Ambiguous genitalia, Disorders of sexual development, Differences of sexual development*

The term 'ambiguous genitalia' covers a variety of disorders labeled as 'disorders of sexual differentiation (DSD)' (also known as 'differences of sexual development'). In these conditions the development of chromosomal, gonadal or anatomical sex is atypical and a wide range of metabolic / anatomic defects lead to an atypical genital appearance. If not sensitively addressed, they often cause significant emotional and psychological distress to the family and affected person.[1]

Terminology

The older terminology, with phrasing such as 'hermaphrodite' and 'pseudo-hermaphrodite' was felt to be pejorative, confusing and stigmatizing. The new classification proposed is sensitive to individuals and families, and also more reflective of our molecular understanding in sex development research and sex differences in the patient.[2, 3] The general principles of the newer terminology are given in Table I. There is still considerable controversy in the field regarding proper and respectful nomenclature. Even terms like DSD are being revised. DSD as 'disorders of sex development' are sometimes being referred to alternatively as 'differences of sex development (DSD)'. While the term 'intersex' has been replaced by DSD in medical literature, some patient support groups still prefer this term. To further this point, it has also been pointed out that the term 'ambiguous genitalia' also should be used carefully. Genital ambiguity should never, by itself, be a diagnosis. It is merely a finding on clinical exam (or symptom, perhaps), through which a proper and careful assessment is performed and where hopefully a true diagnosis can be made. The terms 'gender', 'sex', 'sexual', have discordant interpretations. 'Gender' is a social concept, which is the way the society mirrors the 'individual identity'. It does not take into account the 'individual identity' ('inside identity') and the future 'gender role' ('behavioral identity'), which are invisible at birth and the modalities of which are mostly unknown.[4]

Normal development

To begin with, the bi-potential primordial germ cells migrate from the yolk sac to the urogenital ridges and the development of undifferentiated gonad is initiated at 4-6 weeks. The first 7 weeks of gestation have been considered the indifferent stage, as male and female fetuses would appear grossly indistinguishable from one another. The primitive bi-potential gonad becomes testis in the presence of SRY gene and it becomes ovary by default in its absence. Gonadal differentiation then triggers hormonal responses and along with precise and timely activation of normal/typical external and internal genital development. There is no true 'default' pathway, as is historically taught; however, androgen exposure determines the external genitalia phenotype. For example, androgen exposure from testosterone and its more potent metabolite di-hydro testosterone (DHT) leads to phallic enlargement and the formation of the penis and the fusion of the labioscrotal folds into a scrotum. The spectrum of phenotypes relating to androgen exposure is seen in many DSDs with varying degrees of genital ambiguity. Different scales or scores have been developed to assess this spectrum, though the most commonly used is the Prader Scale.With regard to the

* Professor and Senior Consultant - Pediatric Urology, Sri Ramachandra Institute of Higher Education & Research (SRIHER), Chennai.

email: drrameshbabu1@gmail.com

Table I. DSD terminology and revisions

Old terminology (No longer recommended)	New terminology (Preferred term/classification)
Male pseudohermaphrodite	46XY DSD
Female pseudohermaphrodite	46XX DSD
True hermaphrodite	Ovotesticular DSD
XY sex reversal	46XY complete gonadal dysgenesis
XX sex reversal	46XX testicular DSD
Intersex (some individuals still prefer this terminology)	DSD, difference of sex development.

internal genitalia, the mesonephric duct / Wolffian duct develops into internal male genital organs, while the paramesonephric duct / Müllerian duct develops into internal female genital organs. In the presence of anti-Müllerian hormone (AMH) secreted by the Sertoli cells of the testes, the Müllerian structures regress, leaving only the Wolffian structures-epididymis, vas deferens, seminal vesicles and ejaculatory ducts. Otherwise, the Müllerian structures persist, developing into the fallopian tubes, uterus, cervix and upper vagina. The effects of AMH are paracrine in nature, meaning, unilateral testicular tissue promotes regression of hemiuterus and tube.

DSD classification and pathology

The new nomenclature and classification was proposed in 2006 by the Lawson Wilkins Pediatric Endocrine Society (LWPES) and the European Society for Pediatric Endocrinology (ESPE) for what was earlier known as 'Intersex disorders'.[2,3,5,6] Box 1 illustrates the typical causes of ambiguous genitalia according to this classification. The most common cause of ambiguous genitalia in 46 XX children is congenital adrenal hyperplasia (CAH). CAH comprises a collection of different adrenal steroid biosynthetic disorders which can result in wide-ranging phenotypes from salt-wasting adrenal crisis in the infant to virilization in young females and delayed puberty in adolescents. CAH should be the primary consideration in any virilized infant with non-palpable gonads. The presence of uterus and ovaries can be confirmed by ultrasonogram. The usual enzyme defect, 21-hydroxylase deficiency, leads to mineralocorticoid deficiency. Adrenal crisis can lead to shock and death if this condition is not promptly recognized and treated. Retrograde feedback stimulation of hypothalamic pituitary axis and subsequent excess production of androgens leads to virilization. Suppression of the axis with steroid replacement thus controls adrenal crisis and virilization.

Box 1. DSD classification with respect to ambiguous genitalia*

46XX DSD:

- Androgen excess: CAH, maternal exposure
- Disorders of ovarian development (gonadal dysgenesis)

46XY DSD:

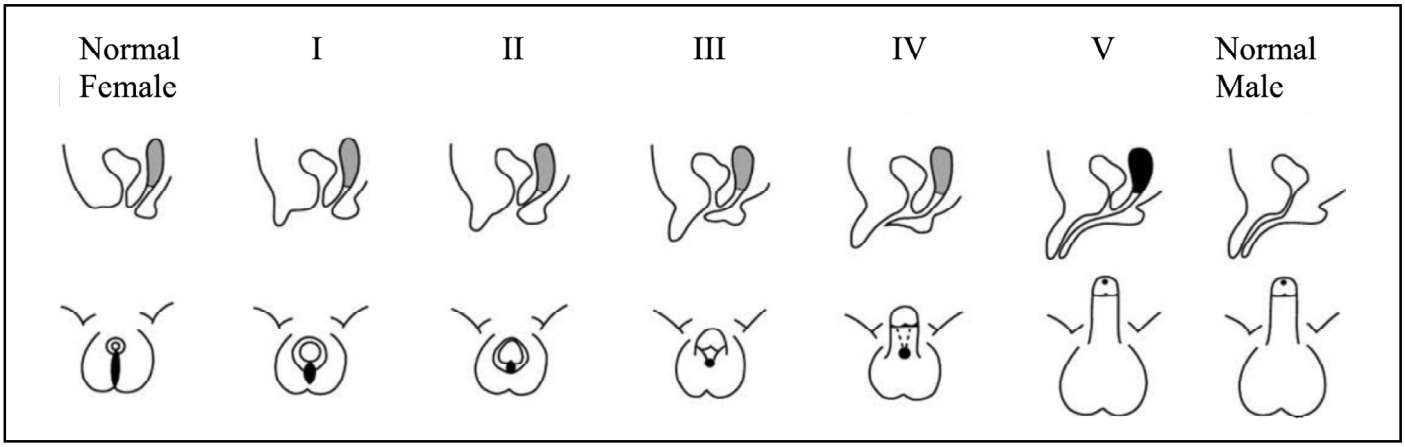
- Disorders of androgen synthesis (5 alpha reductase deficiency)
- Partial androgen insensitivity (PAIS)
- Disorders of testicular development (gonadal dysgenesis)

Sex chromosome DSD:

- 45X/46XY (mixed gonadal dysgenesis, ovotesticular DSD)
- 46XX/46XY (ovotesticular DSD)

**Cases of complete androgen insensitivity syndrome (CAIS - XY chromosome with complete female external genitalia – no ambiguity), persistent mullerian duct syndrome (PMDS), vaginal atresia, cloacal exstrophy, severe hypospadias, Turner, Klinefelter syndromes have also been included in the original classification of DSD[3], although they do not typically cause ambiguous genitalia in the newborn.*

The other notable cause of DSD includes partial androgen insensitivity syndrome (PAIS). It is caused by mutations in the androgen receptor gene on the X chromosome which dictates end organ response to androgens. Complete androgen insensitivity syndrome (CAIS) refers to a complete defect in androgen receptor and thus no response to androgen. CAIS often presents



Stages	Clitoromegaly	Introitus
Normal female		
I	Slightly enlarged clitoris	Normal vaginal orifice
II	Mild enlarged clitoris	Slightly reduced vaginal orifice and posterior labial fusion. The vagina and urethra open into a funnel-shaped urogenital sinus.
III	Clitoromegaly	Incomplete posterior fusion of the labia minora. The vagina and urethra share a single opening in the urogenital sinus.
IV	Clitoromegaly appears as male phallus	Complete posterior fusion of the labia minora. The urogenital sinus opens near of the base clitoris.
V	Male phenotype due to penile transformation (male phallus)	Complete fusion of the labial folds. The urogenital sinus transforming to penile urethra, has single orifice at the glans penis. The normally formed scrotum empty.
Normal male		

Fig.1. Prader staging

with primary amenorrhea in adolescent female or gonad appearing along with inguinal hernia in a toddler and since there is no androgen effect it does not lead to genital ambiguity. PAIS, being an intermediate and partial mutation, leads to some androgen effect and thus partial virilization. This phenotype then results in ambiguous genitalia in a 46XY infant. Unfortunately, a great number of cases among 46XY DSD do not have an identifiable cause, which highlights the importance of an experienced team with multidisciplinary focus. One such cause of XY DSD includes 5 alpha reductase deficiency where there is failure of conversion of testosterone (TST) into its active metabolite di-hydro testosterone (DHT).

Clinical assessment

A thoughtful history and exam, along with an initial workup can be extremely helpful in progressing toward a working diagnosis. A reliable diagnosis is essential for the medical team to assist the family with proper guidance in assigning a sex of rearing and planning for the future. Key points in the history and exam are outlined in Box 2. After the initial assessment for general symmetry of the genitalia, the presence of gonads and evaluation of the phallic structure are two components of the genital exam that can be assessed quickly and relatively easily.[7,8] The first thing to note is, whether the gonads are palpable bilaterally or unilaterally, including palpating the labia majora and inguinal regions for a gonad-like structure. Next, the phallic structure has to be described along a continuum from normal/typical male (penis) to normal/typical female (clitoris). A clinical staging tool called the Prader scale (Fig.1) was developed to describe the external genitalia by the degree of virilization, from the under virilized (normal female genitalia) to complete male virilization with penis-size phallus, complete labial fusion and meatus on the glans (normal male genitalia).

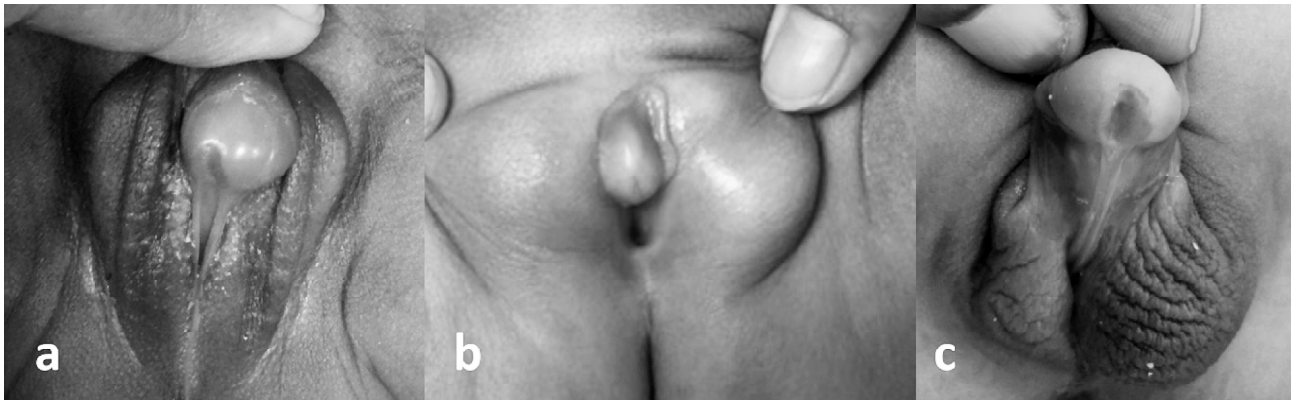


Fig.2 .Different causes of ambiguous genitalia

a) prominent phallus, fused labioscrotal folds, bilateral non palpable gonads and karyotype 46 XX – typical case of XX DSD – in this case CAH; b) small phallus, bilateral palpable gonads with proximal hypospadias and karyotype 46 XY – typical case of XY DSD– in this case PAIS; c) Variable virilisation; proximal hypospadias with palpable left gonad; right labioscrotal fold poorly developed, right gonad absent, right side mullerian remnants present and karyotype 45X/46XY mosaic – typical case of sex chromosome DSD – in this case mixed gonadal dysgenesis/ ovotesticular DSD.

Box 2. Clinical assessment of children with ambiguous genitalia

History

Family history (other cases of DSD or sudden infant death; could point to genetic cause)

Birth/maternal history (medications/exposures or maternal virilization)

Physical exam

Overall appearance: vital signs, sick (adrenal crisis) or well appearing

Dysmorphic features (genetic syndromes)

Skeletal malformations (campomelic dysplasia)

Anatomic malformations (VATER/VACTERL, cloacal exstrophy)

Genital exam

Phallic structure (micropenis vs. clitoromegaly)

Gonads (bilateral, unilateral or non-palpable)

Urethral orifice (hypospadias)

Labioscrotal folds (symmetry, presence of gonads)

Skin exam: hyperpigmentation (possible ACTH elevation and adrenal failure)

Asymmetry in the genital exam, such as unilateral structures can suggest a sex chromosome DSD such as mixed or partial gonadal dysgenesis, or mosaicism. Examples would include ovotesticular DSD or 45X/46XY mosaicism. Palpable bilateral gonads are generally associated with a 46 XY karyotype (Fig.2). Cases with non-palpable gonads should bring up concern for a 46XX infant with virilization such as CAH, or alternatively could be a 46XY infant with either cryptorchidism or absent gonads (congenital anorchia/ "vanishing testes"). The initial laboratory and imaging workup for ambiguous genitalia is listed in Box 3.

Box 3. Evaluation of a child with ambiguous genitaliaInitial evaluation

- Serum electrolytes
- Serum 17OH-progesterone - usually unreliable before the age of 36 hours and is usually done by day 3-4
- The results of PCR or FISH analysis using Y and X-specific markers
- Conventional karyotyping is always performed to confirm the chromosomes.
- Ultrasonogram

Further evaluation

- Testosterone/ Di hydro testosterone ratio (HCG stimulation test)
- Genitogram,
- MRI scan
- Genitoscopy / Laparoscopy

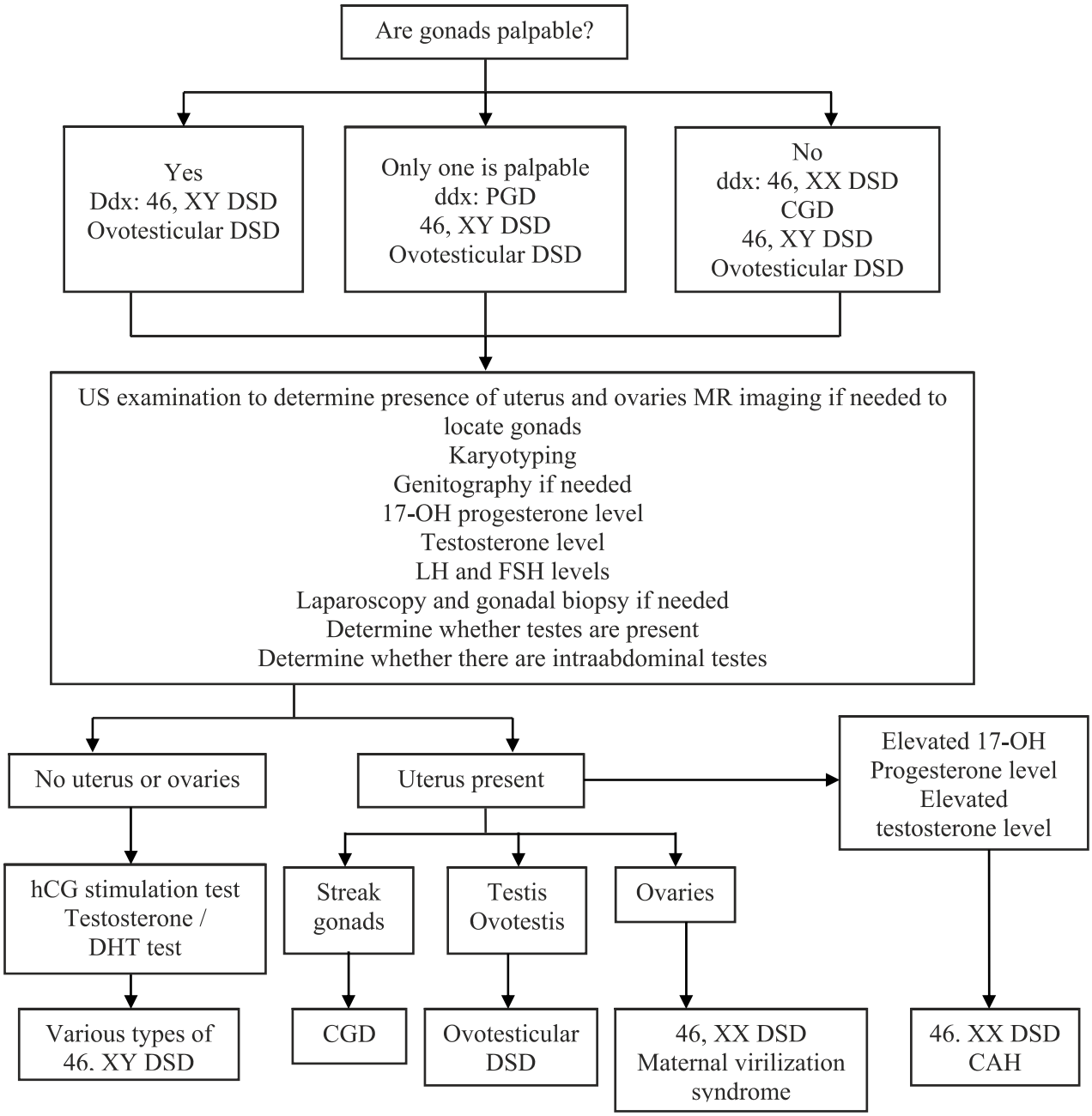


Fig.3. Simplified algorithm in evaluation of children with DSD

Fig.3 depicts a simplified algorithm in evaluation of children with DSD. In cases of non-palpable gonads, the first objective of checking the androgen levels, most importantly 17 hydroxy progesterone (17 OHP) and electrolytes is to evaluate for CAH. In cases of genital asymmetry or cryptorchidism, additional testing is often pursued by the specialist team. For example, AMH levels can help detect functional testicular tissue and the hCG stimulation test can be used to assess testicular/gonadal function. This test assesses the ability of the gonad (in this case, presumed testicle) to synthesize and secrete testosterone and other androgens. Cases of partial virilization in a 46XY infant could represent 5 alpha reductase deficiency or could be PAIS and the TST and DHT response (TST: DHT ratio) to human chorionic gonadotropin (hCG) stimulation could help differentiate these two entities. Diagnosing this is useful because children with 5 alpha reductase deficiency invariably virilise during puberty and a male sex of rearing may be appropriate in them.

In addition to karyotype testing, additional cytogenetic studies can be helpful, such as SRY testing by FISH (fluorescence in-situ hybridization) as well as more advanced techniques such as array CGH (comparative genomic hybridization) and more recently with the use of whole exome sequencing (WES). Significant advances are being made in sequencing technologies, such as WES, and some of these techniques may soon become adequately cost-effective to be considered as first-tier diagnostic testing.

Parental counseling and gender assignment

The first conversations with the family need to set a positive tone where the parents will be respectfully included and guided through the process. In addition, the first impressions tend to have lasting effects in many families. When addressing the infant, it is important to initially be gender-neutral and avoid "he" or "she" pronouns that could inadvertently bias the family towards a gender that may later be reversed. Rather than referring to the child as "it", warmer terms like "your baby" may promote greater bonding. Staying neutral until the decision is finalized helps prevent misunderstandings and confusion. Assigning a sex of rearing is a great responsibility and should not be rushed. Many factors must be taken into account, and thus it is essential to collect all relevant information while still being expeditious.

As a new standard of care according to the consensus statements, a multidisciplinary team including representatives from endocrinology, pediatric surgery/ pediatric urology, social work and behavioral health (psychology/psychiatry) and nursing along with access to experts in gynecology, bioethics, neonatology, genetics and child life should be involved in gender assignment decisions. Gender assignment is often based upon age at presentation, fertility potential, size of the phallus, psychosocial well-being, a stable gender identity, socio-cultural aspect and parental opinions. One has to be aware that gender is more about the role of the individual he assumes in the society and a child born with male aspects could identify as a girl or vice versa. When an older child presents where the family has already reared them to a particular sex, the decisions have to be made in consultation with parents, weighing the benefits versus pitfalls of reassigning the sex. This process is particularly delicate when the child is school going or adolescent, as the orientation of the individual is of more importance than any other consideration.

Gender assignment in the newborn - General principles

- CAH: (XX karyotype; elevated 17 OHP) female sex is usually favoured as they have normal female internal genitalia and fertility potential.
- 5 alpha reductase deficiency: (XY karyotype and post HCG ratio of TST/DHT >30). These children usually virilise at puberty (phallic length increases; testicles descend). Hence, a male sex of rearing is favoured.
- PAIS: (XY karyotype) sex of rearing may be determined by the phallic size. Frequently, due to the small size of phallus, these children are reared up as girls.
- Mixed gonadal dysgenesis (46, X/46, XY) variable sex of rearing depending on internal and external anatomy.
- Ovotesticular DSD variable sex of rearing depending on internal and external anatomy. The fertility potential is more if reared as girl.

Medical management

CAH

The role of pediatric endocrinologist is of paramount importance in medical management of these children. Being the commonest cause of ambiguous genitalia, CAH needs a special mention with regards to medical management. Children with CAH may present as medical emergency with salt loss and dehydration. The labia may be fused partially or completely, looking like scrotum; but the labioscrotal folds are empty and gonads not palpable (Fig.2a). There is usually increased pigmentation of the genitals, areola and axilla. The phallus size may vary from a mild hypertrophy to that resembling penis. There may be two separate openings of urethra and vagina/ or a single opening of urogenital sinus. A digital rectal examination may reveal presence of cervix, felt like a nodule especially in neonates, or uterus which feels like a vertical ridge.

In neonates presenting in shock, investigations will reveal hyponatremia, hyperkalemia and levels of 17-OHP will be elevated. In case of genital ambiguity without shock, serum 17-OHP will be raised with normal electrolytes. There is a rise of 17-OHP in premature children in the immediate post natal period and hence the 17-OHP estimation is done after 48 to 72 hours. It can be done by heel prick method and recently, from saliva of the neonate. Synthetic ACTH stimulation (Synacthen) test helps in identifying the subtypes of CAH. Pelvic sonography will

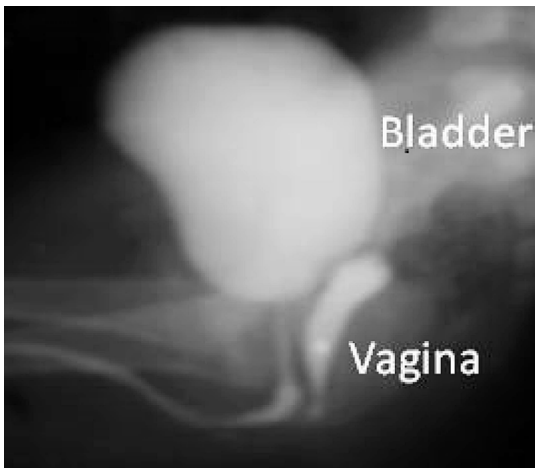


Fig.4. Genitogram - Common urogenital sinus in a child with CAH

reveal uterus. Genitogram (Fig.4) with injection of contrast medium in the common opening may reveal anatomy.

Medical management comprises of replacement of steroids. Cortisol replacement with hydrocortisone in the dose of 10 to 15 mg/M^2 BSA, in three divided doses and aldosterone replacement with fludrocortisone is the standard practice. The latter is given also to the non salt losers as it has been found to help in better control of the condition. The steroid dose needs to be stepped up, even doubled or tripled during times of stress such as surgery, febrile illness, trauma, etc. The steroid support is required lifelong and the dose keeps increasing with the growth of the child. It is important to remember that even severely virilised CAH may undergo significant reduction in the size of clitoris with adequate treatment if treatment is instituted early in neonatal period. Treatment started early in infancy carries better resolution rate compared to older children. CAH, being a genetic disorder with an autosomal recessive inheritance, it is essential to counsel parents regarding possibility of CAH in future pregnancies.

Surgical interventions

There is considerable debate as to the optimal timing of any genital surgery. Decisions about nature and timing of any surgery are made with the family, in a multidisciplinary setting acknowledging the considerable psychological impact of having a child with genital ambiguity. Milder degrees of clitoral enlargement may be left until puberty when the child can be involved with the decision making. Often proper steroid suppression is all that is required to control enlargement of clitoris in children with CAH. The timing of any vaginoplasty depends on the anatomy of the internal and external genitalia and is influenced by local practice. However, there has been a move away from early vaginoplasty in childhood. It may be appropriate to delay surgery until puberty when a single stage reconstruction can be undertaken.

While there is a push to avoid any surgery in all children with DSD, there may be medical indications (obstruction to urine/ menstrual flow) warranting surgery earlier. In children with XY gonadal dysgenesis and some mixed gonadal dysgenesis with streak gonads, the risk of gonadal tumor is high. Early gonadectomy, as soon as pubertal growth is often warranted, to prevent tumors. In such cases, a multidisciplinary panel should be available to guide regarding this.

Conclusion

The main goals in the management of children with DSD include sex assignment and rearing, anticipate early medical problems, explain the etiology to the young person and the parents of an affected newborn and finally, to develop a management plan that leads to optimal long-term outcome. A rational and empathic approach that relies on the skills and knowledge of the experts within the multidisciplinary team is essential for achieving these goals. The stepwise approach to reaching the final diagnosis needs to be explained to parents and the most important goals of the initial period of assessment should be to support the affected child and the parents, assign a sex of rearing and exclude the possibility of any early medical problems. Clinical and molecular biology research have propelled us in breaking down the complexities of male and female sex development, which has been significantly shaped by decades of practical medical experience and the lessons learned from past experiences. A care that is transparent, with full disclosure, focused on a more shared decision-making process is absolutely essential in the management of the complex conundrum of DSD. In addition, multidisciplinary care is equally important in adulthood as it is in childhood and may need to involve specialists from an even wider range of disciplines. It is essential to provide this transitional care and social support to the patients with DSD who often need lifelong counseling.

Points to Remember

- ***The newer terminology for DSD refers to differences of sexual development.***
- ***Molecular genetics and gene sequencing are being widely used in the diagnosis.***
- ***Multidisciplinary team is essential in the management.***

- ***Sex assignment should be postponed until all information is available and all stake holders are informed/ counseled.***
- ***Medical management may be needed lifelong and transitional care should be offered to adolescents. Surgical management is delayed as long as possible so that informed decisions can be made by the patient.***

Acknowledgements

The author acknowledges the inputs and ideas from the following colleagues:

Dr. V.R. Ravikumar, (Retd.) Prof of Pediatric Surgery, Coimbatore.

Dr. Pavai Arunachalam, Prof of Pediatric Surgery, Coimbatore.

Dr. S. Ramesh, Prof of Pediatric Surgery, Bangalore.

Dr. J. Divyalakshmi, Pediatric Endorinologist, Chennai and

Dr. K. Venkatasubramanian, Consultant Pediatrician, Sivakasi.

References

1. Indyk JA. Disorders/differences of sex development (DSDs) for primary care: the approach to the infant with ambiguous genitalia. Transl Pediatr 2017; 6:323-334. doi:10.21037/tp.2017.10.03.
2. Lee PA, Houk CP, Ahmed SF, Hughes IA. International Consensus Conference on Intersex organized by the Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology. Consensus statement on management of intersex disorders. International Consensus Conference on Intersex. Pediatrics 2006; 118:e488-500. doi:10.1542/peds.2006-0738. Accessed on 2nd August, 2019.
3. Houk CP, Hughes IA, Ahmed SF, Lee PA. Writing Committee for the International Intersex Consensus Conference Participants. Summary of consensus statement on intersex disorders and their management. Pediatrics 2006; 118:753-757. doi:10.1542/peds.2006-0737. Accessed on 2nd August, 2019.
4. Mouriquand PD, Gorduza DB, Gay CL, Meyer-Bahlburg HF, Baker L, Baskin LS, et al. Surgery in disorders of sex development (DSD) with a gender issue: If (why), when, and how? J Pediatr Urol 2016; 12:139-149. doi: 10.1016/j.jpurol.2016.04.001.
5. Ahmed SF, Achermann JC, Arlt W, Balen AH, Conway G, Edwards ZL, et al. UK guidance on the initial evaluation of an infant or an adolescent with a suspected disorder of sex development. Clin Endocrinol (Oxf) 2011; 75:12-26. doi: 10.1111/j.1365-2265.2011.04076.x.
6. Cools M, Nordenström A, Robeva R, Hall J, Westerveld P, Flück C, et al. Caring for individuals with a difference of sex development (DSD): a Consensus Statement. Nat Rev Endocrinol 2018; 14:415-429. doi: 10.1038/s41574-018-0010-8.
7. Ogilvy-Stuart A, Brain C. Early assessment of ambiguous genitalia. Arch Dis Child 2004; 89:401-407. doi:10.1136/adc.2002.011312.
8. Moshiri M, Chapman T, Fechner PY, Dubinsky TJ, Shnorhavorian M, Osman S, et al. Evaluation and Management of Disorders of Sex Development: Multidisciplinary Approach to a Complex Diagnosis. Radio Graphics 2012; 32:1599-1618. doi:10.1148/rg.326125507.

NEWS AND NOTES

ISPGHAN – 2019

6th Annual conference ISPGHAN 2019 & 29th Annual Conference of the Pediatrics Gastroenterology Chapter of IAP

Date: 18th – 20th October, 2019

Venue: ITC Grand Chola, Chennai.

Conference secretariat

Dr. Rela Institute & Medical Centre,

No.7, CLC Works Road, Chromepet,

Chennai-600 044.

Phone: +91 8056122134

Email: info@isphghancon2019.com, jagadeeshmenonv@gmail.com

ADOLESCENT MEDICINE

HEADACHE IN ADOLESCENTS

*Amitha Rao Aroor
**Preeti M Galagali

Abstract: *Headache is a common complaint in adolescents seeking medical advice. Primary headache is more common at this age and migraine is the commonest among them. However, detailed clinical evaluation is required to rule out secondary causes. This article focuses on the approach to adolescent headache with specific emphasis on migraine.*

Keywords: *Headache, Migraine*

Headache is a common complaint in adolescents. It can greatly influence the quality of life and could be a pointer towards serious intracranial pathology or stress related disorders.

Classification

Headache can be classified as primary and secondary headache. Primary headache has no identified etiology while secondary headache is a part of symptomatology of another disorder like trauma, vascular causes, infection, tumors, etc. Primary headache is more common during adolescence.

Based on their temporal pattern, headache can be classified as a) Acute, b) Acute recurrent (episodic), c) Chronic non-progressive and d) Chronic progressive (Fig.1). Acute recurrent and chronic non-progressive are commonly due to primary headache disorders. Some of the causes under these types are given in Table I.

Diagnostic criteria for headache have been revised and published in the International Classification of Headache Disorders, 3rd edition, beta version (ICHD-3 beta).[1]

* Professor in Pediatrics and Adolescent Specialist, A.J Institute of Medical Sciences, Mangalore.
email: amithaaroor@gmail.com
** Director and Consultant Adolescent Health Specialist, Bangalore Adolescent Care & Counselling Centre, Bangalore.

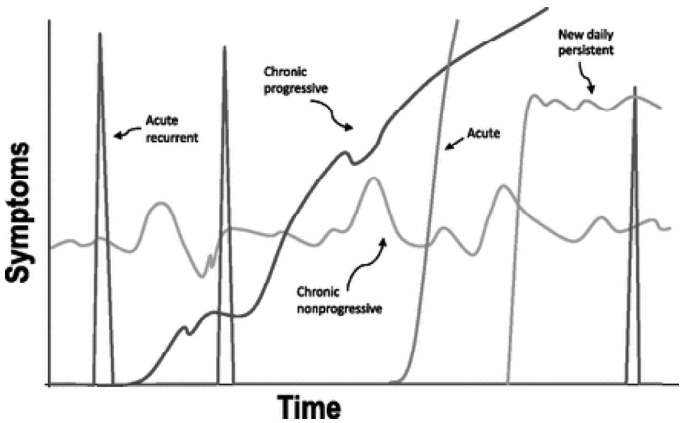


Fig.1. Types of headache

Table I. Etiology of various types of headache

Types	Etiology
Acute	Febrile illness, intracranial pathology
Acute recurrent	Migraine, tension type headache, cluster headache
Chronic non-progressive	Chronic migraine, ocular causes, hypertension, chronic sinusitis
Chronic progressive	Intracranial-SOL
New daily persistent	Post traumatic stress, CSF leak

Primary headache: Includes migraine, tension-type headache (TTH) and trigeminal autonomic cephalalgias (e.g.: cluster headache). The characteristics of each of these is depicted in Table II.

Prevalence

Prevalence of headache ranges from 57% to 82% in different studies and is higher in boys before puberty and in girls after puberty. The estimated prevalence of migraine in adolescents ranges from 6.1% to 22% and that of TTH 0.9-18%.[2] Chronic migraine can occur in up to 1% children and adolescents.[3]

Table II. Characteristic features of different types of primary headache

Feature	Migraine	TTH	Cluster headache
Pain description	Unilateral Throbbing/pulsating Moderate to severe Worsens with exercise	Bilateral Pressing/tightening Mild to moderate Does not worsen with exercise Lasts 30 min to 7 days	Unilateral on or around eye Severe, excruciating, deep Lasts 15 -180 min
Associated symptoms	Photophobia/phonophobia Nausea/Vomiting With or without Aura	None	Autonomic features (tearing, congestion, pallor, sweating, rhinorrhea) on the same side Restlessness/agitation

Evaluation of headache

Diagnosis of headache disorders is based on detailed history and examination. Primary headache is a clinical diagnosis.

- Detailed history of characteristics of headache needs to be asked including age of onset, duration, frequency, site, type, severity, presence of prodromal and associated symptoms, triggers if any, use of medications, aura and for family history of migraine. The Pediatric Migraine Disability Assessment (PedMIDAS) score can be used to assess the level of disability. Disability is graded as little or none (score 1-10), mild (score of 11-30), moderate (score of 31-50) and severe (score of >50).
- Other symptoms which may give clue to possibility of secondary headache should be enquired
- Home, education/employment, eating, activities, drugs, sexuality, suicidal ideation and safety (HEEADSSS) screening identifies comorbid conditions like depression, anxiety, substance use and other contributory psychosocial issues.
- Physical examination including BP, BMI, ENT, eye, dental examination, looking for neurocutaneous markers along with a detailed neurological examination.
- Investigations are not routinely indicated, but neuroimaging should be considered in those with an abnormal neurological examination, in migraine with unusual neurological features and when there are red flag signs of secondary headache. MRI is the imaging modality of choice whenever feasible (Box.1). Further investigations depend on the suspected etiology.

Migraine

In the Global Burden of Disease Survey 2013, migraine was ranked as the sixth most disabling condition worldwide.[4]

Pathophysiology: Migraine is said to occur due to interaction between the neuronal and vascular systems including cortical spreading depression, abnormal neuronal excitability, serotonin activity, inflammatory response and trigeminal neurovascular activation with signal transmission to cortex.[5, 6] It is multifactorial with strong genetic as well as environmental components. Common triggers include poor sleep habits, irregular meals, caffeine excess, excess media use, medication, stress, anxiety, worry and depression.

The classification of migraine is shown in Fig.2.

Migraine without aura: It is an episodic headache $\geq$5 attacks with the features as mentioned in Table I, lasting 2-72 hours. If number of episodes is <5, it is labeled as probable migraine without aura.

Migraine with aura: It has $\geq$2 attacks of migraine with one or more of fully reversible aura symptoms. Aura has at least 2 of these characteristics

- at least one symptom spreads gradually over $\geq$5 minutes, and/or two or more symptoms occur in succession
- each individual symptom lasts 5-60 minutes
- at least one aura symptom is unilateral
- accompanied, or followed within 60 minutes, by headache

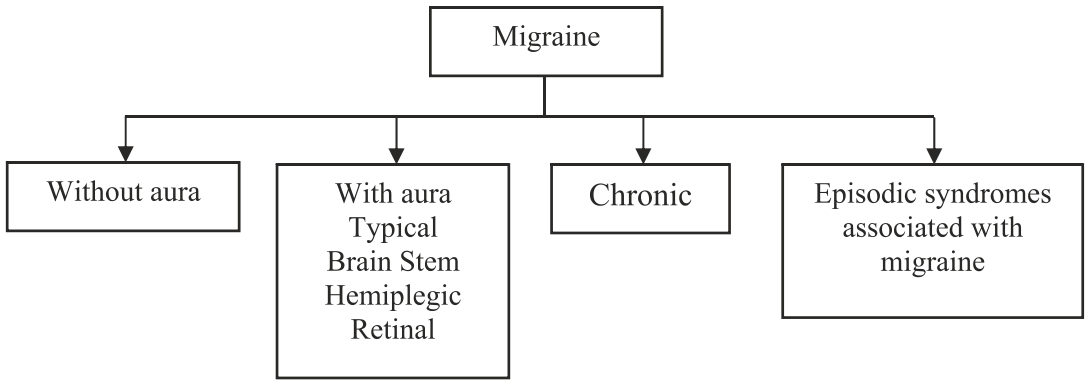


Fig.2. Migraine - Classification

Typical aura: It has visual, sensory and dysphasic symptoms without motor weakness.

Brainstem aura: It has at least two of the brainstem symptoms which include dysarthria, vertigo, tinnitus, hyperacusis, diplopia, ataxia and decreased level of consciousness without motor weakness.

Hemiplegic migraine: Here the aura consists of fully reversible motor weakness (lasts<72 hours) and fully reversible visual, sensory and/or speech/ language symptoms (lasting 5-60 min).

Retinal migraine: The aura consists of fully reversible monocular positive and/or negative visual phenomena.

Presentation of pediatric migraine may slightly differ from that in adults (Table III)

Table III. Adult vs pediatric migraine

Feature	Adult	Pediatric
Side	Unilateral	Can be bilateral
Site	Frontotemporal	Often bifrontal
Duration	4-72 hours	2-72 hours (shorter)
Associated symptom	Photophobia, phonophobia, nausea / vomiting with aura / without aura	Nausea/Vomiting more prominent
Visual aura	Fortification spectra, shimmering scotoma,involve only half of the visual field	Photopsia is more common, randomly dispersed in the field

Chronic migraine: Headache occurring on ≥15days/month for > 3 months, with characteristics of migraine on at least 8 days/month are features of chronic migraine. It can be complicated by medication overuse headache (MOH).

Complications of migraine and episodic periodic syndromes are depicted in Table IV and V respectively.

Table IV. Complications of migraine

Status migrainosus	Debilitating migraine lasting >72hours.
Migrainous infarction	≥1 migraine aura symptoms with an ischemic brain lesion in the appropriate territory
Migraine aura triggered seizure	Seizure triggered by an attack of migraine with aura. Occurs during or within 1 hour after an attack of migraine with aura

Table V. Episodic syndromes associated with migraine

Cyclical vomiting syndrome	Recurrent attacks of intense nausea and vomiting, usually stereotypical in the individual with predictable timing of episodes. Completely asymptomatic in the interval period.
Abdominal migraine	Recurrent attacks of moderate to severe midline or poorly localized abdominal pain, associated with vasomotor symptoms, nausea and vomiting, lasting 1-72 hours and with normality between episodes.
Benign paroxysmal vertigo	Recurrent brief attacks of vertigo, occurring without warning and resolving spontaneously, in otherwise healthy children.

Treatment: The usual reasons for consultation with doctors are impact of the headache on education and fear of having serious illness. The risk of conversion to daily headache becomes more likely as the frequency of migraine increases or when the acute episodes are not effectively treated.[3] Treatment is multi-tiered which includes pharmacologic as well as non-pharmacologic methods (Table VI).

Table VI. Migraine - Treatment modalities

Tier Level	Treatment	Measures
1st	Life style modification (SMART)[5]	**S**leep-Good sleep hygiene **M**eals-Regular healthy meals, hydration, limit caffeine intake **A**ctivity- regular exercise **R**elaxation-stress reduction **T**rigger avoidance
2nd	Integrative therapies	Behavioral therapies Nutraceuticals
3rd	Pharmacotherapy	Abortive and Preventive Therapies
4th	Other treatment	Onabotulinum toxin A

General measures: These include educating the child and family about the benign nature of headache, reassuring that there is no serious illness and counselling them to follow healthy life style. Keeping headache diary helps to identify the pattern of headache, triggers as well as assess response to therapy.

Integrative therapies: Behavioral therapies: These include various therapies like mindfulness, cognitive-behavioral therapy (CBT), progressive muscle relaxation and biofeedback training.

Nutraceuticals/supplements: Alone or in combination, magnesium, riboflavin, coenzyme Q10 and the herbal extracts of butterbur have all been suggested as preventives for migraine.

Pharmacotherapy: Abortive therapy: The aim of abortive therapy should be to alleviate pain so that patient is able to return to normal functioning within 1-2 hours. Treatment should start as soon as possible with optimum dose of drugs. Drugs commonly used are NSAIDs and triptans. To prevent the development of medication overuse headache (MOH), duration of NSAID use should be limited to <15 days/month and that of triptans for <10 days/month.

Table VII. Triptans in adolescent migraine

Drug	Dose and Route
Sumatriptan(10-17yrs)	PO: 50-100mg. IN: 10 mg
Rizatriptan (>6yrs)	PO:5mg(<40kg),10mg(>40kg)
Zolmitriptan(>12yrs)	PO:2.5-5mg IN:5 mg. Max-10mg/d
Almotriptan(>12yrs)	PO:6.25-12.5mg
Sumatriptan/Naproxen	10mg/60mg, Max-85mg/500mg

PO=Per oral, IN=Intranasal

1. NSAIDs: These are used in mild to moderate headaches. Common drugs used are ibuprofen (10 mg/kg/dose), paracetamol (15 mg/kg/dose) and naproxen (5-7 mg/kg/dose).

2. Triptans: These are indicated in moderate to severe migraine attacks and in mild headaches unresponsive to NSAIDs. Currently 4 triptans are approved by FDA for use in adolescent migraine. These include sumatriptan, almotriptan, zolmitriptan and rizatriptan. Dose and route of these drugs is shown in Table VII. Certain conditions like pregnancy, cardiovascular/cerebrovascular disease and uncontrolled hypertension are contraindications for their use.

Box 1. Red flag signs - Secondary headache

- Early morning headache or vomiting / awaken patient from sleep
- Recent onset of severe headache
- Change in quality or frequency
- Occipital headache
- Progressive headache
- Co-existence of seizures
- Changes in personality, behavior, worsening school performance
- Worsening with cough/Valsalva
- Symptoms of systemic disease
- Abnormal neurological examination/fundus
- Abnormality in growth/puberty
- Hypertension
- Not responding to conventional therapy

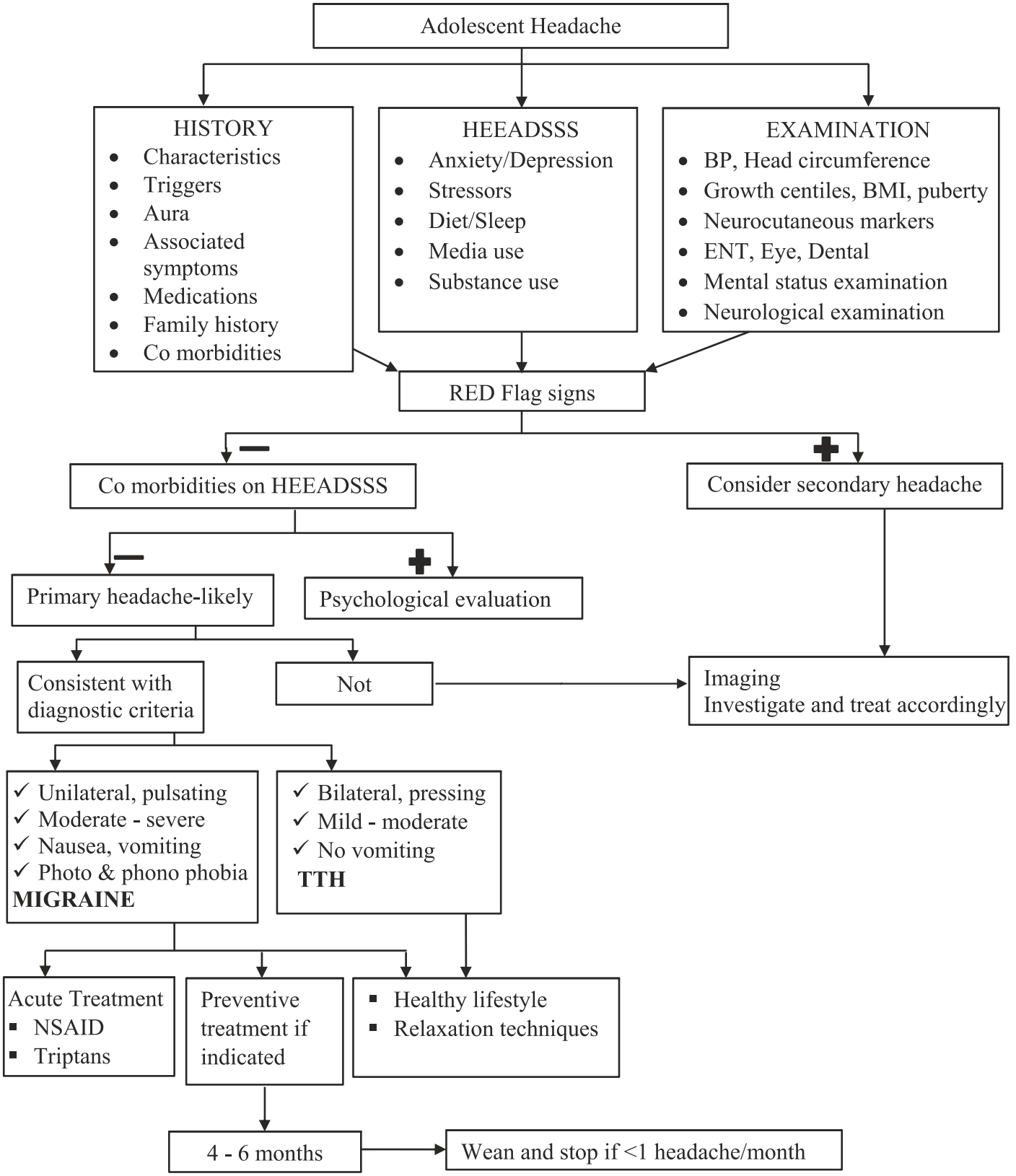


Fig.3. Algorithmic approach to an adolescent with headache

Various studies have demonstrated effectiveness of triptans in adolescent migraine. Sumatriptan nasal spray has been shown to be effective and well tolerated.[7] Studies have shown almotriptan, rizatriptan, both oral and intranasal zolmitriptan also to be effective and well tolerated in adolescent migraine.[8-11] As per the Cochrane review triptans are safe, well tolerated in the adolescent population with an observed increase in minor adverse events without significant increase in serious adverse events.[12] The combination of sumatriptan 85 mg and naproxen sodium 500 mg has shown good efficacy in adolescent migraine.[13]

3. Antiemetics: These are used as adjuncts to therapy especially in those with significant nausea and vomiting. Commonly used drugs are prochlorperazine and metoclopramide.

Preventive therapy

Indications for the use of preventive medications include high frequency of migraine attacks (1 to 2/week or >3 to 4 /month), impairment of both the quality of life and the daily activities or pediatric migraine disability assessment score (PedMIDAS) >20, severe and prolonged attacks (>4 h) and ineffective/ not tolerated / contraindicated/ overused acute treatment. Goal of therapy should be to reduce both frequency of attacks (1-2 headaches or fewer/month) and disability level (PedMIDAS score <10). Treatment should be evaluated for 6-12 weeks before considering ineffective. Prophylaxis treatment can be interrupted when frequency of severe migraine attacks is reduced to 1-2/ month for 3-6 months.[14] Drugs commonly used for preventive therapy include flunarizine (5-10mg at bed time), topiramate (100-200mg/ day in 2 divided doses), amitriptyline (0.5-1 mg/kg at bed time), propranolol, valproate and levetiracetam. Choice of drug used should be individualized keeping in mind the coexisting medical conditions. Topiramate is the first drug approved by FDA in 2014 for prevention of migraine in children >12 years.

Onabotulinum toxin A

It was approved by the FDA for the use of chronic migraine in adults. However, experience on its use in children is limited. Few studies have shown beneficial effects in pediatric patients.

Chronic daily headache

It is defined as headache occurring for ≥15 days per month. It can be due to chronic migraine, chronic TTH and new daily persistent headache (NDPH). NDPH is the occurrence of a new headache that becomes daily within 3 days of onset and is not caused by another disorder. NDPH requires evaluation to rule out secondary causes.

An algorithmic approach can be considered in an adolescent with headache (Fig.3).

Points to Remember

- ***Primary headache is more common than secondary headache during adolescence, with migraine being the commonest.***
- ***Evaluation requires detailed history, HEEADSSS screening and physical examination to differentiate primary from more serious secondary causes.***
- ***Treatment of migraine should be individualized based on the individual and headache characteristics.***
- ***Secondary headache needs detailed evaluation with imaging and other investigations.***

References

1. Headache Classification Committee of the International Headache Society (IHS), The International Classification of Headache Disorders, 3rd edn (beta version). Cephalalgia 2013; 33: 629-808.
2. Jin Z, Shi L, Wang YJ, Yang LG, Shi YH, Shen LW, et al. Prevalence of headache among children and adolescents in Shanghai, China. J Clin Neurosci 2013; 20(1):117-121.
3. Robert Kliegman, Joseph St. Geme. Nelson textbook of paediatrics, 2019; 2-Volume set, 21st edn /Philadelphia PA: Elsevier/Saunders.
4. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015; 386(9995):743-800.
5. Blume HK. Pediatric headache: a review. Pediatr Rev 2012; 33:562-576.
6. Hershey AD. Current approaches to the diagnosis and management of paediatric migraine. Lancet Neurol 2010; 9(2):190-204.
7. Winner P, Rothner AD, Saper J, Nett R, Asgharnejad M, Laurenza A, et al. A randomized, double-blind, placebo-controlled study of sumatriptan nasal spray in the treatmentof acute migraine in adolescents. Pediatrics 2000; 106(5):989-997.
8. Linder SL, Mathew NT, Cady RK, Finlayson G, Ishkanian G, Lewis DW. Efficacy and tolerability of almotriptan in adolescents: a randomized, double-blind, placebo-controlled trial. Headache 2008; 48: 1326-1336.

9. Ahonen K, Hämäläinen ML, Eerola M, Hoppu K. A randomized trial of rizatriptan in migraine attacks in children. Neurology 2006; 67: 1135-1140.
10. Linder SL, Dowson AJ. Zolmitriptan provides effective migraine relief in adolescents. Int J Clin Pract 2000; 52:466-469.
11. Lewis DW, Winner P, Hershey AD, Wasiewski WW. Efficacy of zolmitriptan nasal spray in adolescent migraine. Adolescent Migraine Steering Committee. Pediatrics 2007; 120:390-396.
12. Richer L, Billinghurst L, Linsdell MA, Russell K, Vandermeer B, Crumley ET, et al. Drugs for the acute treatment of migraine in children and adolescents. Cochrane Database Syst Rev 2016; 4:CD005220.
13. Derosier FJ, Lewis D, Hershey AD, Winner PK, Pearlman E, Rothner AD, et al. Randomized trial of sumatriptan and naproxen sodium combination in adolescent migraine. Pediatrics 2012; 129(6):e1411–1420.
14. Pasculli M, Striano P, Ledda MG. Pediatric Migraine Treatment: An Updated Review. Neonat Pediatr Med 2018; 5:178.

CLIPPINGS

Nebulised hypertonic saline in moderate-to-severe bronchiolitis: a randomised clinical trial.

An open, multicentre, randomised clinical trial was conducted from 1 April 2013 to 31 March 2016, in Swiss children's hospitals. Patients aged 6 weeks to 24 months with a primary diagnosis of moderate or severe bronchiolitis were included. Children with previous episodes of wheezing, cardiac disease, chronic respiratory disease, immunodeficiency, prematurity (gestational age <34 weeks), corticotherapy in the preceding 2 weeks or inhaled bronchodilators within 24 hours before presentation were excluded. Patients were randomised to receive standard SC with nebulisation of 4mL of 3% sodium chloride every 6 hours versus SSC. Main outcomes and measures were LOS duration of oxygen therapy, transfer to intensive care unit (ICU), readmission within 7 days following discharge and adverse events.121 children were randomised. No statistically significant differences were found between treatment groups at baseline (age, Wang Score, atopic history, smoking exposure). Children in the HS group had a non-significant difference in length of stay "2.8 hours ("10; 16) compared with the SC group. There were no differences in oxygen therapy duration, transfer to ICU, readmission rate or adverse events. The intervention was discontinued at the parents' request in 16% of the cases. The study does not support the use of Hypertonic Saline nebulisation in children with moderate to severe bronchiolitis.

Pilloud JR, Verga ME, Russo M, Gehri M, Pauchard J. Nebulised hypertonic saline in moderate-to-severe bronchiolitis: a randomised clinical trial. Arch Dis Child. Published Online First: 05 September 2019. doi: 10.1136/archdischild-2019-31716.

Preschool respiratory hospital admissions following infant bronchiolitis: a birth cohort study.

A retrospective population-based birth cohort study was done in Public hospitals in England. A birth cohort of 613 377 infants born between 1 April 2007 and 31 March 2008 were included, followed up until aged 5 years by linking Hospital Episode Statistics admissions data. The risk of respiratory hospital admission due to asthma, wheezing and lower and upper respiratory tract infections (LRTI and URTI) was compared in infants who had been admitted for bronchiolitis with those who had not, using Cox proportional hazard regression. The hazard ratios (HR) were adjusted for known respiratory illness risk factors including living in deprived households, being born preterm or with a comorbid condition. 16 288/613 377 infants (2.7%) with at least one admission for bronchiolitis were identified. Of these, 21.7% had a further respiratory hospital admission by age 5 years compared with 8% without a previous bronchiolitis admission (HR (adjusted) 2.82, 95% CI 2.72 to 2.92). The association was greatest for asthma (HR (adjusted) 4.35, 95% CI 4.00 to 4.73) and wheezing admissions (HR (adjusted) 5.02, 95% CI 4.64 to 5.44), but were also significant for URTI and LRTI admissions. Hospital admission for bronchiolitis in infancy is associated with a threefold to fivefold risk of subsequent respiratory hospital admissions from asthma, wheezing and respiratory infections. One in five infants with bronchiolitis hospital admissions will have a subsequent respiratory hospital admission by age 5 years.

Skirrow H, Wincott T, Cecil E, Bottle A, Costelloe C, Saxena S. Preschool respiratory hospital admissions following infant bronchiolitis: a birth cohort study. Arch Dis Child 2019; 104:658-663.

RADIOLOGY

CONGENITAL RENAL ABNORMALITIES

*Vijayalakshmi G
**Balaji S
**Abirami Mahadevan
***Thangalakshmi A
***Raveendran J

One of the common indications for ultrasound abdomen is to diagnose renal problems. Ultrasound plays an important role in the detection and periodic follow-up of congenital renal abnormalities in addition to day to day problems. In this issue, we will see some congenital abnormalities of the kidneys.

The kidney is normally situated in the renal fossa. If not seen in the renal fossa, it is either agenesis or ectopic. Renal agenesis is often associated with Wolffian and Mullerian duct abnormalities. In renal agenesis, the contralateral kidney is large because of compensatory hypertrophy. At birth the kidneys are roughly about 4 to 5 cm in length, 6 cm by 1 year, 7 cm by 5 years and 8 to 9 cm by 10 years. The left kidney is longer by about 2 mm and also narrower by the same measure. Larger differences may be a pointer to hypoplasia or atrophy. The atrophic or contracted kidney has increased echoes, while the hypoplastic kidney has a normal appearance. Renal artery stenosis is also associated with a small kidney with normal echoes, but Doppler study of the renal vessels will help in the diagnosis.

The ectopic kidney is found anywhere along the route it takes as it ascends from the pelvis (Fig.1) where it is formed, to its destination in the renal fossa. The thoracic kidney is extremely rare. Sometimes it is seen on the opposite side. It is the left kidney that commonly crosses over to the other side. Majority (90%) of the crossed ectopic kidneys are fused. The fusion is usually the upper pole of the crossed kidney with the lower pole of the orthoptic kidney.

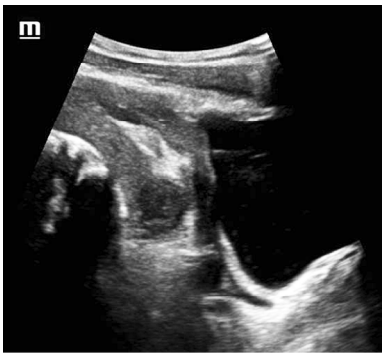


Fig.1. Pelvic kidney near bladder

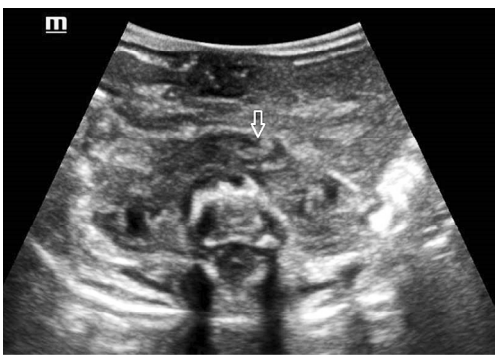


Fig.2. Horse-shoe kidney. Note thick isthmus (arrow)

One of the common fusion abnormalities is the horse-shoe kidney (Fig.2) where the kidneys are united by a band of connecting tissue running in front of the aorta. This may consist of a thick functioning isthmus or a thin band of connective tissue. A suspicion of horse shoe kidney is raised if the lower pole is not seen well. This is because the orientation of the kidney is changed. The horse shoe kidney is also low placed because the inferior mesenteric artery arrests its ascent as it moves up in front of the aorta. When both kidneys are completely fused it is called pancake kidney and lies in the pelvis.

Now we will see some abnormalities of parenchyma. For this, let us see how a normal kidney appears. The kidney is formed in utero from multiple lobules that eventually fuse. This can cause smooth indentations of the renal

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

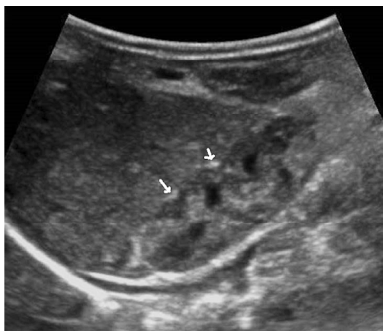


Fig.3.Kidney in the neonate. Note the cortical echoes and the lobulated (arrows) contour

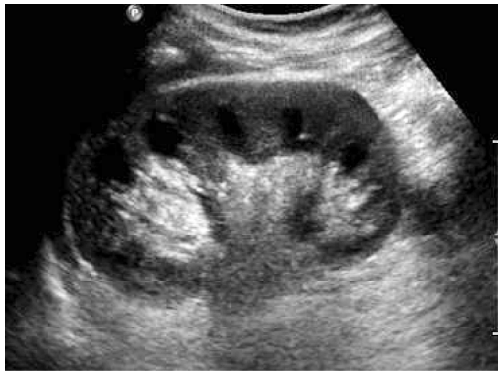


Fig.4. Normal kidney in older infant and child

outline (Fig.3) that are seen in the neonate and which gradually disappear by 4 to 6 months. Rarely they may persist. These lie in between the renal pyramids while indentations due to scarring are irregular and overlie the renal pyramids. The kidney has a reniform shape. It has a peripheral cortex that is grey in colour, the echogenicity of which is less than that of the liver. In case of renal disease the echogenicity of the cortex is higher than that of the liver. The cortex surrounds dark triangular shadows that are the pyramids.The pyramids are dark as they consist mostly of urine contained in the loops of Henle and the collecting tubules. In the centre is a white area that is hyperechoic because of the presence of fat. Dilatation of pelvis and calyces is seen as black or fluid densities within the pelvis. This is the picture in the adult and in the older child (Fig.4). In the neonate and young infant, the appearance is different. The renal cortex is brighter and is equal to or sometimes more than that of the liver (Fig.3). This is because of greater volume of tissue per unit area and larger glomerular tuft in the neonate. Since the cortex is whiter, the cortico-medullary distinction is exaggerated. Sometimes echogenic spots are seen at the tips of the medullary pyramids in many neonates. This is physiological. In the older child, it denotes dehydration. The central sinus is also not seen separately in the neonate and young infant because of the lack of fat.

Fig.5 is that of an infant with Bartter syndrome where the medullary pyramids are white. This is called reversal of cortico-medullary differentiation. There is a loss of sodium, potassium, chloride along with calcium, magnesium and water. The neonatal variety is complicated by polyhydramnios. The calcium and magnesium deposits are seen as the white shadows. Nephrocalcinosis in the older child also has a similar picture.

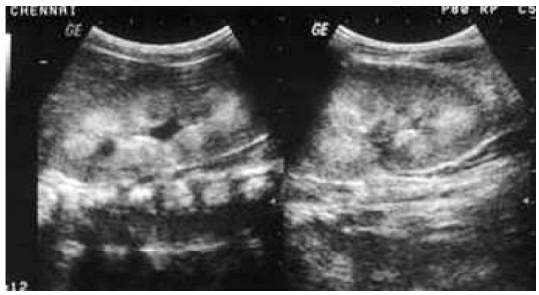


Fig.5. Reversal of cortico-medullary differentiation

Fig.6 is that of a 10 year old child with chronic renal failure. The kidneys show increased echogenicity of the parenchyma than that of the adjacent liver. There are many cysts and they are mostly in the medulla. This is nephronophthisis which shows an autosomal recessive inheritance. There are only two medullary cystic diseases – nephronophthisis and medullary sponge kidney. Medullary sponge kidney presents in adolescents and adults, where there is cystic dilatation of the collecting

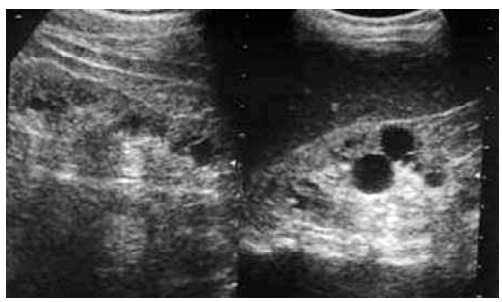


Fig.6. Medullary cysts in nephronophthisis

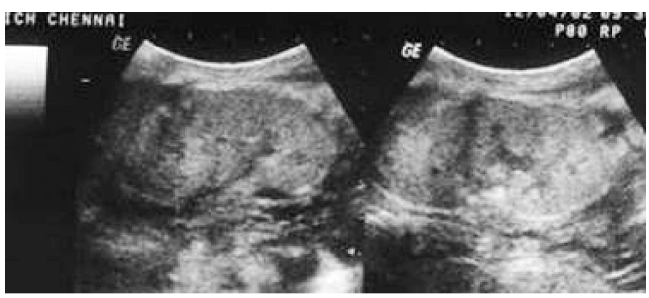


Fig.7. Autosomal recessive polycystic kidney disease (ARPKD) in infant

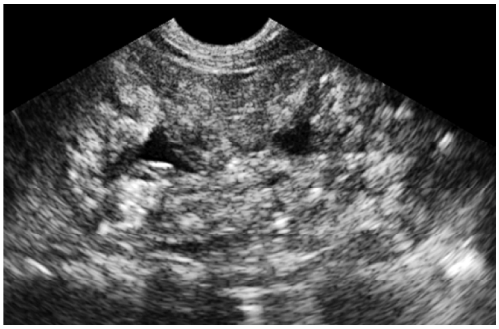


Fig.8. ARPKD. Juvenile type

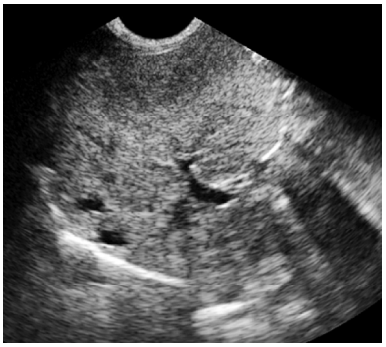


Fig.9.ARPKD (juvenile type) showing liver cysts

tubules seen as echogenic medullary pyramids. There are no large cysts. There may be calculi in them. They do not present with chronic renal failure and are usually a chance finding.

Fig.7 is that of a young infant with renal failure. Both kidneys are large and bright. There is no cortico-medullary distinction. This is autosomal recessive polycystic kidney disease (ARPKD). Fig.8 and 9 are that of a 8 year old with juvenile onset type of ARPKD. Again both kidneys are large and bright with no cortico-medullary distinction. The bright central pelvis merges with the bright parenchyma. These children also have cysts in the liver, hepatic fibrosis and portal hypertension. The hepatic features might predominate in some with only mild change in renal echoes. In this case the increase in size of the kidneys is a good clue.

In this issue we have covered congenital renal anomalies in number, position, fusion abnormalities and cysts. Abnormalities in the collecting system will be discussed in the next issue.

CLIPPINGS

Prednisolone Versus Dexamethasone for Croup: a Randomized Controlled Trial.

A prospective, double-blind, noninferiority randomized controlled trial based in 1 tertiary pediatric emergency department and 1 urban district emergency department was done in Perth, Western Australia. Inclusions were age >6 months, maximum weight 20 kg, contactable by telephone, and English-speaking caregivers. Exclusion criteria were known prednisolone or dexamethasone allergy, immunosuppressive disease or treatment, steroid therapy or enrollment in the study within the previous 14 days, and a high clinical suspicion of an alternative diagnosis. A total of 1252 participants were enrolled and randomly assigned to receive dexamethasone (0.6 mg/kg; n = 410), low-dose dexamethasone (0.15 mg/kg; n = 410), or prednisolone (1 mg/kg; n = 411). Primary outcome measures included Westley Croup Score 1-hour after treatment and unscheduled medical re-attendance during the 7 days after treatment. Mean Westley Croup Score at baseline was 1.4 for dexamethasone, 1.5 for low-dose dexamethasone, and 1.5 for prednisolone. Adjusted difference in scores at 1 hour, compared with dexamethasone, was 0.03 (95% confidence interval “0.09 to 0.15) for low-dose dexamethasone and 0.05 (95% confidence interval “0.07 to 0.17) for prednisolone. Re-attendance rates were 17.8% for dexamethasone, 19.5% for low-dose dexamethasone, and 21.7% for prednisolone (not significant [P = .59 and .19]).Noninferiority was demonstrated for both low-dose dexamethasone and prednisolone. The type of oral steroid seems to have no clinically significant impact on efficacy, both acutely and during the week after treatment.

Parker CM, CooperMN. Prednisolone Versus Dexamethasone for Croup: a Randomized Controlled Trial. Pediatrics 2019; 144(3) e20183772; DOI: 10.1542/peds.2018-3772.

CASE REPORT

ANAPHYLAXIS FOLLOWING INTRAVENOUS VITAMIN K IN AN INFANT

*Abinaya Srinivasan
**Jagannathan Krishnasamy
***Ayyammal Palaniappan

Abstract: *Anaphylaxis following intravenous vitamin K in infants is reported rarely in literatures. A 7 month old infant, a childhood wheezer with intrahepatic cholestasis, previously on oral vitamin K supplements developed serious anaphylaxis following administration of intravenous vitamin K during hospital stay. He was resuscitated with appropriate measures. Fatal adverse events following intravenous vitamin K although rare should be anticipated.*

Keywords: *Vitamin K, Anaphylaxis, Epinephrine, Children*

The reported incidence of anaphylaxis following administration of vitamin K is around 3 per 10,000 doses according to the available literature.[1] Prior treatment with antihistamines or corticosteroids before administration of vitamin K is not recommended.[2] Preparation for resuscitation in all settings where vitamin K is administered to children of all age groups is emphasized.

Case report

A 7 month old boy, born to non-consanguineous parents, presented with abdominal distension, jaundice, high coloured urine, pruritus and pale coloured stools for 2 months duration. Further evaluation was suggestive of intrahepatic cholestasis. Supportive medications were prescribed on an out-patient basis including oral vitamin K. He was admitted previously for wheezing episodes requiring nebulisations. He was admitted electively in the ward for liver biopsy the next day.

* DNB Trainee
** Consultant Pediatric Gastroenterologist
*** Pediatric intensivist,
Department of Pediatrics,
G.Kuppuswamy Naidu Memorial Hospital,
Coimbatore.
email: aashriyaa@yahoo.co.in

On the day of admission, the child received the first dose of intravenous (IV) vitamin K (0.36mg/kg) administered as a bolus. Immediately parents noticed that his face turned red with flushing followed by apnoea, unresponsiveness and the child sustained cardiac arrest with ECG monitor showing asystole. Cardio-pulmonary resuscitation (CPR) was initiated according to the pediatric advanced life support (PALS) protocol. Return of spontaneous circulation (ROSC) was achieved within 10 minutes requiring 3 doses of adrenaline and 2 normal saline boluses. He was transferred to the pediatric intensive care unit (PICU) and was connected to a mechanical ventilator. He required epinephrine infusion for a few hours. He had recurrent episodes of desaturation and bradycardia while on mechanical ventilation and required muscle relaxants to stabilize. A component of severe bronchospasm was considered. He was started on IV methyl prednisolone along with terbutaline infusion after which he gradually improved.

Subsequently, liver biopsy was performed which confirmed the diagnosis of progressive familial intrahepatic cholestasis (PFIC) type 2. Blood culture and tracheal cultures were negative for sepsis. He was discharged on a low dose of oral vitamin K.

Discussion

Vitamin K is widely used to prevent bleeding in children due to various underlying pathologies.[3] Adverse reactions to Vitamin K_1 injection include facial flushing, weakness, abdominal and low back pain, nausea, vomiting, dyspnoea, chest pain, hypotension, cardio-pulmonary arrest and even death in severe cases.[1,4] Adverse reactions occur mainly with IV routes, even when given slowly and diluted.[5,6] But the exact incidence of adverse reaction following intramuscular and oral administration of the same is not available in the paediatric literatures.

Vitamin K_1 can trigger both anaphylaxis and anaphylactoid reaction mainly due to the solubilizer. The difference between the two is mentioned in Table I. Altering the vitamin K_1 preparation, using a highly safe solubilizer like lecithin and glycocholic acid (MM form) instead of polyethoxylated castor oil rather than decreasing

Table I. Difference between anaphylaxis and anaphylactoid reactions[8]

Characteristics	Anaphylactic reaction	Anaphylactoid reaction
Sensitisation required	Yes	No
Reaction on first exposure	No	Yes
How much exposure to elicit reaction	Very little	More
Predicted by skin allergy tests	Yes	No

the solubilizer dosage may be a good strategy to reduce the anaphylactoid reactions however the safety remains questionable.[7] Oral route is by far much safer than intravenous route.[9] Preparations like Konakion MM and Orokay are available internationally (not in India) which can be used in both parenteral and oral routes but the cost and compliance are limiting factors.[10] Oral preparations are preferred whenever feasible and facilities for emergency resuscitation should be made available in all areas where parenteral vitamin K is being administered.

References

1. Choudhary B, Kumari S, Dhingra B, Jhaj R. A clinically suspected case of Anaphylactoid reaction to vitamin K injection in a child–a case report and review of literature. Indian journal of pharmacology 2016; 48(4):455.
2. Riegert-Johnson DL, Volcheck GW. The incidence of anaphylaxis following intravenous phytonadione (vitamin K1): a 5-year retrospective review. Annals of Allergy, Asthma & Immunology 2002; 89(4):400-406.
3. Johnson BC. Post-translational carboxylation of preprothrombin. Mol Cell Biochem 19811; 38 (Pt 1): 77-121.
4. Pereira SP, Williams R. Adverse events associated with vitamin K1: results of a worldwide postmarketing surveillance programme. Pharmacoepidemiol Drug Saf 1998; 7:173-182.
5. Rich EC, Drage CW. Severe complications of intravenous phytonadione therapy. Two cases, with one fatality. Postgrad Med 1982; 72:303-306.
6. Songy KA Jr., Layon AJ. Vitamin K-induced cardiovascular collapse. J Clin Anesth 1997; 9:514-519.
7. Mi YN, Ping NN, Xiao X, Zhu YB, Liu J, Cao YX. The severe adverse reaction to vitamin K1 injection is anaphylactoid reaction but not anaphylaxis. PLoS One 2014; 9(3):e90199.
8. Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: J Allergy Clin Immunol 2006; 117: 391-397.
9. Van Cries R. Oral versus intramuscular phytomendione: Safety and efficacy. Drug Safety 1999; 21:1-6.
10. Tiwari. M. Oral vitamin K administration at birth: Indian Pediatrics 2003; 909-910.

NEWS AND NOTES

20TH NATIONAL PEDIATRIC CONFERENCE, 2019

Date: 18th – 20th October, 2019

Venue: Pearl Continental Hotel, Lahore, Pakistan

Email: ppaconference2019@gmail.com

Website: ppaconference2019

11TH WORLD CONGRESS OF PEDIATRIC INFECTIOUS DISEASE (WCPID)

Date: 5th – 8th November, 2019

Venue: Philippine International Convention Center, Vicente Sotto St, Pasay, Metro Manila, Philippine.

For registration: reg_wspid19@kenes.com

INDIAN JOURNAL OF PRACTICAL PEDIATRICS
SUBSCRIPTION TARIFF

JOURNAL OFFICE
1A, Block II, Krsna Apartments
50, Tamil Salai (Halls Road), Egmore,
Chennai 600 008.
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

For office use
Ref. No.
NEFT / DD / Cheque / Cash
Transaction / DD / Cheque No.
Receipt No. & Date

Enter subscription for

Individual	Institution
ONE YEAR	ONE YEAR
TEN YEARS	FIVE YEARS

(Subscription period is between January and December only)

Name .....

Address .....

.....

City .....State .....

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

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

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

I am enclosing a DD / cheque No. ..... dated ..... drawn on .....

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

Signature

SUBSCRIPTION RATE			BANK ACCOUNT DETAILS (for NEFT)		
Individual	Annual	Rs.750/-	Bank Name	:	**THE KARUR VYSYA BANK**
	Ten years	Rs.6,500/-	Account Name	:	**Indian Journal of Practical Pediatrics**
Institution	Annual	Rs.4,000/-	Account Number	:	**1154115000004720**
	Five years	Rs.16,000/-	IFSC code	:	**KVBL0001878**
Foreign	Annual	US $ 75/-			

Send your subscription, only by crossed demand draft, drawn in favour of **INDIAN JOURNAL OF PRACTICAL PEDIATRICS**, payable at **Chennai** and mail to DR.N.C.GOWRISHANKAR, Editor-in-Chief, **1A, Block II, Krsna Apartments, 50, Tamil Salai (Halls Road), Egmore, Chennai - 600 008, Tamilnadu, India.**

INDIAN JOURNAL OF PRACTICAL PEDIATRICS

ADVERTISEMENT TARIFF

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

Name .....

Address .....

.....

.....

City .....

State ..... **Pin** .....

Black & White Advertisement	
Half Page	Rs.5,000.00
Ordinary	Rs.10,000.00
Back cover	-
Second cover	-
Third cover	-

Colour Advertisement		
Single Ordinary Page	Rs.15,000.00	Full Page
Back Cover	Rs.25,000.00	
Second Cover	Rs.20,000.00	
Third Cover	Rs.20,000.00	

Signature

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

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