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Dr. K.Nedunchelian Dr. S.Thangavelu
Editor-in-Chief Executive Editor

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ACUTE DISSEMINATED ENCEPHALOMYELITIS

* Kumaresan G

Abstract: Acute disseminated encephalomyelitis (ADEM) is common in children. The diagnosis is made with illness of acute onset with encephalopathy and polysymptomatic presentation after excluding acute infective processes. It can be monophasic, recurrent or multiple episodes. There is no specific diagnostic biological marker. MRI greatly aids to arrive at the diagnosis. Treatment with steroids is effective. Intravenous immunoglobulin or plasmapheresis can be tried if steroid therapy is ineffective. Differential diagnosis includes pediatric multiple sclerosis (MS), macrophage activation syndrome and isolated cerebral angiitis.

Keywords: Acute disseminated encephalomyelitis (ADEM), Multiple sclerosis (MS), Children.

Acute disseminated encephalomyelitis (ADEM) is an immune mediated inflammatory disease of the nervous system which consist of a wide spectrum of disorders (Table I).

1. Post-vaccination: This constitutes about 3-6%. This is common with vaccines using neural tissue like Semple vaccine (1/300-1/700). With the use of recombinant protein based vaccine, the incidence of post vaccination ADEM has come down. Incidence following vaccines against Japanese encephalitis (2/100,000) have been reported. ADEM following measles vaccine is reported to occur in a frequency of 1/million compared to frequency of 20-30 /million cases of natural measles infection.

2. ADEM can follow a number of common childhood infections like rubella, measles, mumps, influenza, acute tonsillitis, varicella, gastroenteritis, mycoplasma and streptococcal infections.

3. Spontaneous: No prodromal illness. Reported to be around 30%.
The pathological mechanism is described as molecular mimicry by antigens simulating various natural neural antigens neither being recognized as foreign to be cleared nor as self to be immune tolerated. They are processed leading to T and B cell activation and enter CNS. There, they recognize homologous myelin proteins and trigger inflammatory response against presumed foreign protein. This is followed by perivenular inflammatory response and subsequent damage to myelin. Re-infection or post-infectious break down in blood brain barrier, leads on to exposure of CNS confined auto antigens to systemic circulation which can also trigger the events.

Clinical presentation

There is no definitive definition of ADEM. The age is usually below 10 years. There may be a history of prodromal illness. Onset is with headache, fever and lethargy.

Encephalopathy: It is characterized by altered mental status and behaviour changes. A prerequisite for diagnosis is the presence of encephalopathy combined with polysymptomatic presentation namely ataxia, brain stem and pyramidal signs. All the components are important and there should be no evidence of previous destructive white matter changes or previous history of demyelinating event. If there is no encephalopathy and is a monophasic illness, the diagnosis is clinically isolated syndrome. If the involvement is only an isolated structure like optic nerve, spinal cord or cerebellum the diagnosis is more specific like, transverse myelitis or neuro-myelitis optica. Post infectious demyelination can also involve isolated areas and can cause acute cerebellitis (varicella), deafness (mumps) and Sydenhams chorea (poststreptococcal).

Investigations

CSF may show non specific changes. Oligoclonal bands in CSF is seen only in 12.5% of children and may be transient. Thus, there is no specific biological marker for the confirmation of the diagnosis.

MRI has greatly helped in the diagnosis; shows extensive lesion load which may involve juxta cortical regions (more than 2 in number) (Figs.1 and 2) and may involve supra tentorial, infra tentorial regions (Fig.3) and spinal cord. The lesions are predominantly in the white matter and are ill defined and confluent. They may also involve deep grey matter like basal ganglion or thalamus (Fig.4). There may be perifocal edema or occasionally mass effect. The lesions remain status quo or may show resolution. The previous old lesions may be seen as black holes in T1 weighted images.

Four types of MRI findings have been described in ADEM. These include 1) bilateral small hyperdense subcortical lesions (62%). 2) large confluent lesions (24%). 3) bilateral deep grey matter lesions (12%) and

<table>
<thead>
<tr>
<th>Monophasic demyelination</th>
<th>Recurrent demyelination(^1)</th>
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<tbody>
<tr>
<td>Acute disseminated encephalomyelitis (ADEM)</td>
<td>Recurrent ADEM</td>
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<tr>
<td>Neuro myelitis optica (NMO)</td>
<td>Multiphasic ADEM</td>
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<tr>
<td>Clinically isolated syndrome</td>
<td>Relapsing neuro myelitis optica</td>
</tr>
<tr>
<td>Initial presentation of multiple sclerosis</td>
<td>Pediatric multiple sclerosis.</td>
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</tbody>
</table>

Table I. Immune mediated inflammatory diseases of nervous system
4) acute hemorrhagic encephalitic pattern (2%). Presence of periventricular lesions, perpendicular lesions to long axis of corpus callosum (Dawsons finger sign) or black holes in T1 weighted images suggest multiple sclerosis.

The differential diagnosis include:
1) single large lesions - brain tumours, abscesses, Marburg variant of MS. 2) bilateral thalamic lesions - deep cerebral vein thrombosis, hypernatremia, extrapontine myelinolysis and acute necrotizing encephalopathy 3) basal ganglion lesions- organic acidurias, Japanese B encephalitis and bilateral striatal necrosis are to be differentiated.

**Differential diagnosis**

1. **Macrophage activation syndrome:** Isolated involvement of central nervous system without hemophagocytosis, splenomegaly, lymphadenopathy or intravenous coagulation may mimic ADEM. Elevated serum ferritin levels and triglycerides as well as early necrotic lesions in MRI will help in confirming the diagnosis. Bone marrow transplantation may help.

2. **Isolated angiitis of CNS:** Sub acute presentation, headache, multiphasic neurodegeneration, narrowing of cerebral vessels on angiogram may mimic ADEM at onset especially without macular lesions or episodes of transient ischemic episodes. Angiogram or biopsy may confirm the diagnosis. Treatment with steroids or cyclosporins will help.

3. **Pediatric multiple sclerosis:** Dissemination in time alone is not a specific feature for the diagnosis of multiple sclerosis. ADEM can also be recurrent or multi-phasic. 20% pediatric multiple sclerosis have at the onset ADEM like presentation. The transition from ADEM to MS is suspected by two or more non-ADEM like events or new T2 lesions three months after the episode (Table II).

4. **Neuro myelitis optica:** MRI lesions of spinal cord extends more than three segments and there may be anti aquaporin-4 antibodies in CSF.

Though dissemination in time and space is characteristic of multiple sclerosis, on follow up about 30% of ADEM can recur. The recurrences can be of three types (Table III).

1. Same episode: If relapses occur, within three months after an episode or when treated within one month after steroid withdrawal, it is considered as same episode.

2. Relapse: Occurs after three months: First ascertain that the initial event has truly terminated with complete remission before considering a relapse. The relapse can be of two types:

2a. Recurrent ADEM: New events more than three months after the initial episode or more than

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**Table II. Comparison of multiple ADEM and multiple sclerosis**

<table>
<thead>
<tr>
<th>Multi phasic ADEM</th>
<th>Pediatric multiple sclerosis</th>
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<tbody>
<tr>
<td>• At least three weeks after first episode</td>
<td></td>
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<tr>
<td>• Encephalopathy always, poly symptomatic</td>
<td></td>
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<tr>
<td>• Initial MRI: New lesions with resolving old lesions</td>
<td></td>
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<tr>
<td>• Follow up MRI Partial or complete resolution of the lesions</td>
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<tr>
<td>• Discrete events separated by at least 4 weeks. Multiple episodes disseminated in time and space</td>
<td></td>
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<tr>
<td>• Encephalopathy rare</td>
<td></td>
</tr>
<tr>
<td>• McDonald criteria Ongoing accrual of asymptomatic lesions</td>
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</tbody>
</table>

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Table III. Comparison of recurrent types of ADEM

<table>
<thead>
<tr>
<th>Same ADEM</th>
<th>Recurrent ADEM</th>
<th>Multiphasic ADEM</th>
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<tbody>
<tr>
<td>Acute Encephalopathy + Polysymptomatic Presentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Recurrence within 12 weeks/within 4 weeks of steroid withdrawal</td>
<td></td>
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<tr>
<td>• Considered as same episode</td>
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<td></td>
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<tr>
<td>• Recurrence after 12 weeks/4 weeks of steroid withdrawal</td>
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<td></td>
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<tr>
<td>• Sites same as first episode</td>
<td></td>
<td></td>
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<tr>
<td>• Complete remission and then recurrence involved.</td>
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<tr>
<td>• Different sites</td>
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Table IV. Magnetic resonance imaging criteria (McDonald criteria) for brain abnormality in pediatric multiple sclerosis

Three of four of the following

1. One gadolinium-enhancing lesion or nine T2-hyperintense lesions if there is no gadolinium enhancing lesion
2. At least one infratentorial lesion
3. At least one juxtacortical lesion
4. At least three periventricular lesions (One spinal cord lesion can substitute a brain lesion)

Table V. Magnetic resonance imaging criteria for dissemination of lesions in time

1. If a first scan occurs 3 months or more after the onset of the clinical event, the presence of a gadolinium-enhancing lesion is sufficient to demonstrate dissemination in time, provided that it is not at the site implicated in the original clinical event. If there is no enhancing lesion at this time, a follow-up scan is required. The timing of this follow-up scan is not crucial, but 3 months is recommended. A new T2- or gadolinium-enhancing lesion at this time then fulfills the criterion for dissemination in time.

2. If the first scan is performed less than 3 months after the onset of the clinical event, a second scan done 3 months or more after the clinical event showing a new gadolinium-enhancing lesion provides sufficient evidence for dissemination in time. However, if no enhancing lesion is seen at this second scan, a further scan not less than 3 months after the first scan that shows a new T2 lesion or an enhancing lesion will suffice

one month after steroid withdrawal but with polysymptomatic encephalopathy and involving same areas as first event.

2b. Multiphasic ADEM: Same time interval as above, polysymptomatic with encephalopathy and new signs and symptoms. Comparison of recurrent types of ADEM is given in Table II. This has to be differentiated from pediatric multiple sclerosis. Absence of encephalopathy and 2 or more events disseminated in space and time suggest MS (Table III, IV and V). Various diagnostic criteria to differentiate ADEM from
pediatric MS have been reported in various studies⁵ and proposed diagnostic criteria for pediatric MS.

**Treatment**

There is no standard therapy for ADEM.

**Steroid therapy:** Intravenous methyl prednislone (10-30mg/kg/day upto a maximum of 1gm) or dexamethasone (1mg/kg/day) for 3-5 days followed by tapering dose of oral prednislone over 4-6 weeks is the first line of approach. Side effects of steroid therapy have to be borne in mind.

**Intravenous immunoglobulins:** This is well tolerated and can be tried after failed steroid therapy or recurrent demyelination.

**Plasma exchange:** Can be used as the last and rescue therapy when other modalities have failed.
Prognosis

Recovery in 50-70% of cases have been reported. Recovery period is shortened in treated cases. Residual deficits observed are focal motor deficits in 16-30%, behaviour problems in 6-50%, recurrent/multiphasic in 6-33% and progression to MS in 0-28% are noticed.

Points to Remember

- *ADEM is characterised by acute/subacute neurological illnesses with encephalopathy and polysymptomatic features.*
- *The diagnosis is guided by MRI.*
- *It may present as monophasic, recurrent or multiphasic illness. Encephalopathy is an important component.*
- *The differentiation between ADEM and pediatric MS is difficult. Long term follow up will show dissemination in space and time in MS.*
- *Good recovery is seen in ADEM, though residual deficits may be seen.*
- *Steroids followed by IVIG or plasmapheresis help in recovery.*

References


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**CLIPPINGS**

**Tzarouchi LC. Diffuse periventricular leukomalacia in preterm children: assessment of grey matter changes by MRI. Pediatric Radiology, 09/13/2011.**

Preterm children with diffuse periventricular leukomalacia (dPVL) have increased regional grey matter (GM) volume in some areas probably related with a process of brain plasticity-regeneration and reduced GM volume in areas associated with cognition and memory.
RICKETTSIAL INFECTIONS

* Janani Sankar

Abstract: Rickettsial diseases are some of the most covert re-emerging infections of the present times. They are generally incapacitating and notoriously difficult to diagnose; untreated cases can have fatality rates as high as 30-35% but when diagnosed properly, they are often easily treated.

Keywords: Rickettsia, Eschar, Fever.

Rickettsiae comprise a group of microorganisms that phylogenetically occupy a position between bacteria and viruses. The genus Rickettsia is included in the bacterial tribe Rickettsiaceae, family Rickettsiaceae and order Rickettsiales. They are obligate intracellular gram-negative coccobacillary forms that multiply within eukaryotic cells. Rickettsiae do not stain well with Gram stain, but they take a characteristic red color when stained by the Giemsa or Gimenez stain. They have typical gram-negative cell walls and lack flagella. Their genome is very small, composed of 1-1.5 million bases.

Rickettsiae are a rather diverse collection of organisms with several differences; this prohibits their description as a single homogenous group. A general characteristic of rickettsiae is that mammals and arthropods are natural hosts. Rickettsial diseases are usually transmitted to humans by arthropods. Rickettsial illnesses caused by organisms within the genus of rickettsiae are recognized and can be divided into the following three biogroups:

1) Spotted fever biogroup

This group includes
- Rocky Mountain spotted fever (RMSF), caused by Rickettsia rickettsii
- Rickettsialpox, caused by Rickettsia akari

2) Typhus group

The diseases are similar but differ epidemiologically. The causative organisms (Rickettsia prowazekii and Rickettsia typhi) are similar to those of the spotted fever group but are antigenically distinct. This group includes
- Louse-borne (epidemic) typhus
- Brill-Zinsser disease (ie, relapsing louse-borne typhus)
- Murine (endemic or flea-borne) typhus

3) Scrub typhus biogroup (Tsutsugamushi disease)

The rickettsial agents of scrub typhus have a single taxonomic name: Orientia tsutsugamushi. However, these organisms represent a heterogeneous group that strikingly
differs from Rickettsial species of the spotted fever and typhus groups.

**Pathophysiology**

Rickettsiae microorganisms appear to exert their pathologic effects by adhering to and then invading the endothelial lining of the vasculature within the various organs affected. The adhesins appear to be outer membrane proteins that allow the rickettsia to be phagocytosed into the host cell. Once inside, the rickettsial organisms either multiply and accumulate in large numbers before lysing the host cell (typhus group) or they escape from the cell, damaging its membrane and causing the influx of water (spotted fever group).\(^3\)

Rickettsiae rely on the cytosol of the host cells for growth. To avoid phagocytosis within the cells, they secrete phospholipase D and hemolysin C, which disrupt the phagosomal membrane, allowing for rapid escape.

The most important pathophysiologic effect is increased vascular permeability with consequent edema, loss of blood volume, hypoalbuminemia, decreased osmotic pressure, and hypotension. On the other hand, disseminated intravascular coagulation is rare and does not seem to contribute to the pathophysiology of rickettsiae.

**Tsutsugamushi disease (ie, scrub typhus):** After invading the host cell and replicating in its cytoplasm, the Orientia tsutsugamushi exits by budding, enveloped by part of the host cell membrane as it invades adjacent cells. Perivasculitis of small blood vessels occurs similar to other rickettsial diseases. Usually, a necrotic inflammatory skin lesion occurs at the site of the mite-bite. Regional and generalized lymphadenopathy is associated with this infection. There is increased microvascular permeability resulting from discontinuities in interendothelial adherens junctions and the effects of TNF\(\alpha\), IFN\(\alpha\), IL-1\(\alpha\), and vascular endothelial growth factor (VEGF) and COX-2 dependent production of PGE2 and PGI2 lead to endothelial breach and severe vasculitis.

**Clinical features**

Early signs and symptoms of these infections are notoriously nonspecific and may mimic benign viral illnesses, making the diagnosis more difficult. Certain features that aid in making the early diagnosis of rickettsial diseases include (1) a history of tick bite or exposure, (2) recent travel to endemic areas and (3) similar illness in family members, coworkers from same geographical area or family pets (especially dogs).

In Tsutsugamushi disease (ie, scrub typhus) which is more prevalent in our region the incubation period is approximately 1-2 weeks.\(^4\) In fewer than half of patients, the site of the mite bite develops a necrotic eschar with enlargement of regional lymph nodes similar to rickettsial pox. Unlike in other rickettsial diseases, generalized lymphadenopathy is a common feature (80%) of scrub typhus. It develops concomitantly with other manifestations, such as fever, headache and rash. The rash, which occurs 1-3 weeks following exposure to the vector, is frequently truncal and has a short duration. In 50% of cases, patients have an inoculation eschar. Hepatosplenomegaly, ocular pain and conjunctival injection are relatively common. Other less common manifestations include deafness, tinnitus, myocarditis, atypical pneumonia, and acute respiratory distress syndrome.\(^4\)

**Laboratory diagnosis**

Rickettsiae are not evident on blood smear findings and do not stain with most conventional stains.\(^{3,5}\) No rapid laboratory tests are available to diagnose rickettsial diseases early in the course of illness. Serologic assays that demonstrate
antibodies to rickettsial antigens (eg, indirect immunofluorescence, complement fixation, indirect hemagglutination, latex fixation, enzyme immunoassay, microagglutination) are preferable to the nonspecific and insensitive Weil-Felix test based on the cross-reactive antigens of Proteus vulgaris strains. Serologic findings usually take 10-12 days to become positive. The value of testing 2 sequential serum or plasma samples together to show a rising antibody level is considerably more important in confirming acute infection with rickettsial agents because antibody titers may persist in some patients for years after the original exposure.  

Immunofluorescence assay (IFA) is currently considered to be the reference serological method. However, it cannot determine the causative agent to the species level.

Polymerase chain reaction (PCR) to detect rickettsiae in blood or tissue provides promise for early diagnosis. PCR testing and immunohistochemical staining of skin specimen obtained by performing a biopsy may help confirm the clinical diagnosis in patients with rash (high expertise is usually needed to interpret the biopsy result). However, serology remains the mainstay of diagnosis because other tests are expensive and less available to clinicians.

Rickettsial isolation in culture is laborious and hazardous to laboratory personnel.

**Medical care**

**Specific therapy**

Adequate antibiotic therapy initiated early in the first week of illness is highly effective and is associated with the best outcome. Fever usually subsides within 24-72 hours after starting antibiotic therapy. If fever fails to subside within 72 hours of the use of a suitable antibiotic, the diagnosis of rickettsial disease should be reconsidered.

Doxycycline is the drug of choice at a dose of 2.2mg/kg/dose, twice daily for a week to 10 days. It is preferred over other tetracyclines for treatment of rickettsial infections and, at such low dose and short duration, is rarely associated with staining of teeth in children younger than 8 years.

Recent data suggest that fluoroquinolones, such as ciprofloxacin and ofloxacin, rifampicin, azithromycin and chloramphenicol may be effective in the treatment of certain rickettsioses (Typhus group).

**Supportive therapy**

Thrombocytopenia, hypoalbuminemia, hypotension and coagulation defects require supportive management. Hyponatremia is best managed with maintenance fluids or even modest fluid restriction.

**Poor prognostic factors**

Absence of eschar, older age, WBC counts > 10000/mm³, hemoglobin ≥ 10 g/dL, albumin ≤ 3g/dL, serum creatinine > 1.4 mg/dL and CRP > 10 mg/dL are poor prognostic factors.

**Predictors of mortality**

Metabolic acidosis, ARDS, altered sensorium and shock are found to be associated with increased mortality.

**Points to Remember**

- **High index of suspicion is the key to early diagnosis**
- **Suspect scrub typhus in any child when presented with fever more than one week with organomegaly with or without lymphadenopathy, rash, eschar.**
- **Scrub typhus can involve any system**
- **Absence of eschar does not rule out infection.**
- **Start treatment when you have a clinical suspicion.**
• Failure of early diagnosis may lead to significant morbidity and mortality in Rickettsial infections.

References


CLIPPINGS


Renal scarring after acute pyelonephritis is associated with long-term sequelae. Preventing scarring after acute pyelonephritis depends not only on early diagnosis and rapid treatment to eradicate the bacteria but also ameliorating the destructive inflammatory response.

In this study, an adjunctive short course of oral methylprednisolone therapy significantly reduced the occurrence and/or severity of renal scarring after acute pyelonephritis in children.


Acute septic arthritis of childhood is a potentially devastating disease that causes permanent disability and can result in death. Traditional treatment consists of a prolonged course of intravenous antibiotics combined with aggressive surgery. However, this approach is challenged by trials showing satisfactory outcomes with shorter treatment and less invasive surgery. Diagnostic arthrocentesis alone and an antibiotic for a fortnight, including initial intravenous administration for 2–4 days, suffice in most non-neonatal cases. A good penetrating agent, such as clindamycin or a first-generation cephalosporin, exceptionally high doses, and administration four times a day are probably key factors. If the symptoms and signs subside within a few days, and the serum C-reactive protein level drops below 20 mg/L, the antibiotic can usually be safely discontinued. Methicillin resistant Staphylococcus aureus is a concern, but fortunately, most strains have retained susceptibility to clindamycin. The above guidance is not applicable to neonates and immunocompromised patients who may require a different approach.
NEONATAL RESUSCITATION
2010 GUIDELINES

* Rema Chandramohan

Abstracts: The guidelines in this article are an interpretation of the evidence presented in the 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations.¹

They apply primarily to newly born infants undergoing transition from intrauterine to extraterine life, but the recommendations are also applicable to neonates who have completed perinatal transition and require resuscitation during the first few weeks to months following birth.

Neonatal resuscitation skills are essential for all health care providers who are involved in the delivery of newborns. The transition from fetus to newborn requires intervention by a skilled individual or team in approximately 10% of all deliveries. This figure is concerning because 80% of all babies in India are born in nonteaching, nonaffiliated level I or II hospitals.

Nearly one half of newborn deaths (many of which are extremely premature infants) occur during the first 24 hours following birth. Many of these early deaths also have a component of asphyxia and/or respiratory depression as an etiology. For the surviving infants, effective management of asphyxia in the first few minutes of life may influence long-term outcome.

Keywords: Cardiopulmonary resuscitation, Newborns.

Numerous sources of information concerning the training of skills and procedures that are needed for the delivery room resuscitation of the newborn are available. One highly respected source of information concerning the preparation and practice of neonatal resuscitation is the Neonatal Resuscitation Program, which has been co-developed by the AAP and the American Heart Association.¹²

Although the current program for neonatal resuscitation is considered a highly respected reference, it is important that more research continue to evaluate the effectiveness of the techniques of neonatal resuscitation.

Rapid assessment: Those newly born infants who do not require resuscitation can generally be identified by a rapid assessment of the following 3 characteristics:

- Term gestation?
- Crying or breathing?
- Good muscle tone?

If the answer to all 3 of these questions is “yes,” the baby does not need resuscitation and should not be separated from the mother.
The baby should be dried, placed skin-to-skin with the mother, and covered with dry linen to maintain temperature. Observation of breathing, activity, and color should be ongoing.

If the answer to any of these assessment questions is “no,” the infant should receive one or more of the following 4 categories of action in sequence:

A. Initial steps in stabilization (provide warmth, clear airway if necessary, dry, stimulate)
B. Ventilation
C. Chest compressions
D. Administration of epinephrine and/or volume expansion

Approximately 60 seconds (“the Golden Minute”) are allotted for completing the initial steps, reevaluating and beginning ventilation if required. The decision to progress beyond the initial steps is determined by simultaneous assessment of 2 vital characteristics: respirations (apnea, gasping, or labored or unlabored breathing) and heart rate (whether greater than or less than 100 beats per minute). Assessment of heart rate should be done by intermittently auscultating the precordial pulse.\(^3\)

A pulse oximeter can provide a continuous assessment of the pulse without interruption of other resuscitation measures, but the device takes 1 to 2 minutes to apply, and it may not function during states of very poor cardiac output or perfusion.

Once positive pressure ventilation or supplementary oxygen administration is begun, assessment should consist of simultaneous evaluation of 3 vital characteristics: heart rate, respirations and the state of oxygenation, the latter optimally determined by a pulse oximeter

The most sensitive indicator of a successful response to each step is an increase in heart rate.

**Trained personnel**

For all deliveries, at least one person should be present who is skilled in neonatal resuscitation and has responsibility for only the infant. Additional personnel should be immediately available to assist in tasks that may be required as part of the resuscitation, including intubation, medication administration and emergency procedures, if needed.

**Initial steps**

The initial steps of resuscitation are to provide warmth by placing the baby under a radiant heat source, positioning the head in a “sniffing” position to open the airway, clearing the airway if necessary with a bulb syringe or suction catheter, drying the baby, and stimulating breathing.

**Temperature control**

Very low-birth-weight (<1500 g) preterm babies are likely to become hypothermic despite the use of traditional techniques for decreasing heat loss. For this reason additional warming techniques are recommended eg, pre warming the delivery room to 26°C, covering the baby in plastic wrapping (food or medical grade, heat-resistant plastic) (Class I, LOE A1), placing the baby on an exothermic mattress (Class IIb, LOE B), and placing the baby under radiant heat (Class IIb, LOE C).\(^4\)

Animal studies indicate that hyperthermia during or after ischemia is associated with progression of cerebral injury. (Class IIb, LOE C).

The goal is to achieve normothermia and avoid iatrogenic hyperthermia.
Clearing the airway

When amniotic fluid is clear

It is recommended that suctioning immediately following birth (including suctioning with a bulb syringe) should be reserved for babies who have obvious obstruction to spontaneous breathing or who require positive-pressure ventilation (PPV) (Class IIb, LOE C).

When meconium is present

In the absence of randomized controlled trials, there is insufficient evidence to recommend a change in the current practice of performing endotracheal suctioning of non vigorous babies with meconium-stained amniotic fluid (Class IIb, LOE C). However, if attempted intubation is prolonged and unsuccessful, bag-mask ventilation should be considered, particularly if there is persistent bradycardia.5

Pulse oximetry

It is recommended that oximetry be used when resuscitation can be anticipated, when positive pressure is administered for more than a few breaths, when cyanosis is persistent, or when supplementary oxygen is administered (Class I, LOE B).6 The probe should be attached to a preductal location (ie, the right upper extremity, usually the wrist or medial surface of the palm). There is some evidence that attaching the probe to the baby before connecting the probe to the instrument facilitates the most rapid acquisition of signal (Class IIb, LOE C).6,7

Administration of supplementary oxygen

Two meta-analyses of several randomized controlled trials comparing neonatal resuscitation initiated with room air versus 100% oxygen showed increased survival when resuscitation was initiated with room air.8 If blended oxygen is not available, resuscitation should be initiated with air (Class IIb, LOE B).8 If the baby has bradycardia (HR <60 per minute) after 90 seconds of resuscitation with a lower concentration of oxygen, oxygen concentration should be increased to 100% until recovery of a normal heart rate (Class IIb, LOE B).

Positive-pressure ventilation (PPV)

If the infant remains apneic or gasping, or if the heart rate remains <100per minute after administering the initial steps, start PPV.

Initial breaths and assisted ventilation

Initial inflations following birth, either spontaneous or assisted; create a functional residual capacity (FRC). The optimal pressure, inflation time, and flow rate required to establish an effective FRC when PPV is administered during resuscitation have not been determined.

Assisted ventilation should be delivered at a rate of 40 to 60 breaths per minute to promptly achieve or maintain a heart rate >100 per minute (Class IIb, LOE C).

End-expiratory pressure

Starting infants on CPAP reduced the rates of intubation and mechanical ventilation, surfactant use and duration of ventilation, but increased the rate of pneumothorax. Spontaneously breathing preterm infants who have respiratory distress may be supported with CPAP or with intubation and mechanical ventilation (Class IIb, LOE B).9

Assisted - Ventilation devices

Effective ventilation can be achieved with either a flow-inflating or self inflating bag or with a T-piece mechanical device designed to regulate pressure.
T Piece resuscitator

Depends on a compressed gas source. It must have a tight mask to face seal to inflate the lung. It can deliver up to 100% free flow oxygen. It requires selection of PIP and PEEP. May require adjustments of PIP during resuscitation to achieve physiologic improvement, audible breath sounds and perceptible chest movements. Gas flow is directed to the baby or the environment when you alternately occlude and open the aperture in the PEEP cap with your thumb.

The T piece resuscitator provides more consistent pressures than the self inflating or flow inflating bags. But the duration of the inspired time may be longer if the occlusion of the PEEP cap is not monitored.

Laryngeal mask airways

Laryngeal mask airways that fit over the laryngeal inlet have been shown to be effective for ventilating newborns weighing more than 2000 g or delivered >34 weeks gestation (Class IIb, LOE B). A laryngeal mask should be considered during resuscitation if facemask ventilation is unsuccessful and tracheal intubation is unsuccessful or not feasible (Class IIa, LOE B). The laryngeal mask has not been evaluated in cases of meconium-stained fluid, during chest compressions or for administration of emergency intra tracheal medications.

Endotracheal tube placement

Endotracheal intubation may be indicated at several points during neonatal resuscitation:

- Initial endotracheal suctioning of non vigorous meconium-stained newborns
- If bag-mask ventilation is ineffective or prolonged
- When chest compressions are performed
- For special resuscitation circumstances, such as congenital diaphragmatic hernia or extremely low birth weight

Exhaled CO2 detection is the recommended method of confirmation of endotracheal tube placement (Class IIa, LOE B). However, it should be noted that poor or absent pulmonary blood flow may give false negative results.10

Chest compressions

Chest compressions are indicated for a heart rate that is <60 per minute despite adequate ventilation with supplementary oxygen for 30 seconds. Compressions should be delivered on the lower third of the sternum to a depth of approximately one third of the anterior-posterior diameter of the chest (Class IIb, LOE C) using either the 2 thumb (recommended class IIb, LOE2) or the 2 finger method.

Compressions and ventilations should be coordinated to avoid simultaneous delivery at the rate of 3:1 unless cardiac arrest is due to a clear cardiac etiology where ratio of 15:2 may be considered. Respirations, heart rate and oxygenation should be reassessed periodically, and coordinated chest compressions and ventilations should continue until the spontaneous heart rate is >60 per minute (Class IIb, LOE C).

Medications

Drugs are rarely indicated in resuscitation of the newly born infant. If the heart rate remains < 60 per minute despite adequate ventilation (usually with endotracheal intubation) with 100% oxygen and chest compressions, administration of epinephrine or volume expansion, or both, may be indicated. Epinephrine is recommended to be administered intravenously (Class IIb, LOE C). Given the lack
of supportive data for endotracheal epinephrine, the IV route 0.01 to 0.03 mg/kg of 1:10,000 per dose should be used as soon as venous access is established (Class IIb, LOE C).

**Volume expansion**

Volume expansion should be considered when blood loss is known or suspected (pale skin, poor perfusion, weak pulse) and the baby’s heart rate has not responded adequately to other resuscitative measures (Class IIb, LOE C). An isotonic crystalloid solution or blood is recommended for volume expansion in the delivery room (Class IIb, LOE C).

The recommended dose is 10 mL/kg, which may need to be repeated. When resuscitating premature infants, care should be taken to avoid giving volume expanders rapidly, because rapid infusions of large volumes have been associated with intraventricular hemorrhage (Class IIb, LOE C).

**Post resuscitation care**

Babies who require resuscitation are at risk for deterioration after their vital signs have returned to normal. Once adequate ventilation and circulation have been established, the infant should be maintained in, or transferred to an environment where close monitoring and anticipatory care can be provided.

**Naloxone**

Administration of naloxone is not recommended as part of initial resuscitative efforts in the delivery room for newborns with respiratory depression.

**Glucose**

Due to the paucity of data, no specific target glucose concentration range can be identified at present. Intravenous glucose infusion should be considered as soon as practical after resuscitation, with the goal of avoiding hypoglycemia (Class IIb, LOE C).

**Induced therapeutic hypothermia**

It is recommended that infants born at > 36 weeks gestation with evolving moderate to severe hypoxic ischemic encephalopathy should be offered therapeutic hypothermia. The treatment should be implemented according to the studied protocols, which currently include commencement within 6 hours following birth, continuation for 72 hours and slow rewarming over at least 4 hours. Therapeutic hypothermia should be administered under clearly defined protocols similar to those used in published clinical trials and in facilities with the capabilities for multidisciplinary care and longitudinal follow-up (Class IIa, LOE A).

**Guidelines for withholding and discontinuing resuscitation**

**Withholding resuscitation:** When gestation, birth weight or congenital anomalies are associated with almost certain early death and when unacceptably high morbidity is likely among the rare survivors, resuscitation is not indicated. Examples include extreme prematurity (gestational age <23 weeks or birth weight <400 g), anencephaly and some major chromosomal abnormalities, such as trisomy 13 (Class IIb, LOE C).

**Discontinuing resuscitative efforts:** In a newly born baby with no detectable heart rate, it is appropriate to consider stopping resuscitation if the heart rate remains undetectable for 10 minutes (Class IIb, LOE C).
### AHA/AAP Neonatal resuscitation guidelines 2010: Summary of major changes

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<tbody>
<tr>
<td><strong>1) Assessment for need of resuscitation</strong></td>
<td>Four questions • Gestation-term or not? • Amniotic fluid- clear or not? • Tone- Good? • Breathing /Crying?</td>
<td>Three questions • Gestation-term or not? • Tone- Good? • Breathing /Crying</td>
<td>• Instead of 4 questions now 3 questions are asked at initiation of resuscitation. • “Amniotic fluid- clear or not” not part of assessment at birth. However, tracheal suction of non vigorous babies with meconium stained amniotic fluid (MSAF) still to be continued (part of clearing airway in initial steps)</td>
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<tr>
<td><strong>2) Routine care</strong> (Given if answer to all three question is YES)</td>
<td>• Provide warmth • Clear airway • Dry • Assess color</td>
<td>• Provide warmth • Assure open airway • Dry • Ongoing evaluation (color, activity and breathing</td>
<td>Emphasis on placing baby on mothers chest in skin to skin contact</td>
</tr>
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<td><strong>3) Initial steps</strong></td>
<td>• Provide warmth • Position; Clear airway (if required) • Dry, stimulate, reposition</td>
<td>• Provide warmth • Open airway (no routine suction) • Dry, stimulate</td>
<td>No change except for terminology</td>
</tr>
<tr>
<td><strong>4) Assessment (after initial steps and ongoing)</strong></td>
<td>Look for 3 signs • Heart rate • Color • Respiration Palpation of umbilical cord pulsation for 6 sec and multiply by 10</td>
<td>Look for 2 signs • Heart rate • Respiration (Labored, unlabored, apnea, gasping) Auscultation of heart at the precordium is the most accurate</td>
<td>• Color has been removed from the signs of assessment • Pre-cordial auscultation better than umbilical cord palpation for detection of heart rate (LOE2, LOE4)</td>
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<td><strong>5) Positive pressure ventilation (PPV)</strong></td>
<td>Indications are (any 1 out of 3) • Heart rate &lt;100/min • Apnea or gasping • Persistent central cyanosis despite free flow oxygen Heart rate Color Respiration</td>
<td>Indications (1 out of 2) • Heart rate &lt;100/min • Apnea or gasping Heart rate Pulse oximetry Respiration</td>
<td>• Persistent central cyanosis is not mentioned in the indication for PPV; use pulse oximetry to assess oxygenation • Increase in HR most sensitive indicator of resuscitation efficacy (LOE5)</td>
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</table>
| 5) Oxygenation      | • Based on color       | • Based on Pulse oximetry for both term and preterm in case of following situations  
| 5.1) Assessment of oxygenation | • Pulse oximetry recommended for only preterm < 32 weeks with need for PPV |  
|                    |                        | a. Anticipated need for resuscitation  
|                    |                        | b. Need for PPV for more than few breaths  
|                    |                        | c. Persistent cyanosis  
|                    |                        | d. Supplementary oxygen |  
| 5.2) Target saturation (pre-ductal) | Not defined | Target SpO2 ranges provided as part of algorithm  
|                    |                        | 1 min- 60-65%  
|                    |                        | 2 min- 65-70%  
|                    |                        | 3 min- 70-75%  
|                    |                        | 4 min- 75-80%  
|                    |                        | 5 min- 80-85%  
|                    |                        | 10 min- 85-95% (same for both term and preterm) |  
| 6) Initial oxygen concentration for resuscitation in case of PPV | Term babies (≥ 37 weeks)  
|                    | • Start with 100% O2 during PPV  
|                    | • However if room air resuscitation is started supplemental O2 up to 100% should be given if no improvement within 90 seconds following birth  
|                    | • In case non availability of O2 start room air resuscitation | Term babies (≥ 37 weeks)  
|                    |  
|                    | Preterm babies (<32 weeks)  
|                    | • Start with oxygen concentration somewhere between 21-100%  
|                    | • No specific concentration recommended  
|                    | • Advocates use of blender for graded increment or decrement of O2  
|                    | • Pulse oximetry for targeting SPO2 85-95% | Term babies (≥ 37 weeks)  
|                    |  
|                    | Preterm (<32 weeks)  
|                    | • Initiate resuscitation using O2 concentration between 30-90%  
|                    | • Titrate O2 concentration to attain SPO2 values recommended at different time points  
|                    | • Uses blended air oxygen mixture judiciously guided by pulse oximetry |  
|                    |  
|                    | • Paradigm shift from 100% to 21% O2 for resuscitation of term babies needing PPV  
|                    | • Supplemental oxygen started at 90 sec from birth in case of no improvement  
|                    | • Use of blender and pulse oximetry is recommended for term babies also  
|                    | • Preterm start with O2 concentration 30-90% and then increase or decrease  
|                    | • No evidence to give appropriate initial oxygen strategy for infants 32-37 weeks |  

LOE-2
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<tr>
<td><strong>7) Peripartum suctioning for neonates born through meconium stained amniotic fluid</strong></td>
<td>No routine oropharyngeal and nasopharyngeal suction • Tracheal suction only in non-vigorous babies born through meconium stained amniotic fluid (MSAF) • Intrapartum suctioning for MSAF not advised</td>
<td>No routine oropharyngeal and nasopharyngeal suction required • Tracheal suction of non vigorous babies with MSAF still to be continued though evidence for the same is conflicting • Intrapartum suctioning for infants with MSAF, after delivery of head before delivery of shoulder not advised</td>
<td>• No evidence for or refuting tracheal suction even in nonvigorous babies born through MSAF (LOE 4) • However no change suggested to existing practice • If tracheal intubation is unsuccessful or there is severe bradycardia then proceed to PPV</td>
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<tr>
<td><strong>8) Initial breath strategy</strong> Positive pressure ventilation (PPV)</td>
<td>• No specific recommendation for short or long inflation time • No specific PIP recommendation • No specific recommendation for PEEP • Guiding of PPV looking at chest rise and improvement in heart rate</td>
<td>• No specific recommendation for short or long inflation time as evidence is conflicting • PIP- for initial breaths 20-25 cm H2O for preterm and 30-40 cm H2O for some term babies • PEEP likely to be beneficial for initial stabilization of preterm infants, if provided with suitable equipment (T-piece or flow inflating bags) • Guide the PPV looking at heart rate and oxygenation especially in preterm, chest rise less reliable • Pressure monitoring device facilitates consistent delivery of pressures without any proven clinical benefit • Routine monitoring of tidal volume not recommended</td>
<td>• No specific recommendation for inflation time (LOE 1) • Addition of PEEP in preterm suggested (LOE 5)</td>
</tr>
<tr>
<td><strong>9) CPAP in delivery room</strong></td>
<td>Suggested for preterm babies (&lt; 32 weeks) with respiratory distress</td>
<td>Spontaneously breathing preterm infants with respiratory distress may be supported with CPAP or ventilation as per local practice (Class IIB; LOE B)</td>
<td>• CPAP is now mentioned in the algorithm for persistent cyanosis or labored breathing after initial steps, • CPAP in term babies no evidence to support or refute its use. • May be considered for preterm infants with respiratory distress</td>
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<tr>
<td>10)Airway management 10.1)Confirmation of endotracheal tube placement</td>
<td>Exhaled CO2 detection is recommended except in cardiac asystole where direct laryngoscopy may have to be done</td>
<td>Exhaled CO2 detection is recommended except in cardiac asystole where direct laryngoscopy may have to be done</td>
<td>Indications for endotracheal intubation are same as are recommendations for confirming its placement in trachea. LMA not recommended – in cases of meconium stained AF, during CCR and for drug administration</td>
</tr>
<tr>
<td>10.2)Laryngeal mask airway</td>
<td>For near term and term infants &gt;2500g may be used with no definite mention of indications</td>
<td>LMA may be used for infants &gt;2000g and ≥ 34 weeks in case bag and mask is ineffective and tracheal intubation is unsuccessful or not feasible (LOE 2)</td>
<td></td>
</tr>
<tr>
<td>11)Upper airway interface</td>
<td>• Mask- rounded cushioned of appropriate size • Other alternative is anatomical shaped mask</td>
<td>• Evidence for anatomical shaped or rounded mask to maintain seal is conflicting (LOE 5) • PPV by nasal prongs superior to facial masks for providing PPV(LOE2)</td>
<td>Nasal prongs are an alternative way of giving PPV</td>
</tr>
<tr>
<td>12)Method of providing PPV</td>
<td>Bag mask ventilation</td>
<td>Bag mask superior to mouth to mask or mouth to tube ventilation</td>
<td>In resource limited setting mouth mask (LOE 2) or mouth tube ventilation may be used (LOE 5)</td>
</tr>
<tr>
<td>13)Chest compression</td>
<td>• Ratio of compression 3:1 • Two thumb technique better than two finger technique • The compression is applied at the lower one third of sternum • The depth of compression should be one-third of the antero-posterior diameter of the chest</td>
<td>• Ratio of compression 3:1 unless cardiac arrest is due to a clear cardiac etiology where ratio of 15:2 may be considered • Two thumb technique better than two finger technique • The compression is applied at the lower one third of sternum • The depth of compression should be one-third of the antero-posterior diameter of the chest</td>
<td>No major changes in the guidelines and most recommendations are based on low level of evidence(LOE5)</td>
</tr>
<tr>
<td>14)Drugs 14.1) Naloxone</td>
<td>Naloxone considered in case of infants born to mothers with history of opiod exposure within 4 hours of delivery and there is persistent respiratory depression even after restoration of heart rate and color by effective PPV</td>
<td>• Naloxone is not recommended as part of initial resuscitation in babies with respiratory depression. • Focus needs to be on effective ventilation</td>
<td>• Safety and long term effects on naloxone not established(LOE 5) • Naloxone is not indicated in delivery room</td>
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<tr>
<td>15) Supportive care</td>
<td>No sufficient evidence to recommend routine use of modest systemic or selective cerebral hypothermia after resuscitation in infants with suspected asphyxia. Avoid hyperthermia in such cases</td>
<td>Therapeutic hypothermia (wholebody or selective head cooling) recommended for infants ≥ 36 weeks with moderate to severe hypoxic ischemicencephalopathy as per the protocol used in major cooling trials with provision for monitoring for side effects and long term follow up. For uncomplicated births both term and preterm not requiring resuscitation – delay cord clamping by at least 1 min.</td>
<td>Lack of supporting evidence from resource-limited settings, need of intensive and multidisciplinary care during therapeutic hypothermia and established follow-up services after discharge limit the applicability in middle- and low-income countries.</td>
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<tr>
<td>15.1) Therapeutic Hypothermia</td>
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<td>15.2) Delayed cord clamping</td>
<td>Not recommended</td>
<td></td>
<td>Delays cord clamping for at least 1 min in all infants not requiring resuscitation at birth (LOE1)</td>
</tr>
<tr>
<td>16) Changes in ongoing care</td>
<td>After birth 3 types of care mentioned - routine care, observational care and post resuscitation care</td>
<td>Post resuscitation two types of ongoing care mentioned - routine care and post resuscitation care</td>
<td></td>
</tr>
<tr>
<td>17) Withholding Resuscitation</td>
<td>• The guidelines need to be interpreted according to local policy In general withhold care for - Gestational age &lt; 23 weeks - Birth weight &lt; 400 grams - Major chromosomal anomalies (e.g. Trisomy 13) - Anencephaly - The decision to this regard should be taken only after examining the baby after birth and with parental agreement.</td>
<td>• The guidelines need to be interpreted according to local policy In general withhold care for - Gestational age &lt; 23 weeks - Birth weight &lt; 400 grams - Major chromosomal anomalies (e.g. Trisomy 13) - Anencephaly - The decision to this regard should be taken only after examining the baby after birth and with parental agreement.</td>
<td>No change in the guidelines</td>
</tr>
<tr>
<td>18) Discontinuing care</td>
<td>If there is no detectable heart rate for &gt;10 min despite adequate measures, it is appropriate to discontinue resuscitation measures.</td>
<td>If there is no detectable heart rate for &gt;10 min despite adequate measures, it is appropriate to discontinue resuscitation measures.</td>
<td>In situations of prolonged bradycardia with heart rate &lt; 60 /min for &gt; 10-15 min, there is insufficient evidence to make recommendation regarding continuation or discontinuation of resuscitation.</td>
</tr>
<tr>
<td>19) Educational program to teach</td>
<td>No mention of such a section</td>
<td>AHA/AAP NRP should adopt simulation, briefing-debriefing techniques in designing an educational programme for acquisition and maintenance of skills necessary for effective neonatal resuscitation.</td>
<td>This recommendation is newly added to desin NRP programme in a more effective manner.</td>
</tr>
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</table>

* LOE : Level of evidence
Levels of evidence

1 Randomized controlled trial (RCT),
2 Concurrent controls, no randomization,
3 Retrospective (historical) controls,
4 No controls (case series),
5 Not related to the specific patient or population (other human populations, animal studies, mechanical/virtual models).

Grading of evidence

• Ia: systematic review or meta-analysis of RCTs.
• Ib: at least one RCT.
• IIa: at least one well-designed controlled study without randomisation.
• IIb: at least one well-designed quasi-experimental study, such as a cohort study.
• III: well-designed non-experimental descriptive studies, such as comparative studies, correlation studies, case-control studies and case series.
• IV: expert committee reports, opinions and/or clinical experience of respected authorities.

Points to Remember

• Three questions determine the need for resuscitation  1] Gestation-term or not?  2] Tone- Good?  3] Breathing /Crying?
• Color has been removed from the signs of assessment.
• Increase in heart rate most sensitive indicator of resuscitation efficacy.
• Assessment of oxygenation based on pulse oximetry for both term and preterm. Use blender for graded increase in delivered oxygen concentrations.

• Intrapartum succioning not advised for infants with MSAF, after delivery of head before delivery of shoulder.
• Labour ward CPAP may be considered for preterm infants with respiratory distress.
• Therapeutic hypothermia (whole body or selective head cooling) recommended for infants ≥36 weeks with moderate to severe HIE.

References


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**Steroids for acute sinusitis in adults and children**

Acute sinusitis is a common reason for primary care visits; it is one of the 10 most common diagnoses in outpatient clinics, presenting with various symptoms and signs that include purulent nasal discharge and congestion and cough lasting beyond the typical seven to 10 days of a viral upper respiratory infection. There have been suggestions, based on studies of allergic rhinitis and chronic sinusitis, that intranasal corticosteroids (INCS) may relieve symptoms and hasten recovery in acute sinusitis due to their anti-inflammatory properties.

A critical systematic review of the literature found four well-conducted, randomised, placebo-controlled intervention studies, involving 1943 participants treated for 15 or 21 days. The results suggest that there may be a modest effect with INCS in the resolution or improvement of symptoms. Only minor adverse events such as epistaxis, headache and nasal itching were reported. Given the small number of studies included in this review, it is recommended that further randomised controlled trials be conducted.

Abstract: Dengue is one disease entity with different clinical presentations, unpredictable clinical evolution and outcome. WHO guidelines for dengue in 2009 is suitable for triage and assessment of the disease at primary care level. Classification as dengue with or without warning signs and severe dengue clearly differentiates the severity and the phase of the illness. This is a good tool to triage patients and make decisions as to who gets admitted to hospital and who can be sent home. The classification further guides the intensity of care for individual patients.

Keywords: Dengue, Severe dengue, WHO guidelines 2009.

Dengue guidelines by WHO in 2009 classifies the levels of severity with a potential for use by clinicians to triage the children especially in case of an epidemic. The present guidelines differ from the previous guidelines with regard to the classification and management. Previous classification categorizes dengue into 5 groups as dengue fever, dengue hemorrhagic fever which has 4 grades. This has not been clearly able to differentiate the severity of dengue in a given clinical setting without laboratory parameters. Dengue hemorrhagic fever needs all the four criteria (Fever, decreasing platelet count less than one lakh, plasma leak, hemorrhage) for diagnosis and various studies have expressed difficulty in using this classification. Whereas 2009 guidelines classify as dengue with or without warning signs and severe dengue, which can be done by a primary care physician. Also the presence or absence of warning signs help to decide on the intensity of monitoring. The term dengue hemorrhagic fever puts undue emphasis on hemorrhage while clinically the plasma leak and shock are the hallmark of severe dengue. Obvious hemorrhage may or may not be seen in dengue and if severe hemorrhage develops it is a late manifestation in dengue. The suggested dengue classification and levels of severity are given in Fig.1.

Dengue follows three phases namely febrile phase, critical phase and recovery phase. Management is based on timely intervention by understanding the clinical problems in different phases of the illness.

Febrile phase: Characterized by high grade fever lasting for 2-7 days and is accompanied by facial flushing, erythematous skin, generalized body pain, myalgia, arthralgia, headache, anorexia, nausea and vomiting. Petechiae and mucosal bleeds can be seen. A positive tourniquet test favors the diagnosis of dengue at this stage. Tender hepatomegaly may be encountered after a few days of fever. Lab investigations may show a declining white cell count.

Critical phase: With declining fever child develops capillary leak. The duration of plasma
leak is 24 - 48 hours. Critical loss of volume leads to shock. The warning signs should be carefully watched for at this stage of illness and appropriate intervention is warranted. In the initial phases of shock systolic blood pressure is maintained with tachycardia and peripheral vasoconstriction. Progression of shock leads to decreased skin perfusion and delayed capillary refill. With increasing peripheral resistance the diastolic pressure rises and the pulse pressure narrows. A narrow pulse pressure ≤ 20 mm Hg with signs of poor capillary perfusion signify shock. Systolic blood pressure is maintained in compensated shock. Further progression of illness leads to hypotension and multi organ dysfunction. Though coagulation abnormalities occur in dengue, significant bleed is almost always associated with profound shock and multi organ dysfunction. Progressive leucopenia and decreasing platelet counts are encountered prior to plasma leak. Chest X-ray and ultrasound may be useful investigations to identify the pleural effusion and ascites. The rise in hematocrit is a simple bedside investigation, to assess the degree of plasma leak.

**Recovery phase:** In this phase child may show evidence of fluid overload and needs adequate monitoring. Presence of rashes and low platelet count should not be worrisome if the child is otherwise stable. Hematocrit in this phase has to be assessed and interpreted in parallel with the fluid load as hemodilution rather than as evidence of bleed.
Recommendations for management

Emergency triage assessment is the key for management and is outlined as 3 steps below.

**Step 1:** Overall assessment, which includes history and physical examination, date of onset of fever, details of oral intake, presence of warning signs, change in mental status, urine output and presence of dengue cases in the neighbourhood. Also presence of comorbid conditions like diabetes, hypertension and obesity should be recorded in the history. Physical examination should include assessment of mental status, hydration status, hemodynamic status, evidence of plasma leak in the form of pleural fluid and ascites. Abdominal tenderness, hepatomegaly, rashes and bleeding manifestations are to be checked and the tourniquet test is performed. This should be followed by a complete hemogram. Additional tests would include tests for liver dysfunction, glucose, serum electrolytes, urea, creatinine, bicarbonate and lactate.

**Step 2:** Based on the findings in step 1 categorize the phase of illness and the severity of illness to plan treatment.

**Step 3:** Includes disease notification and management. In dengue endemic areas, the later the notification, the more difficult would it be to contain the epidemic.

**Management of dengue:** Categorize the children as group A, B or C. Group A includes children who can be sent home. Group B includes children who need in hospital management and group C includes children who need emergency treatment and urgent referral.

**Group A management:** This group includes children with a presumptive diagnosis of dengue but no warning signs. These children should tolerate adequate oral fluids and void urine once in 6 hours. Encourage intake of oral fluids, give paracetamol at appropriate doses for fever and instruct the care givers to return for follow up and report in case of any warning signs by giving them a card mentioning the warning signs. Avoid acetylsalicylic acid, ibuprofen and other NSAIDs. These children should be monitored daily by the health care workers.

**Group B management:** These children need to be admitted as inpatients for care. Children with warning signs and those children without warning signs but who have co-morbidities or is an infant comprise group B. Children who cannot be followed up daily due to certain social circumstance should also be included in group B.

Flow chart in Fig.2 depicts the management of children in Group B with warning signs.

The child is to be followed up for 24-48 hours with clinical assessment and repeat hematocrit to decide on the fluid infusion rates. Any worsening of vital signs with treatment should place the children in appropriate classification and further management done according to the flow chart.

Children without warning signs can be managed with oral fluids alone. If oral fluids are not tolerated treat them as above. For obese and overweight children use the ideal body weight to calculate the fluids. Intravenous fluids may be not be needed for more than 24-48 hours. Give minimum fluids to maintain good perfusion and a urine output of 0.5ml/kg/hour. Monitor the vital signs 1-4 hourly, urine output 4-6 hourly, hematocrit after every fluid replacement, monitor glucose and other organ functions.

**Group C management:** Group C includes children with severe dengue who need emergency care and referral to a tertiary care facility. Judicious administration of fluids is the sole intervention required. Frequent monitoring of the hemodynamic status will guide fluid therapy.
These children need continuous replacement for plasma leak to maintain the effective circulation for 24-48 hours. The goals of management will be to maintain effective central and peripheral circulation, improving end organ perfusion – i.e. stable conscious level, urine output of ≥0.5 ml/kg/hr and decreasing metabolic acidosis. Management is categorized into children with compensated shock and those with hypotensive shock. Studies have shown that crystalloids are comparable to colloids when used for resuscitation in dengue and they are preferable as they are easily available in any setting. However colloids may be preferred in a child with hemodynamic instability with pulse pressure <10mm Hg. In children with shock colloids have been found to bring down the hematocrit much faster than crystalloids. Ringer’s lactate may not be the preferable fluid in children with hyponatremia and in those with liver cell failure. However following normal saline if the serum chlorides have exceeded the normal range it is advised to change over to Ringer’s lactate.

Flow chart for management of severe dengue with compensated shock is shown in Fig.3.

These children are to be followed up with intensive monitoring until 24-48 hours as they can go in and out of shock repeatedly. Only isotonic fluids like 0.9% saline / Ringer’s lactate to be used for maintenance fluids. Following improvement at any stage reduce the fluids and change over to oral fluids as early as possible. Monitor serum glucose and bicarbonate. If the child worsens at any stage increase the IVF and modify treatment according to the hematocrit.

Fig.4. is the flow chart for management of children with hypotensive shock.

Children with shock need to be monitored for peripheral perfusion and vital signs every 30 minutes until they are out of shock and then 1-2 hourly. Frequent monitoring is warranted if they are on higher fluid infusion rates as there are increased chances of fluid overload.
Fig. 3. Management of severe dengue with compensated shock

Fig. 4. Management of hypotensive shock
The estimation of blood pressures using a cuff is commonly inaccurate in shock. Hence if resources are available an arterial line is preferable. Acceptable urine output would be 0.5 ml/kg/hr. Monitor the blood gases, lactate, blood glucose and other organ functions in any child treated for severe dengue. The hematocrit changes which serve as a guide to fluid therapy should be interpreted in parallel with the hemodynamic status. A rising hematocrit or persistently high hematocrit with stable hemodynamic status and adequate urine output warrants monitoring but not fluid boluses. Similarly decreasing hematocrit with stable hemodynamics and adequate urine output implies fluid load which warrants decrease in fluids immediately.

**Treatment of complications in dengue**

**Hemorrhagic manifestations:** Mucosal bleeding in a patient with stable hemodynamics is considered as minor bleed. Thrombocytopenia in a hemodynamically stable child does not need platelet transfusion and they have not been found to be useful. Risk factors for major bleeds include prolonged and refractory shock, hypotensive shock with renal failure or liver cell failure, severe metabolic acidosis, intake of nonsteroidal anti inflammatory drugs, anticoagulant therapy and preexisting peptic ulcer disease. Fresh blood transfusion is indicated in hypotensive shock with normal or low normal hematocrit prior to fluids, unstable hemodynamics with overt bleeding, decreasing hematocrit with unstable hemodynamics and persistent or worsening metabolic acidosis. Hemorrhagic complications are managed by 5-10 ml/kg of fresh packed red blood cells or 10-20 ml/kg of fresh whole blood. Further transfusions can be planned if there is further blood loss or there is no improvement in the hematocrit.

**Fluid overload:** Excessive and/or too rapid fluid therapy, use of hypotonic fluids, inappropriate fluids in unrecognized severe bleeding, inappropriate fresh frozen plasma, platelet concentrates and continuation of IVF after plasma leak had stopped will lead to fluid overload. Increasing respiratory distress, rapid breathing, chest wall retractions and presence of wheeze, increasing ascites, pleural fluid and raised jugular venous pressure may be clinically evident. Pulmonary edema and shock are delayed manifestations of fluid load. Management includes stoppage of IVF, oral or intravenous furosemide therapy if in recovery phase. If the child is in shock with low hematocrit and signs of fluid load blood transfusion would be ideal and do not give further fluid boluses.

**Other complications:** Watch for hypoglycemia and hyperglycemia, monitor blood gases and electrolytes in children with severe dengue. Other supportive care is needed for cardiac, renal or hepatic involvement.

**Discharge criteria for children with dengue:** Clinical criteria includes no fever for 48 hours, improvement in clinical status, general well being, appetite, hemodynamic stability, adequate urine output and no respiratory distress. Laboratory criteria includes increasing trend of platelet count with stable hematocrit without IVF.

**Lab diagnosis of dengue**

Laboratory diagnosis of dengue includes detection of the virus, viral nucleic acid, antigens or antibodies or a combination of these techniques. The virus can be detected in the serum, plasma, circulating blood cells and other tissues for 4-5 days. During the early stages of the disease virus isolation in cell culture, nucleic acid or antigen detection (Non structural protein 1-NS1) can be used. At the end of the acute phase of illness serology is used for diagnosis. In a primary infection Ig M is the antibody to appear first by about 3-5 days, peak by 2 weeks of illness and becomes undetectable by 2-3 months.
IgG antibodies appear in low titers by the end of first week and are detectable for months and persist even for life. During secondary infections Ig G is detectable in high titers even in the first week of acute illness and persists probably for life. In the early convalescent stage Ig M levels are much lower and IgM/IgG antibody ratios are more commonly used nowadays than hemagglutination inhibition which needs convalescent sera.

In general the tests like virus isolation and nucleic acid detection are more specific but need more complex technologies and technical expertise and are costly while the rapid tests compromise sensitivity and specificity for the ease of performance and speed. A combination of tests is preferable in diagnosis of dengue rather than an isolated test. Either Ig M + in a single serum sample or IgG + in a single serum sample with a HI titer of 1280 or greater is highly suggestive of dengue. Presence of any one of the following is confirmatory for dengue: PCR+, Virus culture+, Ig M seroconversion in paired sera, IgG seroconversion in paired sera or four fold IgG increase in paired sera.

**Points to Remember**

- **Dengue is classified as dengue with or without warning signs and severe dengue in 2009 WHO guidelines.**

- **Children with no warning signs can be sent home with instructions about intake of fluids, warning signs and follow up (Group A).**

- **Children with warning signs and some at risk children without warning signs need to be admitted to a hospital (Group B). Children with warning signs are given adequate fluids under monitoring for 24-48 hours.**

- **Children with severe dengue need emergency care in an intensive care facility.**

**Fluid management and frequent monitoring are the priority in management of severe dengue. Early recognition of bleeds and blood transfusion is life saving (GroupC).**

- **No role for platelet transfusions in a hemodynamically stable child for hemorrhagic manifestations.**

- **Serological tests lack sensitivity and specificity but can be used for diagnosis when the ease, availability and cost are considered. Virus isolation and nucleic acid detection are more specific but are costly and need expertise. NS1 antigen may help in early diagnosis for patient management.**

**References**


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at
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on Sunday, 10th June 2012

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NON-INVASIVE POSITIVE PRESSURE VENTILATION

* Suchitra Ranjit

Abstract: Non-invasive ventilation is an attractive alternative method of ventilation without intubation. This is used under selective situations where, the patient requires ventilatory support, but not very sick. Some of the indications are pneumonia, atelectasis, dynamic airway obstruction such as laryngomalacia and tracheomalacia, neuromuscular disorder, pulmonary edema and immunocompromised host requiring ventilation. Advantages are shortened ICU stay, avoidance of nosocomial pneumonia, reduction in cost and sedation and patient comfort. It is very useful in chronic respiratory and neurological conditions particularly in home care settings. Nasopharyngeal tubes, nasal prongs, tight fitting oro-nasal or nasal mask are used as interfaces. It is not always safe and can have life threatening consequences. But close monitoring and shifting patients on NIV to invasive ventilation in case of failure will avoid these serious consequences. Contraindications are hemodynamic instability, poor respiratory drive, inability to handle oral secretions and impaired mental status.

Keywords: Ventilation, NIV, NIPPV

Non-invasive ventilation (NIV) is the delivery of mechanical ventilation to the lungs using techniques that do not require an endotracheal airway.

NIV is attractive because it has the potential to avoid complications of conventional ventilators such as intubation complications, ventilator associated pneumonia (VAP), post extubation stridor etc.

The two methods by which NIPPV can be delivered are: 1) Continuous positive airway pressure (CPAP). 2) NIPPV using a stand alone NIV machine or using the conventional ventilator.

Indications for NIPPV

a) Acute hypoxemic respiratory failure (AHRF): This is the commonest use of NIPPV in pediatric patients. Examples of AHRF include pneumonia, atelectasis and episodes of acute hypoxemia in chronic conditions eg, cystic fibrosis (CF). Careful selection of these patients when they have moderate degrees of hypoxemia is important.

b) To facilitate early extubation: Children on invasive ventilation whose disease process has improved but has not resolved and continue to require moderate levels of positive pressure can be extubated to NIPPV.

c) Obstructive airway disease: Patients with dynamic upper airways obstruction such as laryngomalacia and tracheomalacia may benefit from positive pressure applied via NIPPV that acts to splint open the airways. NIV should not be used in those with fixed airway obstruction, eg. subglottic stenosis, webs.

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d) Neuromuscular disorders: NIPPV has been extensively studied in the children with Duchenne muscular dystrophy and Guillain Barre syndrome provided their bulbar functions and airway protective reflexes are preserved. In these disorders, NIPPV prevents ventilator dependency and atelectasis by improving functional residual capacity.

e) Cardiogenic pulmonary edema: CPAP applied via mask decreases the afterload of the failing heart, improves WOB by recruiting fluid filled alveoli, thus improving lung compliance and oxygenation.

f) Immunocompromised hosts: NIV is an attractive option in immunocompromised patients requiring positive pressure support as the ventilator associated pneumonic (VAP) rates are lower.

Mechanism of NIPPV modes

In CPAP, a continuous positive pressure is delivered during the spontaneous respiratory cycle. In NIPPV, two levels of positive pressure are delivered viz: IPAP and EPAP. [IPAP – Inspiratory positive airway pressure; EPAP – Expiratory positive airway pressure (which functions like PEEP)]. The difference between the two levels of pressure generates the pressure support and tidal volume.

Types of ventilators that deliver NIPPV

NIPPV can be delivered by a conventional ICU ventilator (where the operator can dial in the IPAP and EPAP) or through portable standalone NIV ventilators. These portable ventilators are pressure targeted or volume targeted and the former is more common. The pressure targeted ventilators are also known as Bilevel CPAP ventilators or BiPAP.

Oxygen delivery and \( \text{CO}_2 \) elimination during NIPPV

NIPPV has several limitations compared to conventional ventilation and cannot be used in severe respiratory failure:

1. Oxygen delivery is variable: The FiO\(_2\) is not measured in most NIV machines. When supplemental oxygen is required it must blend into the system through the mask or through the additional port near the outlet. Therefore the FiO\(_2\) may vary and is affected by four factors namely, Oxygen flow rate, type of leak port in the system, site where the supplemental oxygen is introduced into the circuit and IPAP and EPAP.

<table>
<thead>
<tr>
<th>Acute care settings</th>
<th>Chronic care settings</th>
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<tbody>
<tr>
<td>Reduces need for intubation</td>
<td>Alleviates symptoms of chronic hypoventilation.</td>
</tr>
<tr>
<td>Reduces incidence of nosocomial pneumonia</td>
<td>Improves duration and quality of sleep</td>
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<tr>
<td>Shortens ICU stay</td>
<td>Improves functional capacity of the lungs</td>
</tr>
<tr>
<td>Preserves airway defences</td>
<td>Prevents disuse atrophy of respiratory muscles</td>
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<tr>
<td>Improves patient comfort: Allows direct oral feeds, permits communication and improves sense of well being.</td>
<td>Prolongs survival</td>
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<tr>
<td>Reduces need for sedation.</td>
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<td>Reduces the cost.</td>
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2. Rebreathing of CO₂ is a concern with any NIPPV that uses a single circuit gas delivery system because exhalation occurs through a single leak port and depends on the adequate continuous flow of gas in the circuit. If gas flow is inadequate, flushing of exhaled gas may be incomplete and patient may rebreathe the exhaled gas. The flow of gas depends on the EPAP settings and the patient’s I:E ratio. At low EPAP settings (<4cm of H₂O) and faster respiratory rates, flow may not be adequate to flush the CO₂.

**NIPPV interfaces**

An interface is a device that permits the tubing of the machine to be connected to the patient. The type of NIPPV interfaces are

a) nasopharyngeal tubes (endotracheal tubes inserted with depth of insertion from nose to tragus) or nasal prongs to deliver CPAP,

b) oro-nasal / nasal mask to deliver NIPPV and newer interfaces like helmets and full face masks.

In addition to the interfaces, mouth seals and lip seals are provided to prevent mouth leakages during nasal ventilation.

**Initiation and titration of NIPPV**

The initiation of NIPPV has to be done in a controlled manner as many children do not tolerate the tightly applied interfaces with high gas flow blasting on the face. Following this, the parents/caregivers should slowly initiate the NIPPV at a lower settings and gradually increase it rather than beginning at the higher target pressures. A nasogastric tube may be inserted to initiate feeds and it can be used to decompress stomach. A mild sedative agent (trichlorofos) can be given if the child is not tolerating the interface provided hypoxia is not the cause for agitation. Over the initial 2 hours, the set pressures may be titrated by continuous monitoring of clinical parameters like heart rate, respiratory rate, breathing pattern, breathing sounds and chest excursion along with O₂ saturation and blood gases. A decrease in heart rate by approximately 20% from the baseline, 10% reduction in respiratory rate with improvement in work of breathing, saturation and blood gases within 1-2 hours of initiation of NIPPV indicate that the patient is benefiting from and tolerating the device well.

**Contraindications for NIPPV**

a) Hemodynamic instability, b) Impaired mental status with poor respiratory drive, c) Moderate to severe bulbar weakness, d) Inability to handle oral secretions, e) Inability to tolerate the mask, f) Refractory hypoxemia and g) Upper gastrointestinal bleed.

NIPPV is best for patients who are sick but not too sick.

**Monitoring during NIPPV**

Close monitoring is the rule. It is important that patients who fail NIPPV (not improving or even worsening) should be immediately shifted to invasive ventilation. Deaths have been reported from failure to recognize that the patient is deteriorating on NIPPV. Monitor HR, RR, BP, pulse oximetry, alertness and patient’s comfort level. Other variables to be monitored are adequacy of seal, patient discomfort, skin irritation and pressure points, gastric distension. Ensure that humidification is adequate. Nurses and duty doctors must be fully aware of signs of deterioration.

**Weaning of NIPPV**

Two options are used while weaning: 1) Once steady improvement of clinical condition has begun, NIPPV settings are lowered. The IPAP levels are weaned first followed by EPAP. 2) The second option is intermittent discontinuation of NIPPV for brief periods (30-60mins). If tolerated, the duration of discontinuation may gradually be increased until
patient is off for 3-4 hours. Eventually, NIPPV may be provided only at night times when the patient is asleep. Intermittent NIPPV allows reconditioning of the respiratory muscles while simultaneously preventing fatigue by permitting a sufficient period of rest.

Complications include a) epistaxis due to absence of humidification, b) eye irritation, c) intolerance due to high gas flows, d) gastric distension / sinusitis.

**Always remember NIPPV may have life threatening consequences if**: a) the expiratory ports are closed. b) over-reliance on NIPPV when disease is worsening. c) patient who demonstrates continued respiratory distress despite maximum support, poor tolerance of mask, onset of hemodynamic instability, excessive airway secretions unable to handle requires immediate intubation else can progress to cardio-respiratory failure and death, d) NIPPV is a good option to conventional ventilation in carefully selected patients in select conditions. Overreliance may be hazardous.

### Points to Remember

- **NIPPV** can provide positive pressure to a patient without the need for intubation, thereby minimizing costs and complications.
- **Ideal candidates for NIPPV** are those who are “Sick” but not “Too Sick”.
- Although overall very safe, NIPPV can have adverse consequences if used in patients in whom respiratory distress persists or progresses.
- Obtunded patients and those with impaired airway protective reflexes may not be good candidates for NIPPV.

### Bibliography


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### Antibiotic prophylaxis for preventing meningitis in patients with basilar skull fractures

Basilar skull fracture (7% to 15.8% of all skull fractures) places the central nervous system in contact with bacteria from the nose and throat and may be associated with cerebrospinal fluid leakage (occurring in 2% to 20.8% of patients). Blood or watery discharge from nose or ears, bruising behind the ear or around the eyes, hearing loss, inability to perceive odours or facial asymmetry may lead physicians to the diagnosis of basilar skull fracture. Patients with a basilar skull fracture may develop meningitis and some doctors give antibiotics in an attempt to reduce this risk. This review examined five randomised controlled trials, comprising a total of 2085 participants, that compared those who received preventive antibiotic therapy and developed meningitis with those who did not receive antibiotics and developed meningitis. The available data did not support the use of prophylactic antibiotics, as there is no proven benefit of such therapy. There was a possible adverse effect of increasing susceptibility to infection with more pathogenic organisms. The review authors calls for research to address this question, as there are too few studies available on this subject and they have overall design shortcomings and small combined numbers of participants studied.

MANAGEMENT OF URINARY TRACT INFECTION

*Vijayakumar M*

**Abstract:** Young children with upper urinary tract infection are at risk of renal scarring and subsequent complications such as hypertension, proteinuria with or without focal segmental glomerulosclerosis, pregnancy-related complications and even end-stage renal failure. Risk factors for scarring include young age—especially infancy, delay in initiating antibacterial treatment, recurrent UTI, voiding dysfunction and higher grades of vesicoureteric reflux. Vague symptomatology of UTI in children leads to delay in diagnosis and hence management. Initial management is decided by the age and the clinical status of the child. The need for imaging studies in children with febrile first UTI and recurrent UTI is well defined. Antimicrobial prophylaxis gives better outcome in childhood UTI if used correctly. Long-term follow-up of children with recurrent UTI and anatomical anomalies is mandatory. Voiding dysfunction should be always remembered in childhood recurrent UTI.

**Keywords:** Urinary tract infections, Vesicoureteric reflux, Voiding dysfunction, Imaging studies, Antimicrobial prophylaxis

Urinary tract infection (UTI) is one of the common bacterial infections in infants and children next only to respiratory infection. The risk of UTI before 14 years is 1-3% in boys and 3-10% in girls. During infancy, the male to female ratio is 3-5:1 and beyond 1-2 years, it is 1:10. Children with acute pyelonephritis are at risk of renal scarring and subsequent complications such as hypertension, proteinuria with or without focal segmental glomerulosclerosis, pregnancy-related complications and even end-stage renal failure. Risk factors for scarring include young age—especially infancy, delay in initiating antibacterial treatment, recurrent UTI, voiding dysfunction and higher grades of vesicoureteric reflux (VUR). Revised statement on management of UTI from Indian Society of Pediatric Nephrology is also available at present.

**Clinical features of UTI**

In neonates, UTI is part of septicemia and presents with fever, vomiting, lethargy, jaundice and seizures. In infants and young children UTI usually presents with recurrent fever, diarrhea, vomiting, abdominal pain and failure to thrive. In older children fever, dysuria, urgency, frequency and abdominal or flank pain are the usual features. Adolescents may have symptoms more of lower tract with or without fever. Fever without focus, more so in less than 2 years age should be suspected as UTI.

**Diagnostic features**

As it requires a minimum of about 48 hours before urine culture result is known, rapid tests are often used to guide the initial management. Urine examined by dipstick and microscopy are two rapid tests. Combining a positive test for
leucocyte esterase and nitrite by dipstick in a child with clinico-biological features of upper tract UTI will direct us towards the diagnosis.\(^6\)\(^8\) Leukocyturia (>5 WBC/HPF in centrifuged urine and >10 WBC/mm\(^3\) in uncentrifuged urine) and bacteria on gram stain can indicate UTI by microscopic examination. Enhanced urinalysis using uncentrifuged urine sample for leucocyturia in Neubauer counting chamber along with presence of any bacteria per 10 oil immersion field of Gram-stained smear is useful for supportive evidence of UTI. Gram-stained urine for bacteria has a better sensitivity (91\%) and specificity (96\%) than all other rapid tests used alone or in combination.\(^3\) A combination of positive enhanced urinalysis and rapid test will indicate UTI in 95\% of the children. Ultimately the gold standard for the diagnosis of UTI is positive urine culture.

**Urine sampling**

The criterion for the diagnosis of UTI depends on the method of collection of urine. In older children, a midstream urine specimen is obtained. Urine samples may be obtained by suprapubic bladder aspiration or urethral catheterization in neonates and infants where collecting midstream urine sample is difficult. Ideally clean catch midstream urine specimen is useful and contamination from periurethral flora should be avoided. In infants and young children when collection of midstream urine sample is difficult or when contamination of culture is noted, suprapubic aspiration is ideal. Due to high false positive rates bag samples are not useful. More than the positive culture the negative culture from a bag specimen is found useful in ruling out UTI. Repeat cultures are indicated when contamination is suspected with mixed growth as well as with growth of organisms normally constituting the periurethral flora like lactobacillius in healthy girls and enterococci in infants and toddlers.\(^1\)

**Definitions**

Infection of the urinary tract is identified by growth of a single species in the urine, in the presence of symptoms and a positive urine culture is always mandatory. The number of bacteriuria to define UTI depends on the methodology used for urine sampling.\(^1\) The probability of infection with midstream clean catch showing a colony count of >10\(^5\) CFU/ml is 90-95\% and with suprapubic aspiration it is 99\% even with any number of pathogens. If catheterized urine is used, it is 95\% for a colony count of >5 x 10\(^4\) CFU/ml. Significant bacteriuria in the absence of symptoms of UTI is called asymptomatic bacteriuria (ABU) and is commonly seen in school going and adolescent girls and documented usually on screening. For an upper tract UTI which is otherwise termed a complicated UTI, the child should have fever >39\°C, systemic toxicity, persistent vomiting, dehydration, renal angle tenderness with or without raised serum creatinine. In simple UTI like lower tract UTI, children will have dysuria, frequency, urgency, with or without fever and none of the symptoms of complicated UTI.\(^1\) In this lower tract UTI, the symptoms are essentially due to inflammation of bladder mucosa and is also called as cystitis or dysuria-frequency syndrome. Usually fever is not the rule. Lower tract infection is common in females and can be benign with less chance of associated anomalies. Upper tract infection is a significant infection of renal parenchyma and hence is termed as acute pyelonephritis. Most of the times, upper tract infection is associated with urinary tract anomalies. Second attack of UTI is termed as recurrent UTI. It is the recurrence of symptoms and significant bacteriuria in a child who had previously recovered clinically with appropriate treatment. A relapse is recurrence of UTI within two weeks and re-infection if it is later than two weeks.\(^9\)
Initial evaluation

Look for toxicity, dehydration and ability to retain oral intake. Recording of blood pressure should be done and history regarding bowel and bladder habits elicited.

The child is examined for features that suggest an underlying functional or urological abnormality. Features suggesting underlying structural abnormality should be documented which include distended bladder, palpable, enlarged kidneys, tight phimosis, vulval synechiae, palpable fecal mass in the colon, patulous anus, neurological deficit in lower limbs, urinary incontinence and history of previous surgery of the urinary tract, anorectal malformation or meningomyelocele. Complete blood counts, serum creatinine and a blood culture should be done in infants and in children with complicated UTI. Elevated peripheral WBC count, polymorphonuclear leucocytosis, elevated C-reactive protein levels and elevated ESR will aid in the diagnosis. Renal dysfunction is assessed by blood urea, serum creatinine and electrolytes estimation. Mild to moderate renal dysfunction can occur with severe acute pyelonephritis, more so if it involves both the kidneys or the single functioning kidney. Hyperkalemic metabolic acidosis may be a feature in acute pyelonephritis especially when it occurs in a single functioning kidney. Ultrasound (USG) examination is done to rule out underlying anatomical defects like obstruction and to assess the number, position, size and shape of kidneys. Dilated collecting system, renal stones and pyelonephritis as suggested by variation in size, increased echo texture of the kidneys, pelvic wall thickening (pyelitis) and turbid urine in the collecting system can also be detected.

Management at diagnosis

Children less than 3 months of age and those with complicated UTI should be hospitalized and treated with parenteral antibiotics. Initial parenteral medications include ceftriaxone, cefotaxime, aminoglycoside or coamoxiclav. Therapy with a single daily dose of aminoglycoside may be used in children with normal renal function.

Once the result of antimicrobial sensitivity is available, the treatment may be modified. IV therapy is given for first 2-3 days followed by oral antibiotics once the clinical condition improves. Oral medications used in childhood UTI include cefixime, coamoxiclav, ciprofloxacin or cefdinir. Children with simple UTI and those above 3 months of age are treated with oral antibiotics. With adequate therapy, there is resolution of fever and reduction of symptoms by 48-72 hours. Failure to respond to therapy may be due to the presence of resistant pathogens, complicating factors, non-compliance and these children require reevaluation. The duration of therapy is 10-14 days for infants and children with acute pyelonephritis and 7-10 days for simple UTI. In children with severe pyelonephritis as in acute lobar nephronia prolonged parenteral therapy may help to prevent progression to renal abscess. Following the treatment of UTI, prophylactic antibiotic therapy is initiated in children below 1 year of age, until imaging of the urinary tract is completed. Child will need supportive therapy to maintain adequate hydration and paracetamol to relieve fever. It is better to avoid NSAIDs for fever in this background for the fear of renal dysfunction. Routine alkalization of the urine need not be done. A repeat urine culture is not necessary, unless there is persistence of fever and toxicity despite 72 hours of adequate antibiotic therapy.

Imaging evaluation

The aim of investigations is to identify children at high risk of renal damage, chiefly those below 1 year of age, and those with VUR or urinary tract obstruction. Imaging studies are
needed in all children with UTI is the original concept. There is limited evidence that intensive imaging and subsequent management alters the long-term outcome of children with reflux nephropathy diagnosed following a UTI.

With availability of antenatal screening, most important anomalies have already been detected and managed after birth. Therefore, there is considerable debate regarding the need and intensity of radiological evaluation in children with UTI.¹³,¹¹,¹²

The recent ISPN guidelines suggest an algorithm (Fig.1) for this purpose with first attack of febrile UTI.¹ Ultrasonography should be done soon after the diagnosis of UTI. The MCUG is recommended 2-3 weeks later, while the Dimercaptosuccinic acid (DMSA) scintigraphy is carried out 2-3 months after treatment. An early DMSA scintigraphy, performed soon after a UTI, is not recommended in routine practice as per ISPN guidelines.¹ Children showing hydronephrosis in the absence of VUR should be evaluated by diuretic renography using ⁹⁹mTc-labeled diethylenetriaminepentaacetic acid (DTPA) or mercaptoacetylglycine (MAG-3) after treatment of UTI. These techniques provide quantitative assessment of renal function and drainage of the dilated collecting system.¹ There is a consensus that children with recurrent UTI should have USG, DMSA scintigraphy and MCUG irrespective of age to detect underlying anatomical anomalies without ambiguity.

Fig.1. Imaging evaluation following initial febrile UTI¹

# As per Guidelines of Indian Society of Pediatric Nephrology¹

MCU: micturating cystourethrogram; DMSA dimercaptosuccinic acid

*All children with recurrent UTI need detailed evaluation with ultrasonography, DMSA scan and MCU
Spinal dysraphism and radio opaque calculi are detected by X-ray of the KUB region. Intravenous urogram is useful in double collecting system evaluation and for delineating the level of obstruction in obstructive uropathy associated with UTI. But in recent days for the evaluation of double system and ectopic insertion of ureter, MR urogram is found useful.

Prevention of recurrent UTI

General: Adequate fluid intake should be maintained. Timed voiding and double and triple voiding should be stressed. Parents should look into avoidance of constipation. (Circumcision reduces the risk of recurrent UTI in infant boys, and might therefore have benefits in children with high grade reflux.) Treatment of vulval synechiae in infant girls will prevent re-infection.

Voiding dysfunction: In every UTI more so in a complicated UTI, always look for bowel bladder dysfunction which can be doubted with features like abnormal patterns of micturition in the presence of intact neuronal pathways without congenital or anatomical abnormalities. Abnormal bladder pressure and urinary stasis predispose these children to recurrent UTI. Features of bowel bladder dysfunction include recurrent UTI, persistent high grade VUR, constipation, impacted stools, maneuvers to postpone voiding (holding maneuvers, e.g., Vincent curtsy, squatting), voiding less than 3 or more than 8 times a day, straining or poor urinary stream, thickened bladder wall >2 mm, post void residue >20 ml and spinning top configuration of bladder on MCU. In the management we have to take good history and monitor urinary stream. Always it is advisable to look for post-void dribbling. Urodynamic studies are needed only in selected cases. Treatment of bowel bladder dysfunction include exclusion of neurological causes, institution of structured voiding patterns and management of constipation.

In overactive bladder, anticholinergic drug like oxybutynin is given; with large post void residue, timed voiding, bladder retraining and clean intermittent catheterization (CIC) are useful.

Antimicrobial prophylaxis: It is usually recommended for children with vesicoureteric reflux UTI below 1 year of age, awaiting imaging studies. Antimicrobial prophylaxis is not advised in children with urinary tract obstruction (e.g., Posterior urethral valves, urolithiasis, neurogenic bladder and when the child is on CIC. Review of literature gives differing insight on the benefits of antimicrobial prophylaxis.

In general, they reduce the problem of recurrent febrile UTI with or without associated anomalies. Cotrimoxazole (2 mg/kg/night) in children above 6 months and cephalexin (10 mg/kg/night) in 0-6 months age group are popular chemoprophylactic agents. Cefixime in a dose of 2 mg/kg/night is also found useful. The other drug commonly used is nitrofurantoin at a dose of 1-2 mg/kg/night but is usually associated with gastrointestinal upset with vomiting. It is better given with food and avoided in less than 3 months of age and in children with G6PD deficiency and renal insufficiency. Duration of antimicrobial prophylaxis therapy is individualized ranging from 6 months to 2 years or till the child reaches the age of 5 years beyond which the chances of febrile UTI increasing the renal damage is relatively less. Breakthrough UTI results either from poor compliance or associated voiding dysfunction. The UTI should be treated with appropriate antibiotics. A change of the medication being used for prophylaxis is usually not necessary. There is no role for cyclic therapy, where the antibiotic used for prophylaxis is changed every 6-8 weeks.

Asymptomatic bacteriuria

Asymptomatic bacteriuria (ABU) is documentation of significant bacteriuria on
screening in a child without symptoms. The incidence varies from 1% of girls to 0.05% of boys in their childhood period. UTI without symptoms with normal CRP levels indicate asymptomatic bacteriuria. ABU is a benign condition, which does not cause renal injury and requires no treatment. The organism isolated in most instances is E. coli, which is of low virulence. Aggressive treatment leads to colonization of virulent strains. A few studies have documented the chance of pyelonephritis in them and hence it is worthwhile to do an USG to rule out major anomalies especially in adolescent females. ABU is also observed in children with neurogenic bladder, particularly if the child is on CIC, but studies have not shown increased risk of renal scarring or the need for prophylactic antibiotics in this group. Recent studies have suggested that renal function and renal growth of scarred and unscarred kidneys is equal in medically treated as well as untreated patients of asymptomatic bacteriuria. The increased scarring would have been due to symptomatic UTI in the past, which was not diagnosed initially.

The presence of asymptomatic bacteriuria in a child previously treated for UTI should not be considered as recurrent UTI.

Vesicoureteric reflex

Vesicoureteric reflux (VUR) is diagnosed and graded by a conventional MCUG done with radio contrast. The severity of VUR is graded in accordance with the International Study Classification from Grade I-V. Radionuclide cystogram can also detect VUR, but its limitations are failure to grade the severity of VUR and identify terminal ureter and bladder anomalies like ureterocele, diverticulum and posterior urethral valve. Hence radionuclide cystogram is not useful as a screening procedure as it will miss anatomical anomalies of the urethra and bladder. Direct radionuclide cystogram (DRNC) is found to detect VUR in some children where MCUG has failed. DRNC is more sensitive and specific compared to MCUG.

The present view is for early diagnosis of VUR, adequate treatment of UTI and antimicrobial prophylaxis therapy in them. Studies have shown that the ultimate outcome following surgical correction of VUR when compared to children managed with medical treatment in terms of break through UTI and renal scars is the same. Children with VUR and otherwise normal urinary tract are treated with long term chemoprophylaxis with antimicrobial prophylactic drugs like nitrofurantoin, cotrimoxazole, cephalexin or cefadroxil. Training the child for double or triple micturition to reduce the residual urine is also beneficial. Urine examination (microscopy and culture) is done if UTI is suspected on follow-up.

As per ISPN guidelines (2011), in grade I and II VUR antimicrobial prophylaxis is given up to one year of age and later they are followed up till 5-7 years of age. Prophylaxis is restarted in them if there is breakthrough febrile UTI. In children with grade III to V VUR, prophylaxis is given up to 5 years of age. Beyond 5 years in this group, antimicrobial prophylaxis is continued for a sufficient period if there is bowel bladder dysfunction. Surgery for VUR is considered if breakthrough febrile UTI is a problem.

Surgical indications as per pediatric surgeons experience will include non-resolution of grades III-V VUR by 5 years of age, VUR grades III-V associated with bilateral renal scarring after 2 years of age, recurrent breakthrough UTI’s in children with VUR on antimicrobial prophylaxis, in children of non-compliant parents, if parents prefer surgical intervention to prophylaxis or in children who show deterioration of renal function and VUR.
associated with paraureteric diverticulum or in duplex systems as resolution is uncommon in this subset.

**Long-term follow-up and referral to pediatric nephrologist**

Children with renal scar (reflux nephropathy) are counseled regarding the need for early diagnosis and therapy of UTI and regular follow-up. Physical growth and BP should be monitored every 6-12 months through adolescence. Investigations include urinalysis for proteinuria and estimation of serum creatinine. Yearly ultrasound examinations are done to monitor renal growth. Usually UTI can be confidently treated by the primary pediatrician but due to their potential for renal parenchymal damage, scarring and subsequent chronic kidney disease, children having essential risk factors that can predispose them to the complications should be managed by the pediatrician in consultation with pediatric nephrologist. The common indications for referral include recurrent UTI, UTI associated with bowel bladder dysfunction, VUR, underlying urologic or renal abnormalities and with renal scar, deranged renal functions and hypertension

**Points to Remember**

The practicing pediatrician should note the following points in the management of childhood UTI.6

- **In infants and young children, unexplained fever, diarrhea, vomiting may suggest UTI; older children may have dysuria, flank or suprapubic pain. Most of the childhood UTI are caused by E.coli, derived from periurethral fecal flora.**

- **Young age, delay in initiating antibacterial therapy, recurrences and associated disorders like vesicoureteric reflux are essential risk factors for renal scarring.**

- **Lower tract infection presents as dysuria-frequency syndrome and is usually benign. But upper tract infection should be always considered as serious infection and is frequently associated with urinary tract anomalies.**

- **In infants and young children when collection of midstream urine sample is difficult or when contamination of culture is noted, suprapubic aspiration is ideal**

- **Parenteral antibiotics are needed definitely in children with complicated UTI and infants < 3 months of age with UTI. Full course of antibiotic therapy for 7-14 days is mandatory for children with acute pyelonephritis. Other children on parenteral drugs can be switched over to oral drugs once the toxicity comes down**

- **Acute cystitis does not require any special medical care, other than appropriate antibiotic therapy and reassurance if urinary frequency and incontinence are a problem. Rarely, analgesics may be needed for dysuria or severe bladder spasms**

- **Ultrasound is needed in every child with first attack of UTI. MCUG and DMSA scintigraphy are mandatory in children less than 1 year of age even if USG is normal for the first attack of febrile UTI since congenital anomalies are common.**

- **With the advent of antimicrobial prophylaxis the morbidity of UTI has been greatly reduced. Low dose sub pharmacological doses of antibiotics are used for this purpose.**

**References**


NEWS AND NOTES

PALS INSTRUCTOR UPDATE - 2010 GUIDELINES

Date: 10th February, 2012

Venue: Kanchi Kamakoti CHILDS Trust Hospital, Chennai

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HAEMATINICS IN HEALTH AND DISEASES

* Thilagavathi V

Abstract: Hematinics are agents required for the proliferation and maturation of red cells. They are iron, folic acid and vitamin B12 and erythropoietin. Deficiency of haematinics manifests commonly as anemias. It is important to determine the cause of anemia to choose the correct hematinics. Sub-clinical deficiencies of these haematinics can compromise the physical growth and mental development.

Keywords: Hematinics, Iron, Vitamins B12, Folic acid, Erythropoietin.

Iron in health

Iron is one of the most important nutrients required throughout life. It plays an important function in the transport of oxygen by the hemoglobin (Hb). Iron is required for synthesis of hemoglobin, myoglobin and cytochromes.

Iron in the human body exists as essential iron or functional iron and storage iron.

Essential iron includes heme iron, cytochromes and iron requiring enzymes.

Storage iron is found in the form of ferritin and hemosiderin. Iron is seen in the macrophages of liver, spleen and bone marrow.

Distribution of iron in the body: 70% of iron is present in the hemoglobin and 10-20% is stored as hemosiderin, 10% is in the form of myoglobin present in the muscle, and < 1% is in the cytochrome, other ferrous containing enzymes.

Heme iron: Heme iron is present as heme proteins which are hemoglobin, myoglobin, catalases and preoxidases. Most of the body iron is found in the hemoglobin within the erythrocytes and only small amount (10%) is found in myoglobin. In the plasma, it is found to be in the form of transferrin i.e apotransferrin + iron. Catalase is an enzyme, which comprises 4 heme groups. It destroys H₂O₂ formed in the tissues.

Peroxidase contains protoheme as the prosthetic group and catalyses the destruction of hydrogen peroxide.

Hemoglobin: Hb synthesis requires co-ordinated production of heme and globin. Heme is the prosthetic group that mediates reversible binding of iron by hemoglobin. Globin is the protein that surrounds and protects the heme molecule. Iron in ferrous state reversibly binds oxygen. When the iron is oxidized to ferric state, methemoglobin is formed which does not bind the oxygen. Free heme without globin protein also does not bind oxygen.

Sources of iron: Iron can be derived from endogenous and exogenous sources.

Iron is obtained endogenously mainly from the destruction of senescent red cells, denuded intestinal epithelial cells and ferritin of the
RE system. Exogenous iron is provided from animal sources (meat, fish liver, spleen, and shellfish) and vegetable sources (cereals, nuts, and amaranth leaves).

**Iron absorption in GI tract**

Iron is the most readily absorbed in the ferrous state in the duodenum and upper part of the jejunum. The mucosal cells contain an intracellular iron carrier protein. Iron is supplied to mitochondria by the carrier protein for heme synthesis (Fig.1).

**Role of iron in immunity**

Ferritin is the non-functional storage form and an acute phase reactant. During active inflammation, the inflammatory cytokine IL-1 enhances the production of acute phase reactant proteins including ferritin. Increased ferritin blocks the release of iron. Hypoferremia serves as an important defence mechanism, by inhibiting the growth of certain micro organisms.

Iron deprivation in infections serves as nutritional immunity. Iron is essential for bactericidal activity of neutrophils. Lymphocytes have reduced proliferative response to mitogens.

**Iron and cognition:** Iron is essential for normal mental and psychomotor development, Iron deficiency results in fatigue with significant physical, emotional, psychological and social consequences. The adaptation to chronic anemia results in lower quality of life.

The recommended daily allowance of iron in preterm and low birth weight infants is 10-15mg/day and in 1st year of life is 5-7 mg/day and throughout childhood it is 10mg/day.

**Iron and disease**

Iron deficiency: Can be asymptomatic but mostly manifests as hypochromic microcytic anemia. Manifest with mental retardation, poor school performance, inadequate growth and development.

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![Fig.1. Iron absorption](image-url)
**Iron excess**: Iron promotes free radical production resulting in toxic effects. Acute iron poisoning occurs due to accidental ingestion. Hemosiderosis - is an iron overloaded state which can be inherited or acquired, in transfusion dependent conditions.

**Iron therapy**

Iron replacement in iron deficiency anemia plays an important role in the management. The oral form of iron is mostly preferred. Given in the dose of 3mg/kg (elemental iron) in 2-3 divided doses daily to minimize the gastro intestinal side effects. It is given 30 minutes before meals or in between meals. It is given for 4-6 months to replicate the iron stores. It is ideal to avoid foods containing phytates and tannic acid (coffee, tea and milk products) as it decreases the bioavailability of iron salts.

**Choice of iron preparations**

It is important to choose the ideal iron preparation that contains ferrous iron in elixir which are better absorbed with high bioavailability than ferric forms. Ferrous sulphate and ferrous fumarate have equal benefits (Table.1). The non ionic polymaltose have no oxidative potency on lipoproteins, and has a better compliance than ferrous sulphate and well tolerated. Heme iron polymaltose which has alternative absorption pathway, found to have improved bio availability with lesser side effects. Iron amino acid chelates are conjugates of ferrous or ferric iron with aminoacid. They have high bio availability in the presence of dietary inhibitors. The treatment of anemia with ferrous bisglycinate showed equivalent rise in Hb as that of ferrous sulphate. Iron polymaltose complex is a non ionic iron with polymaltose. It is a stable complex and the absorption is not affected by food or milk. It is expensive and the rise in hemoglobin is not as expected when compared to other preparations.

**Side effects**

The side effects are mainly gastro-intestinal abdominal discomfort, diarrhoea, constipation, nausea and vomiting. The side effects are dose related - minimized by starting with standard doses and gradually increasing the dose or giving with meals or in between meals.

**Commercially available iron salts**

<table>
<thead>
<tr>
<th>Iron Salt</th>
<th>Elemental iron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron hydroxide polymaltose</td>
<td>50mg/5ml</td>
</tr>
<tr>
<td>Ferrous sulphate</td>
<td>80mg/5ml</td>
</tr>
<tr>
<td>Ferrous fumarate</td>
<td>55mg/5ml</td>
</tr>
<tr>
<td>Ferrous fumarate</td>
<td>33mg/5ml</td>
</tr>
</tbody>
</table>

The earliest response to iron therapy occurs as replacement of intracellular iron in 12-24 hrs followed by decreased irritability and improvement in appetite in 36-48 hrs. The reticulocyte response occurs in 48 -72 hrs and increase in Hb occurs in 4-30 days.

Failure of oral therapy can be due to poor compliance, inadequate doses, malabsorptive states – persistent / chronic diarrhoea, choice of the hematinic used, eg., Ferric hydroxide polymaltose complex, associated folic acid deficiency, chronic blood loss from G.I tract and lungs. Parenteral iron therapy is not routinely followed except in iron intolerance, poor compliance, malabsorption and chronic renal disease.

The dose of parenteral iron therapy is calculated based on the amount needed to correct hemoglobin and to replenish the stores.

Iron to be injected in milligrams is

\[
Wt \text{ (kg)} \times (14.5 - \text{Hb.Conc.}) \times 80/100 \times 3.4 \times 1.5
\]
Half of the amount calculated is given in addition to replenish the stores.

**Prevention of iron deficiency anemia (IDA):**

Iron rich diet (heme iron), use of iron fortified salt, complementary foods, micronutrient sprinkles in powder form over the home made foods (home fortification) are the options available.

**Vitamin B12**

B12 refers to a group of cobalt-containing vitamin compounds called cobalamin.

These are cyanocobalamin – formed using activated charcoal, hydroxocobalamin produced by bacteria, Two naturally occurring co-factor forms in humans are

(i). Adenosycobalamin – cofactor of methylmalonyl Coa mutase (MUT), (ii). Methyl cobalamin Co-factor, 5-methyl tetra hydrofolate-homocysteine methyl transferase (MTR).

**Synthesis**

Vitamin B12 synthesis is mainly by bacteria. Eg., Acetobacterium, aerobacter, flavobacterium, proteus and pseudomonas, etc., industrial production is through fermentation of selected microorganisms like streptomycyes griseus, pseudomonas deni tuficans and profioni bacterium and shermani.

**Functions**

It is normally involved in the metabolism of every cell of the body, affecting DNA synthesis and regulation and also fatty acid synthesis and energy production. Part of the functions of Vit B12 are shared by adequate doses of folic acid, since B12 is used to regenerate folate in the body. Most vit B12 deficiency are actually folate deficiency symptom, since pernicious anemia and megaloblastosis are due to poor synthesis of DNA where there is inadequate folic acid for thymine production.

**Vitamin B12 deficiency**

The most common manifestation is megaloblastic anemia (MA); In 85% of megaloblastic anemia vitamin B12 deficiency was documented. Nutritional deficiency of folate, B12 or both are commonly seen in vegetarians than non vegetarians. H.pylori infection results in B12 malabsorption.

**Sources**

The dietary sources of vitamin B12 are liver, egg and meat.

The recommended daily allowance in normal children it is 2 μg/day, during pregnancy it is 2.6 μg/day.

Vitamin B12 deficiency manifests as megaloblastic anaemia and neurological abnormalities (Subacute combined degeneration of the spinal cord)

**Management**

Megaloblastic anemia / pernicious anemia - (500 microgram) IM once a week till the Hb normalizes then 500 microgram IM every 3 months - life long. Bone marrow returns to normal within 48 hrs, Hb begins to increase within 1st week and return to normal after 1-2 months. Oral / Sublingual forms are available as 1mg tablets - effective in very high doses. Nasal sprays and transdermal patches are also available. Foods fortified with B12 can be recommended for vegans to prevent vitamin B12 deficiency.

**Folic acid (Vitamin B9)**

Folic acid and folate are natural forms of vitamin B9 and itself are not biologically active. They are converted to tetrahydrofolate, a biologically active component.
Functions Folate is essential in infants and pregnancy especially during cell division and growth. RNA synthesis also requires folate. Folate decreases risk of CVA and hypertension in children.

Sources

Green leafy vegetable, spinach, egg yolk, dried/fresh beans (fortified cereals) peas and leaflets, liver and liver products and fruits.

Folate deficiency results in megaloblastic anaemia. The deficiency during pregnancy leads to neural tube defects, preterm delivery, fetal growth retardation and increased homocysteine level - spontaneous abortions.

Recommended daily allowance (RDA): In pregnant women - 600-800 μg/day and normal adults-60-100 μg/day.

Therapy

Folate 1 to 5 mg/day orally. Parenteral preparation is also available containing 5mg/ml of folate.

Erythropoietin

Erythropoietin (EPO) is the principle hormone regulating erythropoiesis secreted by the kidney. Erythropoiesis stimulating agent (ESA) is a derivative of natural EPO manufactured by recombinant DNA technology. ESA stimulates the RBC production by erythroid precursors in the bone marrow. This increases the demand for iron, hence additional parenteral iron supplementation is needed, in patients with chronic renal disease. Indications for erythropoietin are anemias of CRF, prematurity, cancer chemotherapy, HIV infections. The dose of EPO in anemia of prematurity is 30-70 units/kg once a week Subcutaneously for 6-8 weeks.

Novel erythropoiesis stimulating protein (NESP): Is a hyperglycosylated analog of recombinant erythropoietin. NESP has greater metabolic stability, hence can be given once weekly. The optimum dose is 0.45μg/kg once weekly IV or SC.

Points to Remember

- Successful management of anemia lies in identifying the exact cause of anemia.
- Iron deficiency is the most common preventable nutritional deficiency.
- The standard dose is 3mg/kg/day of elemental iron.
- Failure to achieve adequate response to iron therapy in 2-3 weeks is designated as failure to respond.
- Poor compliance, intolerance to oral iron, persistent or chronic diarrhea and chronic renal disease are indications for parenteral iron therapy.
- It is essential to choose the ideal iron salt preparation eg. Ferrous sulphate, ferrous fumarate or iron polymaltose.

References


**CLIPPINGS**

**Antibiotics for preventing meningococcal infections**

Meningococcal disease is a contagious bacterial disease with high fatality rates, up to 15% for infection of the central nervous system (meningitis) and up to 50% to 60% among patients with blood stream infection and shock; up to 15% of survivors are left with severe neurological deficits. It is caused by *Neisseria meningitidis* (*N. meningitidis*). People who have had close contact with someone who has a meningococcal infection and populations with known high carriage rates are offered antibiotics in order to eradicate the bacteria and thus prevent disease. Data from 24 studies including 6885 participants found that rifampin (also known as rifampicin), ciprofloxacin, ceftriaxone and penicillin are effective agents for eradicating carriage of *N. meningitidis*. However, the use of rifampin may have a disadvantage as development of resistance to the antibiotic has been noted following treatment. Mild adverse events are associated with the different antibiotics used. Disease prevention could not be evaluated directly in this review as only data for eradication of the bacteria were available. Different follow-up periods were reported in the studies.


**NEWS AND NOTES**

1st Clinical Genetics Preconference Workshop

“PEDICON 2012”, 18th January, 2012, Gurgaon
Organized by Genetics Chapter, IAP

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RATIONALE OF OXYGEN THERAPY

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** Archana SR

Abstract: The primary goal of oxygen therapy is to correct alveolar and/or tissue hypoxia. Therefore, any disorder causing hypoxia is a potential indication for oxygen administration. But the tissue oxygen delivery depends upon an adequate function of cardiovascular (cardiac output and flow), haematological (hemoglobin and its affinity for oxygen) and the respiratory (arterial oxygen pressure) systems. Therefore, tissue hypoxia is not relieved by oxygen therapy alone – functioning of all the three organ systems also needs to be improved. Oxygen therapy should be administered according to guidelines. Oxygen should be regarded as a drug and should be prescribed precisely as a drug. There are numerous devices available for administering oxygen and the type of device to be used depends on the age, percentage of oxygen needed, whether the child is spontaneously breathing or not and finally the availability of the particular device.

Proper monitoring of oxygen therapy is recommended to ensure adequate oxygenation and to save precious oxygen from wastage.

Keywords: Oxygen transport, Oxygen therapy, Oxygen therapy devices.

Priestly (1777) discovered oxygen and realized its importance as a normal constituent of air. Lavoisier and his colleagues (1780-1789) demonstrated that oxygen was absorbed by the lungs and after metabolism, eliminated as carbon dioxide and water. Since that time, with the understanding of the physiology of oxygen transport from the atmosphere to the cells, its importance in cell metabolism and the derangement produced in disease, the therapeutic value of oxygen is better understood and its method of administration has improved greatly. The aim of oxygen therapy is to increase the partial pressure of oxygen in the arterial blood.

Biological role of oxygen

Oxygen is essential for life as source of energy. In photosynthesis carbon dioxide combines with water deriving energy from the sun and releases oxygen.

\[ 6\text{CO}_2 + 6\text{H}_2\text{O} \rightarrow \text{C}_6\text{H}_{12}\text{O}_6 + 6\text{O}_2 \]  
(Derive energy (From the sun))

In the body, the process is reversed so that energy incorporated in the glucose molecule is released in the presence of oxygen and made available for cell metabolism.

\[ 6\text{C}_6\text{H}_{12}\text{O}_6 + 6\text{O}_2 \rightarrow 6\text{CO}_2 + 6\text{H}_2\text{O} + \text{Energy} \]

The energy is stored in the form of ATP molecules. From one molecule of glucose, 38 molecules of ATP (1270 kilo joules of energy) is synthesised. In the absence of adequate tissue tension of \( \text{O}_2 \) viz. more than 4-5 mm Hg PtO\(_2\) only
two molecules of ATP are synthesized as a short-term store of energy and need to be continuously synthesized. Oxygen is also essential for dehydrogenation of flavoproteins and biotransformation of drugs by the cytochrome p-450 enzymes.

**Oxygen transport**

From the atmosphere, air reaches the alveoli by the act of respiration. At the alveoli, it is transferred to the hemoglobin in the pulmonary blood. Oxygenated blood is returned to the heart. The left ventricle then ejects the blood to be distributed to the rest of the body. There is a pressure gradient from the atmosphere to the tissue which is the O$_2$ Cascade (Fig.1).

**Oxygen cascade (Fig.1)**

PiO$_2$: Oxygen Concentration in the air is 21%, which are equivalents to a PiO$_2$ of 160 mm Hg. The barometric pressure and the extent of humidification affect this.

PAO$_2$: in the alveoli, the PAO$_2$ has dropped to 104 mm Hg. This is due to: 1) Dilution of atmospheric air by alveolar air. 2) Humidification of air at body temperature. 3) Constant uptake of oxygen from the alveolar air.

PaO$_2$: In the arterial blood the PO$_2$ has dropped further to 100 mm Hg due to ventilation perfusion mismatch and true shunt of pulmonary artery blood.

PtO$_2$: As the blood reaches the cell, the PaO$_2$ falls from 100 mm Hg to 40 mm Hg from the arterial to the venous end of the capillary. It falls to 5–22 mm Hg as it reaches the mitochondria.

**Oxygen carriage**

Oxygen is carried in the blood in two forms viz., 1) in simple solution and 2) in combination with hemoglobin (Hb).

1. Oxygen in simple solution: Oxygen is carried in physical solution in the plasma and the erythrocytes to the extent of 0.003ml per
100ml per mm Hg PO\(_2\) at 37\(^\circ\)C. With a PaO\(_2\) of 100mm Hg, the arterial blood carries 0.3ml of O\(_2\). If FiO\(_2\) is one, 100ml of arterial blood will contain 2 ml of oxygen in solution. At pressure of three atmospheres, there will be 6ml of oxygen in solution and enough to meet the oxygen requirement of the tissues. O\(_2\) in physical solution is a pathway to the combination of oxygen with hemoglobin.

2. Oxygen in combination with hemoglobin: Hb is a complex protein molecule in the red blood cell. It consists of 2\(\alpha\) and 2\(\beta\) protein chains each carrying a haem group. It combines rapidly and reversibly with one molecule of oxygen forming oxyhemoglobin. The chains act together and the oxygen combines with the haem in a ‘S’ shaped manner which facilitates both loading and unloading of oxygen. The bulk of oxygen is carried in the blood in combination with Hb. One gm of Hb combines with 1.3ml of oxygen when fully saturated; 100ml of blood which normally contains 15 gms of Hb will thus carry 19.6ml of oxygen. The ODC relates the saturation of Hb to the oxygen tension (PO\(_2\)) in the blood.

Characteristics of Oxygen dissociation curve (ODC): The relationship between SO\(_2\) and PO\(_2\) is not linear, but ‘S’ shaped. It is due to the variable affinity between heme and oxygen for a rise of PO\(_2\), from 0-40 mm Hg the rise in SO\(_2\) is quite steep, and it is still steep rising from 75-90%. As PO\(_2\) rises further, the ODC become relatively flat. P50. PO\(_2\) at which SO\(_2\) is 50% is called P50. Normal value is 27mm Hg. It is used to quantify shifts of ODC.

**Oxygen flux**

It is defined as the amount of oxygen carried by the arterial blood per minute as expressed by the following equation:

\[
O_2 \text{ Flux} = \text{Cardiac out put} \times \text{Hb\%} \times 1.31 \times \text{\% Saturation of Hb}
\]

With a PaO\(_2\) of 100mm Hg, Hb content of 15gm %, SO\(_2\) of 98% and cardiac output of...
5L/m², oxygen flux is 1000ml/min. Decrease in any one of the factors decreases the oxygen flux.

**The goals of oxygen therapy**

- Relieve hypoxemia by increasing $\text{PaO}_2$.
- Prevent hypoxemia.
- Reduce the work of breathing.
- Decrease the work of myocardium.
- Improve exercise tolerance.

**Methods of oxygen therapy**

Those who prescribe oxygen must have a full understanding of the mechanisms of oxygen transport and of its disorders and be aware of the complications which may accrue from injudicious therapy. Currently, oxygen may be administered to spontaneously breathing subjects by various types of facemasks, catheters and cannulae, or by air-oxygen blow-over devices. Alternatively, the patient may be enclosed in an incubator, oxygen tent or hyperbaric chamber. Oxygen-enriched air may be supplied to a ventilator during artificial ventilation.

**Adjuncts to oxygen therapy**

A particular portion of the microcirculation which is affected by ischemia may or may not be amenable to improvement by specific therapy. However, certain measures may be adopted to improve oxygen availability in addition to and sometimes instead of, oxygen therapy.

1) Cardiac output (tissue blood flow) may be increased by transfusions and infusions; dopamine or other positive inotropic agents may be administered under appropriate circumstances.

2) Arterial saturation may be improved by treating the lung pathology appropriately, i.e. reducing venous admixture by: (a) Physiotherapy. (b) Intubation (or bronchoscopy) and suction, or tracheostomy and suction and intermittent positive pressure ventilation (IPPV) with or without positive end expiratory pressure (PEEP). (c) Antibiotics as necessary. (d) Sometimes steroids. (e) Sometimes bronchodilators. (f) Treatment of congestive cardiac failure with digitalis and diuretics if appropriate.

3) Raise hemoglobin to normal or to the optimal value.

4) Measures can also be taken to reduce tissue oxygen demands: (a) Paralysis and IPPV reduce the oxygen cost of breathing. (b) Digitalization reduces the oxygen uptake of heart muscle. (c) Prevention of hyperthermia avoids increasing oxygen requirements, e.g. by fanning or sponging.

**Oxygen therapy for the spontaneously breathing patients**

“If the concentration of oxygen which a patient is receiving is not known with a reasonable degree of accuracy, then the situation is analogous to the administration of an unknown quantity of a drug which may do harm if given in excess, or provide insufficient benefit if the dose is too small”. (Scottish Home and Health Department, 1969)

An appreciation of the pattern of gas flow during spontaneous ventilation is fundamental to the consideration of the composition of inspired gas during oxygen therapy. The pattern of gas flow has three obvious sub divisions that are; inspiratory flow, active expiratory flow and the expiratory pause. The peak inspiratory flow rate is the key determinant of inspired concentration when the capacity of an oxygen therapy device is small compared to tidal volume. Total expiratory time attains more importance with increasing storage capacity of the various devices. Oxygen therapy devices were classified depending on whether their performance was influenced by these variations, i.e. variable
performance devices, or independent of these variations, i.e. fixed performance devices.

**Variable performance device**

These give uncontrolled (uncontrollable) oxygen therapy as they function only in relation to the wearer who creates the inspired mixture by the act of breathing. Various subject and device factors influence performance. The important subject factors are the inspiratory flow rate, which not only varies within each breath but attains a variable peak from breath to breath and the duration of expiration and the expiratory pause. During the latter, oxygen concentration rises and carbon dioxide concentration falls within the storage capacity of the device. The device factors are oxygen flow rate, physical volume and vent resistance, where appropriate. The subtle interplay of these factors results in unpredictable oxygen values within a subject may only reflect the influence of these variables rather than a true change in the state of the lungs under treatment.

Variable performance devices may be subdivided functionally into three characteristic types: (1) No capacity systems – nasal catheters and cannulae. (2) Small capacity systems – any device which consists of a mask shell only (3) Large capacity systems – any device with a bag.

**The oxygen delivery devices can be categorized as**

- Low flow systems. - Nasal cannula, nasal catheter
- Reservoir systems. - Simple mask, partial rebreathing mask, non rebreathing mask
- High flow systems. - Venturi masks
- Enclosure systems. - Oxyhood, Oxygen tent, Incubators
- Special Modes - Hyperbaric Oxygen therapy and ECMO

**Domiciliary oxygen therapy**

Domiciliary oxygen therapy or home oxygen therapy is an effective form of oxygen therapy. There are three basic types.

1. Continuous (> 15 hours /day)
2. Intermittent
3. Nocturnal.

**Points to Remember**

- The object of oxygen therapy, whatever the method chosen, is to increase tissue oxygen availability. This may be difficult when the primary problem is tissue ischemia.
- Logically, the concentration of oxygen should be selectable and unvarying in any situation of patient care since too much may be dangerous, too little may be inadequate, and both diagnostic and prognostic information is contained in the patient’s response to its administration.
- Even assessment of the patient from the end of the bed is easier if his inspired oxygen concentration is known. Similarly, only when inspired oxygen is known and constant can serial measurements of oxygen in blood be interpreted in terms of improvement.
- It is for us to see that the right patient receives the right amount of oxygen for the right length of time to decrease the morbidity and mortality and achieve a better quality of life.

**Bibliography**

Cot-nursing versus incubator care for preterm infants

Prematurely born infants are usually nursed in incubators to provide the warmest environment possible. Using cots instead of incubators, allows mothers to have easier access to their babies. However, additional warmth is needed to maintain their body temperature, such as extra clothing, bedding and a heated room. This updated review randomly assigned 247 preterm infants (in five trials), to an intervention of cot-nursing using a heated water-filled mattress. The control babies received routine care in an air heated incubator. One trial had three-arms, including cot-nursing in a room heated with a manually controlled space heater. In the included trials infants in the incubator groups were nursed naked apart from wearing a nappy, except in one trial in which the infants also wore a cotton jacket and booties. Three comparisons were undertaken: the overall comparison of cot-nursing versus incubator care, and two subgroup comparisons: cot-nursing with heated water-filled mattress versus incubator care, and cot-nursing using warming of the nursery versus incubator care. The results of the review showed no evidence of effect of cot-nursing versus incubator care on weight gain in the overall analysis, or in the subgroup analysis comparing cot-nursing using a heated water-filled mattress with incubator care. However, cot-nursing with warming of the nursery during week one when compared to incubator care revealed poorer weight gain. The primary outcomes related to temperature control (mean body temperature and episodes of cold stress) indicated on overall analysis no effect of cot-nursing compared to incubator care. Episodes of hyperthermia in the cot-nursing group were reported more frequently in one trial. The secondary outcomes of oxygen consumption, breast feeding at hospital discharge, episodes of nosocomial sepsis, maternal perceptions of infant’s condition, maternal stress and anxiety and death prior to hospital discharge revealed there was no effect of cot-nursing compared to incubator care. There was, however, a strong trend towards less death prior to hospital discharge. This was largely related to the results were obtained from the trials undertaken in Turkey and Ethiopia and thus may not be applicable to neonatal nurseries in developed countries. Nevertheless the implications of these findings deserve consideration, particularly in the context of a developing country.

RAPID DIAGNOSTIC TESTS IN PEDIATRIC INFECTIONS

* Lakshmi S  
** Srinivasan P

Abstract: Early detection of infection facilitates immediate intervention and prevents complications. Rapid diagnostic tests (RDTs) are available either as single or multiple step formats and can be used to detect antigen or antibody. Rapid antigen detection tests are useful when smear is negative (malaria), prior antibiotics have been initiated (bacterial meningitis) and culture is negative (enteric fever). Rapid antibody detection tests helps in differentiating acute or chronic infections (dengue). RDTs help in confirming the clinical diagnosis. However caution should be exercised in interpreting the results as chances of false positivity and false negativity persist and results should be confirmed with definitive tests if clinical condition warrants.

Keywords: Rapid diagnostic test, Antigen detection, Antibody detection.

Rapid, accurate diagnosis of infectious diseases accelerates the initiation of appropriate management and may reduce unnecessary investigations and hospitalization. In many developing countries, in an epidemic context requirements for biological confirmation at peripheral level is not possible or feasible. Technologic advances have resulted in the development of an array of rapid diagnostic tests (RDT) suitable for the assessment of patients in the office suspected of having an infectious disease which can be a boon in developing countries like India.

RDT definition

Point-of-care testing (POCT) includes rapid tests and is defined as medical testing at or near the site of patient care and results are obtained within minutes to 1-2 hours.¹

Rapid diagnostic tests suitable for office use should have the following qualities:

- Rapid turnaround time
- High accuracy relative to diagnostic gold standards
- High sensitivity and specificity
- High negative and positive predictive values
- Reproducibility of results
- Simplicity with respect to obtaining specimens, performing tests and interpreting results
- Cost-effectiveness.

In the pediatric age group in India, the infections commonly encountered are malaria, typhoid, dengue, leptospirosis, tuberculosis, pneumonia, meningitis and influenza. The rapid tests available for these infections will be dealt with, in reference to their benefits and pitfalls.

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**Malaria**

WHO recommends prompt parasitological diagnosis either by microscopy or by RDT in all patients suspected of malaria before treatment is initiated due to problems in drug resistance.²

Diagnostic techniques include the gold standard blood smear examination, quantitative buffy coat technique (QBC) and RDTs. Rapid tests for malaria are immunochromatographic tests based on the ‘Dipstick’ format that detects plasmodium specific antigens in blood sample. Common RDTs available are Parasight and OptiMAL.

Targeted antigens in currently available RDTs are-

a. Histidine rich protein II of P. Falciparum (pfHRP-II),

b. Plasmodium aldolase, produced by all plasmodium species.

c. Plasmodium lactate dehydrogenase (pLDH), is produced by all four species of plasmodia. Antibodies produced against pLDH are either specific for P.falciparum or P.vivax alone or a pan specific antibody which reacts with all the four species of plasmodium. Commercially available kit can detect falciparum and vivax but cannot differentiate ovale and malariae.

**Advantages**

Rapid tests are easy to use with minimal training and results are available within minutes. They can diagnose falciparum infection even when the parasite is deeply sequestered.

**Disadvantages**

a. More expensive than microscopy.

b. Limitations in species identification.

c. Persistent positivity even after effective treatment. HRPII remains positive for 4 weeks and pLDH remains positive for 1 week.

d. Treatment failure and monitoring of drug resistance is not possible.

e. No prognostic value- they can not quantify parasites.

**Enteric fever**

Blood culture is the gold standard test for diagnosing enteric fever but has several disadvantages. The Widal test is one test commonly used in spite of the problems with interpretation and standardization. Rapid tests for enteric fever are based on antibody detection by enzyme immunoassay and dipstick assays.

Specific antibodies appear a week after the onset of symptoms. This should be considered when a negative serological test result is being interpreted.

**a. Typhidot test:** A dot enzyme immunoassay that detects specific IgM and IgG antibodies against a 50KD outer membrane protein antigen of S. typhi. Due to persistence of high IgG levels in endemic areas, employing Typhidot to diagnose enteric fever can result in false positive results. Hence, a newer version of the test, Typhidot-M® was recently developed in which IgG is inactivated in serum sample and only IgM is detected. Evaluation studies have shown that Typhidot-M® is superior to the culture method.³ Although culture remains the gold standard it cannot match Typhidot-M® in sensitivity (>93%), negative predictive value and speed.³ Typhidot-M® can replace the Widal test when used in conjunction with the culture method for the rapid and accurate diagnosis of typhoid fever.

**b. IDL Tubex test:** The Tubex® test is simple (essentially a one-step test) and rapid (taking approximately two minutes) detecting IgM antibodies based on particle separation
against O9 antigen specifically found in serogroup D *salmonellae* but not with other serotypes including *S*. *paratyphi*. Positive result given by Tubex® invariably suggests recent *Salmonella* infection as it detects only IgM and not IgG⁴.

c. **IgM dipstick test**: The assay is based on the binding of *S. typhi*-specific IgM antibodies to *S. typhi* lipopolysaccharide (LPS) antigen. It can be done in serum or whole blood and requires incubation for 3 hours at room temperature.

**Dengue**

In Dengue, viremia peaks with the onset of fever. The presence of circulating non-structural glycoprotein (NS1) indicates viraemia. NS1 can be detectable in a patient’s blood from day 0 to day 5 following disease onset.⁵ The detection of NS1 antigen is therefore useful as a test of early acute infection as it detects dengue illness prior to seroconversion and critical period (between 3⁰ and 5⁰ day of dengue illness) during which shock and bleeding occurs.

In primary infection with dengue virus, IgM antibodies against dengue virus can be detected after day 5 which rise quickly to peak at about 2 weeks and declines to undetectable level after 2-3 months, followed by rise in IgG antibodies by day 14. In a secondary infection (from a different serotype of dengue virus) an anamnestic immune response results in a shortened duration of viraemia, a lesser and shorter IgM response and an early detectable increase in serum level of IgG. Given these peculiar characteristics, the timing of the collection of acute samples and the immune status of an infected individual both influence the nature of the laboratory test required to confirm the diagnosis.⁶

There are currently two types of rapid card tests used in dengue: antigen-detection rapid tests and antibody-detection rapid tests. Dengue antibody-detection rapid tests usually employ an immuno-chromatographic test (ICT) format to detect IgM or IgG or IgM/IgG antibodies. Dengue antigen-detection rapid tests also employ an ICT format and are based on the detection of NS1. Some tests incorporate both antigen and antibody in the same test kit. This combined antigen/antibody test aims to detect dengue infection at both the early stage (when virus is circulating) and the later stage (when antibodies appear).

In a recent Tropical Disease research (TDR) study evaluating four IgM rapid tests, sensitivity ranged from 21% to 99%, specificity from 77% to 98%.⁷

Good quality dengue rapid tests are relatively easy to use, providing results in 30 minutes or less and useful in outbreak identifications. However, dengue rapid tests are not recommended as absolute confirmatory assays because antibody-detection rapid tests cannot confirm the current infection since dengue antibodies might have persisted from an infection in the past and rapid tests can yield false positive results due to cross-reactions with other *Flaviviruses*⁷ (including Japanese encephalitis, yellow fever, West Nile virus).

A positive result produced by a rapid test thus should be confirmed by another more reliable testing technique like ELISA (IgM and IgG capture ELISA).

As a result of these pitfalls, clinical assessment remains the mainstay of dengue case identification and management.

**Leptospirosis**

Though microscopic agglutination test (MAT) is the definitive test for serological diagnosis, it is complex to perform, and interpret. Hence rapid assays detecting IgM antibodies are
developed. IgM antibodies are detected from first week of illness and they are more sensitive than MAT when sample is taken in the first week of illness.  

Specific IgM Rapid Diagnostic Tests like LeptoDipstick®, Leptospira, IgM ELISA (PanBio) and Dridot® are serologic tests in a single test format for the quick detection of Leptospira genus-specific IgM antibodies in human sera. The sensitivity rates are between 63%-72% and specificity rates between 93%-96% when tested in illnesses of less than 7 days. If serum samples are taken beyond 7 days, sensitivity improves to > 90%. Therefore, false negative results can be a problem if the tests are performed during the early stage of the illness. A second sample should be obtained for suspected cases with initial negative or doubtful results.  

Most of the commercially available ELISA kits use non-pathogenic L. biflexa patoc 1 strain as an antigen. Hence rapid assays do not discriminate among infections due to pathogenic organism resulting in false positive diagnosis. Hence these assays are more sensitive, but less specific than MAT.  

Polymerase Chain Reaction (PCR) has the advantage of early confirmation of the diagnosis especially during the acute leptospiremic phase (first week of illness) before the appearance of antibodies. Its utilization in the clinical setting is currently not available because of the cost-constraints and the need for trained personnel.  

It is not necessary to confirm the diagnosis or wait for the result of the tests before starting treatment. Even with the best laboratory backup, diagnosis of leptospirosis is essentially clinical and modified Faine’s criteria will be a useful clinical tool for diagnosing leptospirosis.

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**Tuberculosis**

The growth and detection of *Mycobacterium tuberculosis* with traditional laboratory methods requires 1-8 weeks. However, with new direct molecular methods that do not require growth of the bacteria, it is possible to detect *M. tuberculosis* complex within 3-5 hours. Two rapid diagnostic tests based on Nucleic Acid Amplification (NAA) assays are:

- The Gen-Probe AMPLIFIEDTM Mycobacterium tuberculosis Direct (MTD) Test.
- The Roche AMPLICOR® Mycobacterium tuberculosis (MTB) Test.

These tests can distinguish between *M. tuberculosis* complex and non-tuberculous mycobacteria in an Acid fast bacillus (AFB) - positive specimen. With 96% sensitivity and 100% specificity in respiratory specimens, the NAA tests are superior to the AFB smear for diagnosing Tuberculosis. A positive direct amplified test in conjunction with an AFB-positive smear is highly predictive of TB disease.

However, the results of NAA tests are preliminary; the mycobacterial culture is still needed for species identification, confirmation and for drug-susceptibility testing.

A positive result may be misleading as the NAA test can amplify DNA from both viable and non-viable organisms.

ELISPOT, a newer test using antigens specific to *M. tuberculosis* like, Culture filtrate protein (CFP-10) and early secretory antigenic target (ESAT-6) has been developed recently. This test identifies interferon gamma producing macrophages to antigenic stimulation invitro and may identify true infections.
Community acquired pneumonia

The Binax NOW Streptococcus pneumoniae test is an immunochromatographic (ICT) assay for the detection of S. pneumoniae antigen in the urine of patients with pneumonia and in CSF of patients with meningitis.\(^{14}\) Urine antigen detection for pneumococcus has higher sensitivity surpassing Gram stain, but poor specificity in children due to nasopharyngeal carriage of the organism.\(^{14}\)

Positive tests do not require culture confirmation, but cultures should be performed if rapid test results are negative. The Binax NOW is also available for Respiratory syncytial virus and mycoplasma pneumonia and Legionella pneumophila.

Bacterial meningitis

Rapid tests for bacterial meningitis are based on latex agglutination in cerebrospinal fluid which demonstrates the soluble polysaccharide antigen. It is rapid, specific and easy to perform among the available tests. Commercially available kits can detect polysaccharide capsule of S. pneumoniae, H. influenzae, N. meningitides, Group B streptococci, E.coli and C. neoformans. These tests offer good specificity >98% but the sensitivity varies with each organism tested.\(^{14}\)

Advantages: Prior antibiotic therapy does not affect the detection of bacterial antigen and especially useful in partially treated pyogenic meningitis.

Limitations for these tests include: a) Negative result can never rule out bacterial meningitis. b) Cannot distinguish between viable and nonviable organisms and should not be relied upon for test of cure and c) Children recently immunized (48 hrs) with H influenzae vaccine may get false positive latex agglutination in CSF and urine.\(^{15}\)

Influenza

Commercially available rapid diagnostic tests are screening tests for influenza A and B virus infections, which can provide results within 30 minutes. These tests are largely immunoassays which detect influenza viral antigen in nasopharyngeal washes, aspirates, or swabs. Specimens should be collected immediately after symptom onset and not after 4–5 days as virus shedding typically diminishes. In young children, viral shedding may occur for longer periods, and the collection of specimens for testing after 5 days of illness may still be useful.

Binax NOW® Flu A and Binax NOW® Flu B are commercially available rapid tests that detect influenza A and B, respectively.\(^{16}\) In general, the sensitivity of rapid tests is variable (median 70–75%) and lower than that of cell culture, while their specificity is high (median 90–95%).\(^{16}\) Because of the low sensitivity, false negative results are a major concern with these tests.

During periods of low influenza activity, if rapid tests are used, positive results must be interpreted with caution and confirmed by immunofluorescence assay (IFA), viral culture or RT-PCR.\(^{17}\)

Points to Remember

- **Rapid diagnostic tests (RDTs) save considerable time and can be used in places where sophisticated equipment or trained personnel are not available.**

- **RDTs are comparable to gold standard diagnostic methods in Malaria, Enteric fever (Typhidot-M®), and Dengue (NS1 antigen detection).**

- **Antibody detection RDTs should be interpreted after taking into account the**
prevalence of that particular infection in the population.

- When selecting commercially available RDTs, the tests should be thoroughly evaluated, as some RDTs still need more validation before being recommended as routine diagnostic tests for specific infectious disease.

References

FOLLOW-UP OF CHILDREN AFTER CANCER THERAPY

* Arathi Srinivasan
** Vinoth P Nagarajan
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*** Julius X Scott

Abstract: With improvements in therapy for childhood cancer, the expectation that most childhood cancer patients will survive and enter adulthood is a reality. There is clear evidence that survivors are at risk for adverse health-related long-term sequelae associated with their cancer and its treatment. Risk-based health care that involves a personalized plan for surveillance, screening, and prevention is recommended to reduce cancer-related morbidity in childhood cancer survivors. Due to paucity of specialized long-term follow-up centers in our country and their limited geographic access, finding ways to educate pediatricians regarding needed follow-up is a priority in our country.

Keywords: Child, Cancer, Survivors, Late effects.

During the past 5 decades, dramatic progress has been made in the development of curative therapy for pediatric malignancies. Long-term survival into adulthood is the expectation for 80% of children with access to contemporary therapies for pediatric malignancies. The therapy responsible for this survival can also produce adverse long-term health-related outcomes, referred to as “late effects,” that manifest months to years after completion of cancer treatment.

Why should we follow up children after cancer therapy?

Research has clearly demonstrated that late effects contribute to a high burden of morbidity among adults treated for cancer during childhood, with at least two-thirds developing one or more chronic health conditions and at least one-third experiencing severe or life-threatening complications during adulthood.

The common late effects of pediatric cancer encompass several broad domains including growth and development, organ function, reproductive capacity and health of offspring and secondary carcinogenesis. In addition, survivors of childhood cancer may experience a variety of adverse psychosocial sequelae related to the primary cancer, its treatment, or maladjustment associated with the cancer experience.

Late sequelae of therapy for childhood cancer can be anticipated based on therapeutic exposures, but the magnitude of risk and the manifestations in an individual patient are influenced by numerous factors. Factors that should be considered in the risk assessment for a given late effect include the following:

Tumor-related factors

• Tumor location.
• Direct tissue effects.
• Tumor-induced organ dysfunction.
• Mechanical effects.

**Treatment-related factors**

Radiation therapy: Total dose, fraction size, organ or tissue volume, type of machine energy, chemotherapy: Agent type, dose-intensity, cumulative dose, schedule, surgery: Technique, site, use of combined modality therapy, blood product transfusion, hematopoietic cell transplantation.

**Host-related factors**

Gender, age at diagnosis, time from diagnosis/therapy, developmental status, genetic predisposition, inherent tissue sensitivities and capacity for normal tissue repair, function of organs not affected by cancer treatment, premorbid health state, socioeconomic status, health habits.

The need for long-term follow-up for childhood cancer survivors is supported by the American Society of Pediatric Hematology/Oncology, the International Society of Pediatric Oncology, the American Academy of Pediatrics, the Children’s Oncology Group (COG), and the Institute of Medicine. Specifically, a risk-based medical follow-up is recommended, which includes a systematic plan for lifelong screening, surveillance, and prevention that incorporates risk estimates based on the previous cancer, cancer therapy, genetic predisposition, lifestyle behaviors, and comorbid conditions.4,5

**Who should follow up these children?**

Most long-term follow-up centers have a core team consisting of a pediatric oncologist and psychosocial support, with additional optional subspecialist support in the form of endocrinology, cardiology, pulmonology, etc. Many of these long-term follow-up clinics are located within the pediatric oncology units. Some pediatric oncology centers have implemented transition models, in which the care of adolescent and young adult survivors is provided by a more age-appropriate provider, usually after a period of joint care.6 This model is well established in the transitional care of adolescents or young adults with various chronic disorders.7 The wide range of complications that might occur during long-term follow-up of childhood cancer survivors has resulted in the development of specialized oncology-led transition programs in western countries although other long-term follow-up programs have relied on follow-up by nonspecialist primary care providers.8,9

However, a paucity of such specialized long-term follow-up centers in our country and their limited geographic access make these centers an option only for survivors who live nearby or who can afford the time and expenses in order to travel to a distant center. Therefore, finding ways to educate survivors and their local pediatricians regarding needed follow-up is a priority in our country.

**Various models of follow up care**

**Primary oncology care:** In this model, patients continue to see their treating oncologist in the oncology clinic. Although this model is often the most comfortable for the patient who has developed a relationship and a level of trust with the treating physician, the focus may remain on disease surveillance rather than the potential for late effects and associated opportunities for health promotion.

**Specialized late effect clinic:** The specialized long term follow up (LTFU program) model involves transitioning the patient from the primary oncologist to a specialized LTFU team typically when the patient has been off active
therapy for at least two years. This type of clinic is designed to examine and evaluate the patient as well as to provide risk-based screening recommendations and education about potential late effects.

**Shared care:** In this model, a family physician or pediatrician with the primary oncologist’s advice will follow up the child and refer to the oncology centre for review periodically.

**Young adult transition models**

**Formalized transition programs:** Many pediatric institutions have upper age limits for care, recognizing that older survivors may not be able to receive appropriate care in a pediatric setting and that their needs may be better served in an adult-focused healthcare environment. These clinics may be staffed by pediatric and/or adult oncology practitioners or with family practice or internal medicine physicians who will coordinate among themselves for caring the survivors.

**Adult oncology-directed care:** Another option for transitioning young adult patients is to refer them to an adult oncologist for LTFU after 18 years of age.

**Community-based models**

**Community-based care:** Armed with the appropriate knowledge of late effects related to childhood cancer treatment, pediatric and primary care practitioners can successfully provide LTFU care to survivors. In this model, the pediatrician or family practice physician provides LTFU care.

**Need-based models**

Models based on intensity of treatment are being explored to guide decisions about type and frequency of long-term follow-up for pediatric cancer survivors. Three levels of follow-up care have been proposed by Eiser, et al. and include:

- **Level 1** follow-up every 1 to 2 years for patients who had only surgical treatment or “low-risk” chemotherapy, such as stage I or II Wilms tumor or germ cell tumors treated with surgery alone;
- **Level 2** follow-up by primary care provider every 1 to 2 years for patients who received chemotherapy alone or chemotherapy with lowdose (<24 Gy) cranial irradiation, such as those with ALL in first remission;
- **Level 3** follow-up in a medically supervised late effects clinic annually for patients who received any radiation (with the exception of low-dose cranial irradiation), and for patients who received “megatherapy,” such as patients with stage IV tumors, brain tumors or those who underwent bone marrow transplant.

**When do we start follow up in a separate follow up clinic?**

Initiation of long-term follow-up care: Possibilities include: At a set time interval (e.g., one or two years) following completion of active treatment. At a set time interval (e.g., five years) following diagnosis.

**Who all are needed in the follow up clinic?**

The Multidisciplinary team surrounding the core survivorship team is a group of physicians and specialists familiar with evaluating problems in childhood cancer survivors.

Common subspecialties in the team include: Audiology/ENT, endocrinology, cardiology, pulmonology, ophthalmology, nephrology, gynecology, reproductive endocrinology, orthopedics, psychology/neuropsychology and adult primary care or internist.

Other specialists to considered include: Developmental medicine, neurology, genetics, surgery (general, plastics, etc), gastroenterology,
urology, dentist, social worker, psychologist and nutritionist.

What do we need to prepare for the follow up?

Preparation for the clinic visit should begin well before the scheduled date. Essential elements include reviewing and extracting data from the “past medical record” and preparation of a comprehensive “treatment summary”. Exposure-based screening recommendations and a comprehensive medical summary are compiled and shared with the multidisciplinary team.

Medical record review

Ideally, a comprehensive treatment summary should be prepared as patients complete the acute phase of their treatment. Unfortunately, in most institutions, this is not usually done. Therefore, a comprehensive treatment summary must be compiled prior to the initial visit in the follow up clinic. A thorough review of the medical record is the first step. The purpose of the review is to summarize the pertinent information regarding the cancer history and treatment, generate a comprehensive summary, and determine appropriate recommendations for risk-based care, screening, and education.

Preparing the treatment summary

The following information is included in the treatment summary: Demographics, medical history prior to the cancer diagnosis, diagnostic details (eg. diagnosis, date of diagnosis, presenting symptoms, sites involved, stage, pertinent diagnostic features such as physical exam and radiologic findings, histology, morphology, flow, tumor markers, and cytogenetics), complications and significant events, transfusion history, hepatitis B,C and HIV results, adverse drug reactions/allergies, date treatment completed, date of any relapses or second malignancy and associated treatment, therapeutic summary with treatment protocol (chemotherapy agents, including cumulative doses for all agents used), radiation therapy, including a) Field(s) and total radiation dose, number of fractions, dose per fraction, and boost dose/location and b) Radiation type (eg. proton, photon), hematopoietic cell transplant(s), if applicable, including type, conditioning regimen, GVHD prophylaxis and/or treatment, if applicable, surgical summary, including details of surgical procedures, potential long-term effects by organ system and recommendations for necessary screening tests and follow-up exams based on age and treatment received.

What do we do in the clinic?

During the initial clinic visit, the medical, family and psychosocial history should be reviewed. The team should decide which members will collect each component of the history (e.g., the social worker or psychologist may assume responsibility for the psychosocial details, whereas the clinician may focus on the medical and family history). In a multi-disciplinary clinic, to avoid repetition, it is important that not every member of the team ask the same questions. However, critical history may be missed if important questions are not assigned to a specific team member.

The physical examination should be performed by the clinician evaluating the patient. A comprehensive examination should be performed, with a focus on organs at risk due to the underlying disease and therapeutic exposures.

Emphasis on a healthy lifestyle should also be discussed during this visit. For example, avoidance of tobacco use and the importance of a healthy diet and adequate exercise should be stressed.

Documentation of health counseling should be recorded in the patient’s medical record.
A comprehensive psychosocial assessment should be done by the social worker or psychologist. This interview should elicit information related to the impact of the cancer diagnosis on the survivor’s current psychosocial adjustment. The need for subspecialty care will be dictated by the survivor’s underlying medical conditions and the effects of the cancer diagnosis and its treatment. Attention should be paid to thorough follow-up of active medical problems as well as screening for asymptomatic complications. As survivors reach adulthood, facilitating the transition from pediatric to adult medical care providers may be a primary goal of late effects clinics. The common late effects, its potential cause and the needed recommendations are summarized in Table I.

**Conclusion**

Long-term follow-up programs and services are essential in order to address the unique needs of the growing population of childhood cancer survivors as they navigate the challenges of today’s healthcare system. Prevention and/or early identification of complications are crucial in order to decrease the long-term health risks associated with curative treatment for childhood cancer.

<table>
<thead>
<tr>
<th>Table I. Selected exposure – based screening recommendations</th>
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<tbody>
<tr>
<td><strong>Category</strong></td>
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<tr>
<td>Neurocognitive</td>
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<td>Cardiac</td>
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<tr>
<th>Pulmonary</th>
<th>Carmustine; Lomustine; busulfan; bleomycin Bleomycin</th>
<th>Pulmonary fibrosis Pulmonary fibrosis; interstitial pneumonitis; acute respiratory distress syndrome Pulmonary fibrosis; delayed interstitial pneumonitis; restrictive obstructive lung disease</th>
<th>Yearly history and physical exam; baseline measure of pulmonary function including Diffusing capacity of the lung for carbonmonoxide (DLCO) and spirometry; baseline chest x-ray; consider repeat evaluation prior to general anesthesia and as clinically indicated</th>
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<tbody>
<tr>
<td>Endocrine</td>
<td>Radiation impacting the thyroid; radiation impacting the HP axis</td>
<td>Hypothyroidism (primary central); hyperthyroidism growth hormone deficiency; central adrenal insufficiency; hyperprolactinemia</td>
<td>Yearly history and physical exam; yearly thyroid function test (free T4, TSH); 8 a.m. serum cortisol if radiation to HP axis &gt; 40 Gy – test yearly for at least 15 years;</td>
</tr>
<tr>
<td>Gonadal function</td>
<td>Alkylating chemotherapy; surgical removal of both gonads; radiation involving the gonads</td>
<td>Hypogonadism; gonadal failure; infertility; premature menopause (females)</td>
<td>Yearly history and physical exam including evaluation of secondary sexual characteristics and sexual function; baseline (females age 13; males age 14) assessment of gonadal function (LH, FSH, estradiol or testosterone); repeat as clinically indicated in patients with delayed puberty or signs symptoms of hormonal deficiency; additional evaluations as indicated (e.g. semen analysis)</td>
</tr>
<tr>
<td>Second malignancies</td>
<td>Etoposide: Teniposide : Anthracyclines</td>
<td>Acute myeloid leukemia</td>
<td>CBC, platelet, differential yearly for 10 years following exposure</td>
</tr>
<tr>
<td></td>
<td>Alkylating chemotherapy</td>
<td>Acute myeloid leukemia/myelodysplasia</td>
<td>Yearly history and physical exam with inspection and palpation of tissues in radiation field</td>
</tr>
<tr>
<td></td>
<td>Radiation (any field)</td>
<td>Malignancy in radiation field (skin bone, soft tissue)</td>
<td>Yearly thyroid exam</td>
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<tr>
<td></td>
<td>Radiation impacting the thyroid</td>
<td>Thyroid cancer</td>
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<tr>
<td>Radiation impacting the breast</td>
<td>Breast cancer</td>
<td>Monthly breast self-exam; clinical breast exam yearly until age 25, then every 6 mos; mammogram with adjunct MRI yearly beginning 8 years after radiation of at age 25, whichever comes last</td>
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<tr>
<td>Dental</td>
<td>Any chemotherapy Radiation impacting oral cavity</td>
<td>Dental evaluation and every 6 months Supportive care with saliva substitutes, cleaning moistening agents, and sialogogues (pilocarpine)</td>
<td></td>
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<tr>
<td>Dental</td>
<td>Dental developmental abnormalities; Malocclusion Xerostomia/salivary gland dysfunction; periodontal disease; dental caries; oral cancer (squamous cell carcinoma); temporomandibular joint dysfunction Osteoradionecrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td>6-mercaptopurine, 6-thioguanine, methotrexate Radiation impacting liver/biliary tract; HSCT</td>
<td>Hepatic dysfunction Veno-occlusive disease/sinusoidal obstructive syndrome Hepatic fibrosis/cirrhosis Cholelithiasis Screen for viral hepatitis, liver function tests Hepatitis A and B immunizations in patients lacking immunity Gastroenterology/hepatology consultation in patients with persistent liver dysfunction</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>Bladder toxicity (hemorrhagic cystitis, bladder fibrosis, dysfunctional voiding, vesicoureteral reflux, hydronephrosis) Renal toxicity (glomerular injury, tubular injury, [renal tubular acidosis], Fanconi’s syndrome, hypophosphatemic rickets)</td>
<td>Blood pressure, Urinalysis BUN, Creatinine, Na, K, Cl, CO₂, Ca, Mg, PO₄ levels Urine culture, spot urine calcium/creatinine ratio, and ultrasound of kidneys and bladder for patients with microscopic hematuria (defined as ≥5 RBC/HPF on at least 2 occasions) Nephrology or urology referral for patients with culture-negative microscopic hematuria AND abnormal ultrasound and/or abnormal calcium/creatinine ratio</td>
<td></td>
</tr>
<tr>
<td>Auditory</td>
<td>Platinum based chemotherapy like cisplatin</td>
<td>Audiology evaluation Amplification in patients with progressive hearing loss Speech and language therapy</td>
<td></td>
</tr>
<tr>
<td>Contd..</td>
<td>Ototoxicity; sensorineural hearing loss; tinnitus; vertigo</td>
<td></td>
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</table>
The children’s oncology group (COG) has developed a resource guide to assist institutions in establishing and enhancing long-term follow-up programs and services for childhood cancer survivors. The long-term follow-up program resource guide offers a broad perspective from a variety of long-term follow-up programs within the children’s oncology group and can be downloaded from http://www.survivorshipguidelines.org.

### Points to Remember

- **Long-term survival into adulthood is the expectation for 80% of children with access to contemporary therapies for pediatric malignancies.**

- **Late effects contribute to a high burden of morbidity among adults treated for cancer during childhood, with at least two-thirds developing one or more chronic health conditions and at least one-third experiencing severe or life-threatening complications during adulthood.**

- **The common late effects of pediatric cancer encompass several broad domains including growth and development, organ function, reproductive capacity and health of offspring and secondary carcinogenesis.**

- **Long-term follow-up clinics are located mostly within the pediatric oncology centres and hence survivors who live far away cannot afford the time and expenses to travel to a distant center. Therefore, finding ways to educate pediatricians regarding needed follow-up is a priority in our country.**

- **Prevention and/or early identification of complications are crucial in order to decrease the long-term health risks associated with curative treatment for childhood cancer.**

### References


5. Oeffinger KC, Hudson MM: Long-term complications following childhood and adolescent cancer: foundations for providing


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**CLIPPINGS**

**Topical analgesics for acute otitis media**

Antibiotics make little difference to children with an uncomplicated ear infection and ear pain. Some advocate ear drops with local anaesthetic such as amethocaine, benzocaine or lidocaine. Five trials (391 participants) were identified; two compared anaesthetic drops to placebo (inactive) drops; and three compared anaesthetic drops to herbal ear drops. There was no strong evidence that herbal ear drops were effective, but anaesthetic drops did provide better pain relief than the inactive drops. Only one trial looked at adverse reactions and reported no cases of ringing in the ears or unsteadiness when walking and three cases of very mild dizziness.

Children in all the trials experienced a rapid, short-term reduction in pain after using ear drops. It is hard to know if this was the result of the natural course of the illness; the placebo effect of receiving treatment; the soothing effect of any liquid in the ear or the pharmacological effects of the ear drops themselves. Nevertheless, there is some evidence that when combined with oral pain medication, anaesthetic ear drops may help to relieve pain more rapidly in children aged three to 18 years. More good-quality trials are needed.

INTERPRETATION OF CT CHEST

* Vijayalakshmi G

Abstract: CT is a valuable tool in the evaluation of the chest. In children, it is mainly used to diagnose mediastinal masses. For the lungs, it is used to clarify and further study doubtful lesions seen in a chest x-ray. HRCT is for diffuse lung disease. CT carries the risk of radiation exposure and hence should be used with care.

Keywords: Computerised tomography, High resolution CT, Lungs, Mediastinum.

The x-ray chest or the ultrasonogram (US) abdomen can be routine investigations. They can also be screening tests in the absence of specific indications. But the computed tomography (CT) chest is never a routine test. There has to be a definite indication and a strong provisional diagnosis. This is because one should keep in mind the contribution of CT to a relatively large radiation dose\(^1\) to patients. This fact is more important in the context of children, due to greater radiosensitivity of growing tissues and longer life-time risk for radiation induced cancer. In view of this we have to use CT judiciously.

CT evaluation of the chest can be considered under two headings a) study of the mediastinum and b) study of the lungs. These are separately considered because they are read by changing certain parameters when the images are processed. The mediastinum is read in the mediastinal window where a wide range of densities are shown- bone and muscle in the chest wall, blood vessels, fat and lymph nodes. The lungs will be black without any detail. In the lung window low density lung tissue can be seen. All the other tissues will be white without any internal structural features.

* Associate Professor, Department of Radiology, Chengalpattu Medical College, Chengalpattu.

Fig.1. Schematic diagram of location of mediastinal masses
A) Study of the mediastinum: The mediastinum is the space between the two medial pleurae and is divided into three compartments. The most problem which is evaluated is mass lesions. Mediastinitis, edema and hemorrhage are rare possibilities.

The picture shows common lesions occurring in specific areas in the mediastinum (Fig.1). Lymph nodes enlargement can be seen in all these regions

1) Thyroid (retrosternal) masses, parathyroid masses, 2) thymoma, teratodermoid, 3) lipoma, fatpad, pericardial cyst and Morgagni hernia, 4) tumors from trachea and bronchus and pulmonary artery aneurysms, 5) esophageal and vertebral lesions, 6) hiatus hernia, aneurysms and varices, 7) vertebral and paravertebral lesions and duplication cysts.

Based on location and morphology CT can detect and characterize lesions. Masses are generally hypodense with cystic or necrotic areas that appear more hypodense than the solid areas. The extent of masses and involvement of adjacent tissue can be detected. The thyroid is denser than neighboring tissue because of the presence of iodine. Cysts like bronchogenic, pericardial or thymic cysts are of water density with a definite wall.

B) Study of the lungs: Masses of the lung are rare in children. So indications for lung conditions can be listed as, 1) Airway abnormalities like stenosis and foreign bodies, 2) Parenchymal abnormalities- search for parenchymal abnormalities in opaque hemithorax, 3) Clarification of a confusing film like a normal chest x-ray with unusual symptoms, 4) Evaluation of bronchiectasis, 5) Evaluation of primary mass and search for lung metastases, 6) Interstitial lung disease- For this High resolution CT (HRCT) is used. It can accurately diagnose interstitial lung disease and can help to locate the exact site of lung biopsy.

HRCT uses thin sections and a high spatial resolution algorithm that brings out ground glass opacities due to swelling or thickening of the alveolar septal walls. These are not seen in conventional CT. It should be remembered that HRCT uses higher kV and more radiation. In children the milli ampores radiahon (mAs) dose is reduced by half and more which will reduce radiation exposure proportionately.

One important pitfall in HRCT in children is to differentiate high density expiratory lungs and ground glass infiltration. Expiratory films will be useful for this but it is difficult to obtain such films in specific phases of respiration, especially in unco-operative children. Lateral decubitus films will serve the purpose as the dependent lung is in the expiratory phase.

The chest can present with an array of pathologies as diverse as the diversity of tissues in the chest. CT should be used for evaluation of the chest keeping in mind therapeutic benefit and radiation dose.

Points to Remember

- CT is an excellent diagnostic modality but carries the risk of radiation. (125 times that of chest x-ray or more)
- Mediastinal masses definitely require CT.
- But for lungs, therapeutic benefit should be weighed with radiation risk.

References


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**CLIPPINGS**

**Synthetic human growth hormone for treating X-linked hypophosphatemia (or Vitamin D resistant rickets) in children**

Standard treatment of X-linked hypophosphatemia can heal rickets but does not always raise the level of phosphates in the blood or return growth levels to normal. It is unclear whether combining human growth hormone therapy with standard treatment improves the phosphate levels, growth rates and bone mineral density. Only one small trial with five children was included in this review. The human growth hormone treatment improved the z score for height and briefly increased the level of phosphates in the blood. However, we found no conclusive evidence that favours the use of human growth hormone treatment for this condition. There have not been enough trials of human growth hormone treatment for this condition and more research is needed.


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**Evaluation of microalbuminuria in obese children and its relation to metabolic syndrome, Mohammed Sanad and Amal Gharib, Pediatric Nephrology, 06/08/2011.**

High–density lipoprotein (HDL) was significantly lower in obese children with microalbuminuria than in those with normoalbuminuria, with a significant negative correlation with microalbuminuria. Authors found that body mass index, abdominal obesity, hypertension, impaired fasting glucose level and insulin resistance significantly increased the odds of microalbuminuria in the obese children enrolled in this study. High triglyceride, high LDL and low HDL were significantly associated with microalbuminuria.
THE CHILD WITH A V-P SHUNT

* Chidambaram Balasubramaniam

Abstract: Ventriculo peritoneal (VP) shunts are perhaps the commonest neuro surgical procedure performed in the pediatric age group. Children who have had a VP shunt need life long followup.

Keywords: VP shunt, Revision, Malfunction.

The introduction of the ventriculo peritoneal (VP) shunt has been the single most significant event in ensuring a better outcome for children afflicted with hydrocephalus. The outlook which had been abysmal had improved to the extent that children could be integrated into the mainstream of society. Most of the problems were because of a lack of clear understanding of the disease and its management. In 1952, Nulsen and Spitz introduced valvular drainage and later Holter realised that silicone is the ideal material to be used in the manufacture of the shunt. But, in spite of a better understanding of the disease and technologies to diagnose and manage the disease shunting procedures have the highest failure rate among all neurosurgical procedures.

Before addressing the care of the child who has a shunt, it is important to look at the complications and the various kinds of problems a child with a shunt can encounter.

Complications

The complications can be classified as:
a) mechanical, b) functional, c) infective and d) others.

Mechanical

This refers to blockage, breakage, disconnections and similar ways in which a shunt can fail to function. Most of these occur in the first six months after the surgery and by the end of the first year around 40% would have failed.

Functional

Here, there is an overdrainage of the CSF resulting in subdural hygroma (or haematoma) formation. If the shunt performs suboptimally the result is persistence or worsening of hydrocephalus.

Others

A child with a shunt may be afflicted with a host of other complications like extrusion of the tube, formation of abdominal cysts, etc.

Manifestations of shunt dysfunction

There is considerable overlap in the clinical features of a malfunctioning shunt - be it of any aetiology. But all, to a considerable extent, are age dependent. Infants commonly present with a bulging fontanelle, separation of sutures, increasing head size and dilated scalp veins. Irritability, poor feeding and vomiting, lethargy and failure to thrive are also commonly encountered manifestations. The older child...
frequently complains of head aches and vomiting is a commonly associated manifestation. Lethargy, lateral rectus palsy, paralysis of upward gaze and papilledema are also met with. If the onset and progression of the malfunction is rapid neck stiffness will be present. On the other hand if the progression is slow deteriorating scholastic performance and loss of milestones may be the only manifestations.

**Assessment of shunt function**

The commonly practised method of evaluating the shunt i.e. pressing the shunt reservoir is quite unreliable. It is taught if the shunt does not refill on depressing the reservoir the block is proximal i.e. intracranial. But if it does not empty or refills quickly the block is distal to the reservoir. But there are many variables like skin elasticity which can influence the findings. In addition, frequent pumping of the shunt will only cause the shunt to malfunction.

The best way to evaluate the function of the shunt is to elicit a good history. Always remember the parents are always right. If they feel the child is not alright because of a shunt malfunction they are right until proved otherwise.

The salient points in history referred to above must be specifically enquired. Certain aspects unequivocally indicate a malfunctioning shunt. These include fluid collection along the shunt site, bulging fontanelle, dilated scalp veins, lethargy, vomiting, VI nerve palsy and paralysis of upward gaze.

In a child with over drainage, a subdural hematoma collects and features of raised ICP will be present.

**Shunt infection**

The incidence is between 5 - 9%. But many centres have managed to reduce the rate significantly. Most present within 6 months; often within 2 months. The infection may be intracranial, intra abdominal or along the tract. The cardinal feature of shunt infection is shunt malfunction. Fever and pain may not be present in all. Collection and redness along the shunt tube indicate sepsis. Wound erosion and extrusion of the tube may be encountered too. Features of overt meningitis, ventriculitis or peritonitis are not encountered in all the cases. Unexplained fever in a child with a shunt must raise the suspicion of shunt infection and this has to be excluded by a shunt tap. Urinary tract infections and otitis can masquerade as shunt infections. Meningitis is an important manifestation of proximal infection while peritonitis is encountered in distal sepsis.

LP is best avoided. Shunt tap will be a better option since the child may have shunt malfunction with raised ICP. The only unequivocal way of establishing shunt sepsis is a positive culture. Caveat: if the child has received antibiotics before presentation cultures may be negative. Here clinical suspicion should guide the treatment.

**Empirical antibiotic therapy**

The choice will depend on the clinical scenario. Since most are staphylococcal infections, coverage against staphylococci will be a good option. But the final choice will depend on the culture report.

**Prognosis in a child with shunt**

In the preshunt era, the mortality rate was more than 60% in infancy while only 20% survived into adult hood. Those who survived were left with severe motor and mental handicaps. Now in children who have had shunts placed in infancy the mortality is between 3-10%. Around 60% attend normal school while 20% need special attention. Nearly three fourths of the children are socially independent.
Only around 10% fall into the group of uneducable or unemployable. The mortality related to shunt failure is approximately 1%.

The mental/intellectual outcome is etiology dependent. Those with meningo(myelo)cele seem to fare well if there are/ have been no other problems (approximately 80% do reasonably well). Those who have post infectious/hemorrhagic hydrocephalus and hypoxic insults fare the worst, (post infectious faring worse) with 50% needing special care. The thickness of the cerebral mantle does not affect the outcome.

**Follow up of a child with shunt**

There are no clear guidelines for the frequency of follow up. But it can’t be overemphasised that the follow up is a life long process, in which the child (patient), family and the care giver are equally involved.

The child with a shunt must be looked after by the neurosurgeon and the primary care pediatrician. Both have to care for these children. All involved in the care of these children – pediatricians, neonatologists, pediatric neurologists – must be aware of the features of shunt malfunction and there must be close cooperation between these care givers and the pediatric neurosurgeon.

As a simple rule the child is evaluated a week after the surgery, then after a fortnight and then roughly at monthly intervals for about six months. By this time most of the complications would have manifested. After this, depending on the condition of the child, family circumstances, where the family live the aetiology of the condition and the progress of the child, further follow ups can be scheduled. There are no rules here and the follow up has to be tailored for each child.

Before the surgery or discharge, the family is educated about the shunt, the need for life long care periodic follow up and the features of shunt malfunction or infection. Generally two shunt revisions may be required if the shunt is done in infancy.

For all practical purposes the shunt cannot be removed because true shunt independence is rare. True independence can be proved only if the shunt has been proved to be non functional or removed in a shunted child who is asymptomatic. Some can have third ventriculostomies done and the shunt can be removed. But this is on a case by case basis only.

At the first follow up after a general exam, the fontanelle – if open - is palpated- over riding of sutures is recorded , the shunt tract is inspected for fluid collection and the wounds inspected for sepsis. The head circumference is noted but in the older child there may not be a significant drop in the circumference.

At subsequent follow ups, the evaluation and examination are essentially the same and the child’s milestones are noted. In children attending school the scholastic performance is also noted since a falling scholastic performance over a period of time (not just failure in one exam !) may indicate chronic shunt malfunction. Shunted children must be seen and evaluated at least once every year even if they are asymptomatic. During the visits the general wellbeing, family circumstances, awareness of the features of shunt malfunction, the attitude of the child and family are evaluated. Family must be told whom to contact or where to go if there is (or they feel there is) any emergency or crisis situation.

Once the child attains adulthood the care must be transferred to the appropriate adult medical personnel. There is no end point. The patient and family must be made aware of this fact.

It may help to get imaging study done (CT or MRI) sometime between 6 – 12 months
(when the child is asymptomatic) post shunt surgery to check the ventricular size, look for asymptomatic collections and the size of the cortical mantle. In addition this will be a useful baseline for comparison when imaging studies later on raise the doubt of a shunt malfunction.

It is taught sometimes that the shunt must be “pumped” several times a day by the parents. This should never be done. The shunt is best left alone. Pumping may pull the choroid plexus into the catheter. The shunt is a delicate “instrument”, frequent handling will cause earlier dysfunction.

“If in doubt about the functioning of the shunt assume it is shunt failure”, is an oversimplification but a practical way. It should always be remembered that many other systemic illnesses may manifest/ masquerade as shunt malfunction/ infection.

**Points to Remember**

- **In children with hydrocephalus, VP shunt placement ensures better outcome.**

- **Symptoms and signs of increased ICP indicate malfunction of shunt. Frequent pressing or handling the shunt pump is not the right way to assess the function.**

- **Usual features of shunt infection are features of shunt malfunction and unexplained fever.**

- **Shunt tap by neurosurgeon and analysis, is the only way to exclude infection.**

**Bibliography**


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**CLIPPINGS**


Our objective was to compare the inter-observer level of agreement in diagnosing pneumonia using the World Health Organization (WHO) guidelines for the interpretation of radiographs. We conducted a prospective study in a pediatric emergency room. Fifteen observers (13 pediatricians, 2 radiologists) interpreted 200 pediatric (<5 years old) chest radiographs using the WHO guidelines. Observers were blinded to the clinical presentation. Results were analyzed for kappa values. Individual readings were compared to two “gold standard” teams: (1) radiologist and pediatrician and (2) two radiologists. Pediatricians over diagnosed “non-alveolar pneumonia” compared with radiologists. In contrast, for the alveolar pneumonia and no-pneumonia diagnoses, no significant differences were found. The WHO guidelines for interpretation of chest radiographs result in high level of agreement between readers for the definition of “alveolar pneumonia” and “no pneumonia” but poor agreement for non-alveolar pneumonia.
STORAGE OF VACCINES

* Ravisekar CV

Abstract: From the site of manufacturer to the site of administration vaccines must be stored at proper temperature. All vaccines are heat and cold sensitive. Once potency of vaccine is lost it cannot be restored. Do’s and Don’ts regarding vaccines storage and how to store in the domestic refrigerator are discussed in this article.

Keywords: Cold chain, Storage, Vaccines.

Vaccines are sensitive biological substances that progressively loose their potency. This loss of potency is much faster when the vaccine is exposed to temperatures outside the recommended storage range. Once the vaccine potency is lost it cannot be restored. Any loss of potency is permanent and irreversible.

The storage of a vaccine at the recommended temperature is vital in order to retain full vaccine potency from the manufacturing to administration to the individual. Not only the maintenance of cold chain but also proper handling and administration of vaccines are equally important. Any negligence on these fronts could lead to devastating consequences. Although all vaccines are heat sensitive some are far more sensitive than others. The concept of cold sensitive vaccines (damaged by freezing) is equally important.

The following list shows the vaccines arranged in decreasing order of their sensitivity to heat

**Most sensitive**

- Live oral polio vaccine (OPV)
- Measles *
- MMR
- Hepatitis B
- Adsorbed Diphtheria-Pertussis-Tetanus (DPT)
- Adsorbed Diphtheria-Tetanus (DT, Td)
- BCG *
- Rabies
- TT

**Least sensitive**

* Become much more heat sensitive after they have been reconstituted with diluents.

Vaccines highly sensitive to freezing

<table>
<thead>
<tr>
<th>Vaccines damaged by freezing</th>
<th>Vaccines unaffected by freezing</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPT</td>
<td>BCG</td>
</tr>
<tr>
<td>DT</td>
<td>OPV</td>
</tr>
<tr>
<td>Td</td>
<td>Measles</td>
</tr>
<tr>
<td>TT</td>
<td>Mumps</td>
</tr>
<tr>
<td>Hepatitis – B</td>
<td>Varicella</td>
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</table>

* Reader in Pediatrics, Institute of Child Health and Hospital for Children, Chennai.
In addition to being temperature sensitive, several vaccines are also highly sensitive to strong light, e.g., BCG and measles.

The commonest cold chain equipments usually used are walk In Cold rooms (WIC) at the manufacturer level or at regional level where usually the vaccines are stored for three months. The ice lined refrigerator (ILR) with deep freezers (to prepare ice pack, store OPV and Measles) are used at primary health centre, urban family planning centre and tertiary care centers. Most vaccines may be stored up to 4 to 5 weeks between 4 to 8°C at the peripheral centre. Practically every practitioner or consultant keeps vaccine in the domestic refrigerators. But domestic refrigerators are designed for food storage and are not designed to meet the specialized needs of vaccine. Careful monitoring and knowledge of refrigerator is required to minimize risk to the vaccine.

Investment on exclusive refrigerator for storing vaccines, power backup, digital thermometer with alarm, training the staff, alternative storage arrangements, setting written protocols, labels and containers are worthwhile in the long run.

**Do’s for refrigerator**

1. Always keep the storage equipment (refrigerator) in cold room away from sunlight and 10 cm away from wall.
2. Keep the refrigerator leveled.
3. Connect the refrigerator through voltage stabilizer.
4. The power point should never be switched off.
5. Keep the vaccines neatly with space between the stacks. This is to allow free circulation of cool air.
6. Always keep the refrigerator locked and open only when necessary.
7. Defrost periodically; more than 1 cm of ice in the freezer compartment signals the need to defrost the refrigerator.
8. During defrosting transfer the vaccines to an insulated vaccine carrier or another refrigerator set to the correct temperature range.
9. Check the expiry dates and if nearing expiry, move them to the front of the refrigerator and use these lots first.

**Don’ts**

1. Do not keep any other object in refrigerator, like drinking water or eatables.
2. Do not store more than one month requirement at the peripheral centre.
3. Do not keep the expired vaccines.

**Storage recommendation for different vaccines in refrigerator**

- Always store all the vaccines at +2 and +8°C in the clinic or peripheral units.
Keep live viral vaccines such as OPV, measles, MMR, varicella in the first shelf of the refrigerator.

Keep the BCG and non-absorbed vaccines on the second shelf.

Place the DPT, DT, Td, TT and other vaccines on the third shelf.

Keep the sealed water bottles in the bottom shelf and door of the refrigerator.

Do not freeze diluents and preferably keep diluents next to its vaccine or mark it clearly if kept on a different shelf.

**Policy on use of opened vials of vaccine**

Opened multidose vials of OPV, DPT, DT, TT and Hepatitis B vaccines may be used in subsequent immunization session provided each of the following conditions are met:

1. Expiry date has not passed
2. Vaccines are stored under appropriate condition (+2 to 8°C)
3. Opened vials of vaccines which have been taken out of the health facility for immunization activities are discarded at the end of the day.
4. BCG, measles, MMR vaccines reconstituted must be discarded with in four hours

There are certain drawbacks of using domestic refrigerators for vaccine storage:

1. Temperature varies significantly every time when the door is opened.
2. Temperature rises during defrosting cycle in cyclical defrosting in frost free refrigerator.
3. Cabinet temperature is altered by ambient temperature.
4. Temperature monitoring by dial thermometer is crude and inaccurate.
5. All the corners and compartments do not have uniform temperature even on the same shelf.

6. In the modern refrigerator, the top shelf may not necessarily be the coolest part of the unit.²

A cold chain monitor card (CCM) approved by the WHO is always packaged with each consignment of vaccine supplied by UNICEF. CCM monitors the consignment of vaccine. Vaccine Vial Monitor (VVM) shows each vial of the vaccine how it has fared.³

Thus efficient vaccine storage management is an essential quality assurance measure for vaccine service providers.

The loss of vaccine effectiveness is cumulative and cannot be reversed if the cold chain is not maintained properly. Practically it is the duty of the health care providers to store and administer the vaccine in a proper way to maintain the safety and protectivity of the child.

**Points to Remember**

- **Order vaccine carefully.**
- **Store vaccine correctly.**
- **Always use the vaccine with earliest expiry date/old stock.**
- **Monitor and stabilize temperature.**
- **Safe guard the electrical supply to the refrigerator.**

**References**

ANTIVIRAL THERAPY IN CHILDREN

* Ajay Kalra
** Premasish Mazumdar

Abstract: Antiviral therapy has made huge strides in the last three decades. With advancements in understanding of viral pathophysiology newer and safer antivirals are being developed. At present antiviral agents are effective in the treatment or prevention of infections caused by herpes viruses, human immunodeficiency virus, respiratory syncytial virus, influenza A, influenza B, hepatitis B virus, hepatitis C virus, human papillomavirus, and lassa virus. Most of these drugs and many others being developed have limited data in the pediatric age group and it is the clinician’s responsibility to optimize the use of these drugs.

Keywords: Antiviral drugs, Children.

Viral infections have been always thought to be less amenable to treatment as compared to bacterial infections. As viruses take over the host machinery for replication, it was assumed that attacking viruses would lead to adverse effects on normal healthy cells. This central belief has been much dominant through most of the last century tempering the enthusiasm in the development of appropriate antiviral drugs.

The last three decades has seen great advancement in the development of effective and safe antiviral therapies. This has been possible because of advancement in microbiology and biotechnology which has led to identification of virus-specific pathways and enzymes, which in turn can be used as safe targets for antiviral medications. In general, antiviral drugs exert their effects by interfering with attachment, entry or uncoating of virus, thereby disabling their replication.1

The various classes of antiviral agents which act by different mechanisms of action as shown in Table I.

Although there are numerous viral ailments of significance, antiviral drugs are currently available for the treatment of a select few viral infections namely, Herpes virus infections (HSV, VZV, CMV), Respiratory virus infections (influenza A, influenza B, RSV), Hepatitis virus infections (HBV, HCV), Human papilloma virus infections and HIV infections.2

Antiviral agents used for treating herpesvirus infections

Antiviral therapy is established for the treatment and prevention of infections caused by four of the eight human herpesviruses (HHV) (HSV-1, HSV-2, VZV and CMV). Disease by herpes viruses are accentuated in high-risk, immunocompromised patients.2

Table II shows the clinical presentation and therapeutic agents used in herpetic infections.
Table I. Mechanism of action of antiviral agents

<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism of action</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleoside analogues</td>
<td>Monophosphorylated by viral enzyme, then triphosphorylated to active compound by cellular enzymes. Inhibits viral DNA polymerase</td>
<td>Acyclovir, Valaciclovir, Famciclovir, penciclovir, Ganciclovir, Valganciclovir</td>
</tr>
<tr>
<td>Nucleotide analogues</td>
<td>Diphosphorylated to active compound by cellular enzymes. Inhibits viral DNA polymerase</td>
<td>Cidofovir</td>
</tr>
<tr>
<td>Inorganic phosphate analogues</td>
<td>Noncompetitive inhibitor of viral DNA polymerase or HIV reverse transcriptase</td>
<td>Foscarnet</td>
</tr>
<tr>
<td>Tricyclic amines</td>
<td>Blocks M2 protein of influenza virus A, inhibiting initiation of viral replication</td>
<td>Amantadine, Rimantadine</td>
</tr>
<tr>
<td>Neuraminidase inhibitors</td>
<td>Inhibits influenza virus A and B neuraminidase, blocking release of progeny virus from infected cells</td>
<td>Oseltamivir, Zanamivir</td>
</tr>
<tr>
<td>Interferons</td>
<td>Induce production of more than two dozen effector proteins, leading to inhibition of viral penetration or uncoating, synthesis or methylation of mRNA, viral protein translation or viral assembly and release</td>
<td>Interferon alpha, Interferon beta, Interferon gamma</td>
</tr>
</tbody>
</table>

Cytomegalovirus (CMV)

CMV is a herpes virus and as such can cause congenital infection and primary infection. It can also establish a latent infection and reactivate, especially if there is altered cellular immunity. The treatment and prophylaxis of CMV infection is shown in Table III.

Congenital CMV infection: Ganciclovir is the most widely studied drug. Not recommended routinely for all babies with congenital CMV. The only RCT in neonates studied the effect of 6 weeks of IV Ganciclovir on hearing in 42 babies with CNS involvement. The study found that Ganciclovir prevented hearing deterioration at 6 months and may prevent hearing deterioration at 1 year of age. There have been other smaller studies looking at Ganciclovir use in congenital CMV, although promising data is insufficient for standard recommendations. Expert opinion favours Ganciclovir use in babies with significant liver or lung disease from congenital or acquired CMV infection at doses of 5mg/kg IV, 12 hourly for 2-3 weeks. Neutropenia is the only noted significant side effect and needs monitoring.

Post exposure prophylaxis for Varicella Zoster infection with immunoglobulin (VZIG)

Not routinely recommended for healthy children. Indicated in dose of 125U/10kg IM single dose up to a maximum of 625 units in the following conditions:
<table>
<thead>
<tr>
<th>Clinical syndrome</th>
<th>Antiviral agent of choice</th>
<th>Alternative choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal herpes</td>
<td>Acyclovir (IV) 20mg/kg/dose 8 hrly for 2-3 weeks</td>
<td>Acyclovir (IV) 5mg/kg/dose 8 hourly for 5-7 days</td>
</tr>
<tr>
<td>HSV encephalitis</td>
<td>Acyclovir (IV) 20mg/kg/dose 8 hrly in &lt;12 years for 2-3 weeks and 10-15mg/kg/dose 8 hrly in &gt;12 years for 2-3 weeks</td>
<td></td>
</tr>
<tr>
<td>HSV gingivostomatitis</td>
<td>Acyclovir (PO) 40-80mg/kg/day in 3-4 divided doses for 5-7 days.</td>
<td>Acyclovir (IV) 5mg/kg/dose 8 hourly for 5-7 days</td>
</tr>
<tr>
<td>First episode genital herpes</td>
<td>Acyclovir (PO) 40-80mg/kg/day in 3-4 divided doses for 5-10 days.</td>
<td>Valciclovir*</td>
</tr>
<tr>
<td></td>
<td>In adolescents 200mg five times a day for 5-10 days</td>
<td>Famciclovir (PO)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acyclovir (IV) 5mg/kg/dose 8 hrly x 5-7 days if severe</td>
</tr>
<tr>
<td>Recurrent genital herpes</td>
<td>Acyclovir (PO) 40-80mg/kg/day in 3-4 divided doses for 5 days.</td>
<td>Valciclovir (PO)</td>
</tr>
<tr>
<td></td>
<td>In adolescents 200mg five times a day for 5 days</td>
<td>Famciclovir (PO)</td>
</tr>
<tr>
<td>Suppression of genital herpes</td>
<td>Acyclovir (PO) 40-80mg/kg/day in 3-4 divided doses for 12 months.</td>
<td>Valciclovir (PO)</td>
</tr>
<tr>
<td></td>
<td>In adolescents 200mg five times a day for 12 months, re-evaluate after 12 months</td>
<td>Famciclovir (PO)</td>
</tr>
<tr>
<td>Herpetic whitlow</td>
<td>Acyclovir (PO) 40-80mg/kg/day in 3-4 divided doses for 5-7 days.</td>
<td>Acyclovir (IV) if severe &lt;12 yrs ; 10mg/kg/dose 8 hrly x 7 days; ≥ 12 yrs 5mg/kg/dose 8 hrly x 7 days</td>
</tr>
<tr>
<td></td>
<td>In adolescents 200mg five times a day for 5-10 days</td>
<td></td>
</tr>
<tr>
<td>Eczema herpeticum</td>
<td>Acyclovir (PO) 80mg/kg/day in 3-4 divided doses for 5-7 days.</td>
<td>Acyclovir (PO) 40-80mg/kg/day in 3-4 divided doses for 7-14 days; In adolescents 200mg five times a day for 7-14 days</td>
</tr>
<tr>
<td>Mucocutaneous infection in immuno-compromised host (mild)</td>
<td>Acyclovir (IV) ) &lt;12 yrs ; 10mg/kg/dose 8 hrly x 7 days; ≥ 12 yrs 5mg/kg/dose 8 hrly x 7 days</td>
<td>Acyclovir (PO)</td>
</tr>
<tr>
<td>Mucocutaneous infection in immuno-compromised host (mod-severe)</td>
<td>Acyclovir (IV) &lt;12 yrs ; 10mg/kg/dose 8 hrly x 7-14 days; ≥ 12 yrs 5mg/kg/dose 8 hrly x7-14 days</td>
<td></td>
</tr>
<tr>
<td>Prophylaxis in BMT recipient</td>
<td>Acyclovir (IV) autologous patients who are HSV seropositive 250mg/m²/dose 8 hourly</td>
<td>Famciclovir (PO)</td>
</tr>
<tr>
<td>Acyclovir resistant</td>
<td>Acyclovir resistant HSV keratitis/ keratoconjunctivitis</td>
<td>Cidofovir 5mg/kg IV every 2 weeks, with probenecid and hydration OR 3mg/kg IV, once weekly Vidarabine #</td>
</tr>
<tr>
<td>HSV keratitis/ keratoconjunctivitis</td>
<td>Foscarnet 40-60mg/kg/dose IV 12 hrly x 2-3 weeks Trifluridine (T) 1% solution 1 drop every 3 hrly for 2-3 weeks</td>
<td></td>
</tr>
</tbody>
</table>

IV= intravenous; PO= per orally; T= topical

*//**Insufficient clinical data to identify appropriate pediatric dose, # rarely used/available
Table III. Treatment and prophylaxis of opportunistic CMV infections

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Antiviral of choice</th>
<th>Alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinitis in AIDS patient</td>
<td>Valganciclovir 900 mg orally, 12 hourly for 2-3 weeks (for adolescents; no data in children)</td>
<td>Ganciclovir 5mg/kg IV, 12 hourly for 2-3 weeks; Cidofovir 5mg/kg IV every 2 weeks, given with probenecid and hydration OR 3mg/kg IV, once weekly (contraindicated if proteinuria &gt; 2+ or creatinine clearance &lt;55mL/min) Foscarnet 80 mg/kg IV, 12 hourly for 2-3 weeks. (actual dose based on creatinine clearance) Ganciclovir ocular insert</td>
</tr>
<tr>
<td>Pneumonitis, colitis, esophagitis in immuno-compromised patients</td>
<td>Ganciclovir 5mg/kg IV, 12 hourly for 2-3 weeks</td>
<td>Foscarnet 80 mg/kg IV, 12 hourly for 2-3 weeks. (actual dose based on creatinine clearance) Cidofovir 5mg/kg IV every 2 weeks, given with probenecid and hydration or 3mg/kg IV, once weekly Valganciclovir 900 mg orally, 12 hourly for 2-3 weeks (for adolescents; no data in children)</td>
</tr>
</tbody>
</table>

Prophylaxis options for solid organ transplant recipients:
- Ganciclovir 10mg/kg IV, thrice weekly or 5 mg/kg IV, five times weekly
- Foscarnet 90-120mg/kg/day IV, five times weekly (actual dose based on creatinine clearance)
- Cidofovir 5mg/kg IV every 2 weeks, given with probenecid and hydration or 3mg/kg IV, once weekly
- Valganciclovir 900 mg orally, daily (for adolescents; no data in children)

- Neonate whose mother develops chickenpox 7 days or fewer before delivery to 2 days after delivery regardless of maternal history
- Premature infants(<28 weeks/<1000gms) with post natal exposure irrespective of maternal history
- Premature infant 28 weeks gestation or more with no history of maternal chickenpox or no VZV-specific IgG.
- Immunocompromised child (with impaired Tcell immunity), with no prior history of varicella or VZV immunization and no VZV-specific IgG.

Salient features of the drugs against Herpes viruses

Nucleoside or nucleotide analogue

**Acyclovir**: Acyclovir needs activation by the virus-encoded enzyme thymidine kinase (TK). Activity against CMV is poor because CMV does not have a unique TK and CMV DNA polymerase is poorly inhibited by acyclovir triphosphate. The oral bioavailability of acyclovir is poor, with only 15% to 30% of the oral formulation being absorbed. Acyclovir is widely distributed, with high concentrations attained in kidneys, lung, liver, heart and skin vesicles; concentrations in
the cerebrospinal fluid are about 50% of those in the plasma. Acyclovir crosses the placenta and accumulates in breast milk. Dose modification is required in cases of renal insufficiency. Concomitant administration of probenecid prolongs acyclovir’s half-life. Oral acyclovir sometimes causes mild gastrointestinal upset, rash and headache. If it extravasates, intravenous acyclovir can cause severe skin necrosis. If given by rapid intravenous infusion or to poorly hydrated patients or patients with pre-existing renal compromise, it causes reversible nephrotoxicity due to formation of acyclovir crystals precipitating in renal tubules and causing an obstructive nephropathy. High doses of intravenous acyclovir in neonates and prolonged use of oral acyclovir after neonatal disease have been associated with neutropenia. The major side effect of acyclovir is neurotoxicity manifesting as lethargy, altered sensorium, hallucinations, tremors, myoclonus, seizures and extrapyramidal signs. These usually resolve spontaneously on discontinuation of the drug.

Valaciclovir: Valaciclovir is the L-valyl ester of acyclovir that is converted rapidly to acyclovir after oral administration by first-pass metabolism in the liver. It has a safety and efficacy profile similar to acyclovir, but offers potential pharmacokinetic advantages. Valaciclovir dosages in children are not established. Because valaciclovir is metabolized to acyclovir in the bloodstream, antiviral resistance mechanisms are identical to those of acyclovir.

Cidofovir: Cidofovir was first approved for use in AIDS-associated retinitis caused by CMV. In addition to its excellent activity against CMV, cidofovir is active against HSV and VZV, including ganciclovir-resistant and foscarnet-resistant CMV isolates and acyclovir-resistant

<table>
<thead>
<tr>
<th>Chicken pox</th>
<th>Antiviral of choice</th>
<th>Alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chickenpox, healthy child</td>
<td>No antiviral needed</td>
<td>Acyclovir (PO) ≥ 2 yrs and &lt; 40kg: 20mg/kg/dose 4 times/day x 5 days &gt;40kg: 800mg 5 times /day x 5 days</td>
</tr>
<tr>
<td>Chickenpox, immuno-compromised child</td>
<td>Acyclovir (IV) 10mg/kg/dose 8 hrly for 7-10 days</td>
<td></td>
</tr>
<tr>
<td>Zoster (not ophthalmic branch of trigeminal nerve), healthy child</td>
<td>No antiviral needed</td>
<td>Acyclovir (PO) ≥ 2 yrs and &lt; 40kg: 20mg/kg/dose 4 times/day x 7-10 days &gt;40kg: 800mg 5 times /day x 7-10 days</td>
</tr>
<tr>
<td>Zoster (ophthalmic branch of trigeminal nerve), healthy child</td>
<td>Acyclovir (IV) 10mg/kg/dose 8 hrly for 7-10 days</td>
<td>Valaciclovir 20mg/kg 3 times a day x 7-10 days*</td>
</tr>
<tr>
<td>Zoster immunocompromised</td>
<td>Acyclovir (IV) 10mg/kg/dose 8 hrly for 7-10 days</td>
<td></td>
</tr>
</tbody>
</table>

*Corresponds to oral acyclovir 20mg/kg/ 5 times a day

Table IV. Varicella zoster virus clinical presentation and therapeutic agents

For more detailed information on the clinical presentation and therapeutic agents, please refer to Table IV.
and foscarnet-resistant HSV isolates. Aggressive intravenous prehydration and coadministration of probenecid are required with each cidofovir dose. When phosphorylated, it selectively inhibits viral DNA polymerase thereby inhibiting viral replication. Only 2% to 26% of cidofovir is absorbed after oral administration, requiring that cidofovir be administered intravenously in the clinical management of patients. The principal adverse effect is nephrotoxicity. Other toxicities include neutropenia, ocular hypotony and metabolic acidosis. Cidofovir is carcinogenic, teratogenic and causes hyposperma in animal studies. The safety and efficacy of cidofovir in children have not been studied and its use warrants caution.

**Famciclovir and Penciclovir**: Famciclovir is the oral prodrug of penciclovir. The spectrum of activity of penciclovir and famciclovir against herpesviruses is similar to that of acyclovir. In addition to HSV, penciclovir is active in vitro against VZV, EBV and HBV. Famciclovir is effective in the treatment and suppression of genital herpes. Topical penciclovir reduces time to healing and duration of pain in patients with recurrent herpes labialis. Famciclovir also is effective in the treatment of herpes zoster. The oral bioavailability of penciclovir is about 70%. Dosage reduction of famciclovir is recommended for patients with compromised renal function. Side effects like nausea, diarrhea, and headache are seen. The safety and efficacy of famciclovir and topical penciclovir in children have not been established.

**Ganciclovir**: Ganciclovir’s greatest in vitro activity is against CMV. It is also as active as acyclovir against HSV-1 and HSV-2 and almost as active against VZV. Ganciclovir is indicated for the treatment and prevention of life-threatening and sight-threatening CMV infections in immunocompromised patients. Ganciclovir also is useful for prevention of CMV infections in high-risk immunocompromised subjects. Ganciclovir has shown limited benefit in the treatment of neonates with congenital CMV infection. It has shown some benefit in decreasing the hearing loss in children with congenital CMV. As oral bioavailability of ganciclovir is poor needs intravenous administration. Dosage reduction is necessary in persons with impaired renal function. Myelosuppression is the most common adverse effect of ganciclovir. Ganciclovir has been shown to be mutagenic, carcinogenic, and teratogenic and thus its use in pediatric patients warrants caution.

**Valganciclovir**: Valganciclovir is a L-valine ester prodrug of ganciclovir and as such has the same mechanism of action, antiviral spectrum, and potential for development of resistance as ganciclovir. As it is well absorbed after oral administration, it may represent a favorable alternative to intravenously administered ganciclovir. The most common side effects are diarrhea, nausea, neutropenia, anemia and headache.

**Trifluridine**: Trifluridine is a pyrimidine nucleoside active in vitro against HSV-1 and HSV-2 (including acyclovir-resistant strains), CMV and certain adenoviruses. Trifluridine is approved only for topical use in the management of primary keratoconjunctivitis and recurrent keratitis caused by HSV.

**Vidarabine**: Vidarabine was the first antiviral agent to be developed and licensed for use against herpesviruses. However use of systemic vidarabine has been replaced by acyclovir, because of acyclovir’s more favorable toxicity profile and greater ease of administration.

**Inorganic phosphate analogues**

**Foscarnet (PFA, Foscavir)**: Foscarnet inhibits all known human herpesviruses, including
Acyclovir resistant HSV and VZV strains and most ganciclovir-resistant CMV isolates. It also is active against HIV. The safety and efficacy of foscarnet in pediatric patients has not been established. Foscarnet is effective for therapy of life-threatening and sight threatening CMV infections in immunocompromised patients. Foscarnet also is effective in the therapy of CMV infections caused by ganciclovir resistant strains of CMV and has been used successfully in the management of disease caused by acyclovir-resistant HSV isolates. The most common adverse effects of foscarnet are nephrotoxicity and derangements in calcium metabolism. It has potential dental and bone marrow toxicity.

**Antiviral agents used for treating respiratory virus infections**

Infection of the respiratory tract is one of the most common causes of mortality and morbidity in children. Of the respiratory tract viral pathogens, licensed therapies currently exist for influenza A, influenza B and RSV.

Rimantadine: Same dose for treatment and prophylaxis.

In <40 kg 5mg/kg/day in 2 divided doses. In >40kg 100mg twice daily. For treatment give for 5-7 days. For prophylaxis give for at least 10 days after known exposure.

Amantadine: prophylaxis and treatment 1-9 years: 5mg/kg/day in 1-2 divided doses (max 150mg/day) ≥10-12 years : 5mg/kg/day in 1-2 divided doses (max 200mg/day). Treatment is started within 2 days of symptoms and given for 5 days or for 24-48 hours after patient becomes asymptomatic. Prophylaxis is given for 6 weeks after first influenza A vaccine virus dose or until 2 weeks after second dose of vaccine. A 10 days course after exposure is advised.

Oseltamivir: Treatment should begin within 2 days of onset of flu symptoms for 5 days In children ≥1-12 years: ≤15 kg: 2mg/kg/dose(max30mg) twice daily; > 15-23kg: 45mg twice daily; >23-40kg: 60mg/dose twice daily; >40 kg:75mg/dose twice daily.

Prophylaxis of influenza: children ≥13 years: 75mg/dose once daily for at least 7 days or upto 6 weeks. Begin within 2 days of exposure.

Zanamivir: 10mg by inhalation, twice daily x 5 days

Ribavirin aerosol: use with SPAG-2 (small particle aerosol generator) at concentration of

<table>
<thead>
<tr>
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<th>Antiviral of choice</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Influenza A</strong></td>
<td>Treatment</td>
<td>Rimantadine (PO)</td>
</tr>
<tr>
<td></td>
<td>Prophylaxis</td>
<td>Amantadine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oseltamivir (&gt;1yr old)</td>
</tr>
<tr>
<td><strong>Influenza B</strong></td>
<td>Treatment</td>
<td>Rimantadine (PO)</td>
</tr>
<tr>
<td></td>
<td>Bronchiolitis or pneumonia in high risk host</td>
<td>Amantadine Oseltamivir (&gt;1yr old)</td>
</tr>
<tr>
<td><strong>Respiratory syncytial virus</strong></td>
<td>Bronchiolitis or pneumonia in high risk host</td>
<td>Zanamivir (&gt;7yrs old)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zanamivir (7 yrs old)</td>
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</table>
20mg/ml. Continuous aerosolization for 12-18 hours/day for 3-7 days. For intermittent aerosolization use 60mg/ml for 2 hours duration three times a day.

**Salient features of drugs against respiratory viruses**

**Tricyclic amines**

Amantadine and rimantadine: Amantadine and rimantadine are active only against influenza A virus; rimantadine is 4-fold to 10-fold more active than amantadine. Although these agents are useful for the prevention and treatment of infections caused by influenza A virus, vaccination against influenza is a more cost-effective means of reducing disease burden. Amantadine and rimantadine are well absorbed after oral administration. Substantial dose adjustments of amantadine are necessary in persons with impaired renal function. In general, side effects are less frequent and less severe with rimantadine. Common side effects are dose-related gastrointestinal and CNS symptoms. Long-term amantadine therapy has been associated with vision loss, hypotension, urinary retention, peripheral edema and congestive heart failure.

**Neuraminidase inhibitors**

The biologic action of this class of antiviral agents results from inhibition of influenza neuraminidase. Neuraminidase inhibitors are active against all strains of influenza type A and influenza type B viruses.

**Oseltamivir (Tamiflu)**

Oseltamivir is an oral antiviral medication that is effective in the prevention and treatment of infections caused by either influenza A or influenza B viruses. Oseltamivir is licensed for use in children one year of age and older. Oseltamivir is an ethyl ester prodrug, hydrolyzed by hepatic esterases to biologically active oseltamivir carboxylate. The oral bioavailability of oseltamivir is about 75%; coadministration with food does not affect absorption. The half-life of oseltamivir carboxylate is 6 to 10 hours; it is eliminated by glomerular filtration and tubular secretion. Dose adjustment is recommended for patients with impaired renal function. About 10% of patients treated with oseltamivir experience nausea without vomiting, and an additional 10% have nausea with vomiting. These side effects generally are mild and usually occur on the first 2 days of therapy. Insomnia and vertigo also occur occasionally.

**Zanamivir (Relenza)**

Inhaled zanamivir is effective in the prevention and treatment of infections caused by either influenza A or influenza B viruses. Zanamivir is administered by inhalation because it has poor oral bioavailability. Less than 15% of an inhaled dose of zanamivir distributes to the airways and lungs. About 10% of an inhaled dose of zanamivir is absorbed. The plasma half-life of zanamivir ranges from 2.5 to 5 hours; drug is excreted unchanged in the urine. No adjustment in dosing is necessary for renal insufficiency because of the limited amount of systemically absorbed drug. Zanamivir is well tolerated. A decline in pulmonary function and bronchospasm have been reported in some patients with underlying airway disease.

**Nucleoside analogues**

**Ribavirin**

Ribavirin is available for inhaled use for the therapy of severe lower respiratory tract infection caused by RSV. It also is available as an oral and intravenous formulation for the therapy of hepatitis and lassa fever. Ribavirin in combination with interferon alfa (Rebetron) is useful in the management of infections caused
by HCV. Ribavirin is active against a wide range of RNA and DNA viruses, including myxoviruses, paramyxoviruses, arenaviruses, bunyaviruses, herpesviruses, adenoviruses, poxviruses, and retroviruses. The aerosolized formulation of ribavirin (Virazole) and the oral formulation in combination with interferon alfa (Rebetron) are approved for use. Aerosolized delivery of ribavirin is accomplished with a small-particle aerosol generator (SPAG) that delivers a steady flow of small particles. The oral bioavailability of ribavirin is about 40%. Ribavirin is concentrated in red blood cells, and high concentrations of the drug are associated with reversible anemia, hyperbilirubinemia and hyperuricemia.

**Antiviral agents used for treating hepatitis viruses and papilloma viruses**

Antiviral agents in use for the treatment of HBV and HCV include interferon (HBV and HCV), lamivudine (HBV), adefovir (HBV) and ribavirin (in combination with interferon) (HCV). HPV infections are among the most prevalent of sexually transmitted diseases. HPV infections of the genital tract are of medical and public health concern because of their propensity to lead to the development of cervical cancer, and the transmission to the respiratory tract of a newborn child, can lead to juvenile-onset recurrent respiratory papillomatosis.

**Salient features of antiviral agents against hepatitis viruses and papilloma viruses**

**Interferons and pegylated interferons**

Interferons are a family of nonspecific regulatory proteins associated with a variety of antiviral, antiproliferative and immunomodulating activities. There are two major types of interferons. Type 1 (α and β) interferons are secreted by all nucleated cells after viral infection; interferon-α is predominantly produced by virus-infected leukocytes, and interferon-β is produced by fibroblasts. Type II interferon (γ) is the product of antigen-stimulated or mitogen stimulated lymphocytes. Interferons do not have direct antiviral activity, but rather exert their antiviral effects by inducing production of more than two dozen effector proteins in exposed cells. Antiviral activity also can be facilitated by the complex interactions between interferons and other components of the immune system, resulting in modification of host response to infection. Interferons are active against a broad range of viruses, although, in general, they are more active against RNA viruses than DNA viruses.

Interferon alfa therapy is effective in the management of HBV and HCV infections. The combination of oral ribavirin with interferon alfa (Rebetron) improves the efficacy of interferon alfa. Data suggest that the combination of pegylated (long-acting) interferon plus ribavirin produces additional significant improvements in the rate of sustained virologic response compared with nonpegylated interferon plus ribavirin. Interferon alfa also is recommended for the therapy of recalcitrant anogenital warts caused by papillomaviruses. Therapy may be administered directly into lesions or systemically. The most commonly accepted adjuvant therapy for juvenile-onset recurrent respiratory papillomatosis is the systemic administration of interferon alfa-2a. More than 80% of interferon alfa is absorbed after intramuscular or subcutaneous injection; plasma levels peak at 4 to 8 hours. Although the plasma half-life is only 2 to 4 hours, antiviral activity peaks at about 24 hours, slowly decreasing over the next 6 days. Side effects include influenza-like illness, with fever, chills, headache, myalgia, arthralgia, and gastrointestinal disturbances. These symptoms typically appear during the first week of therapy and remit with continued therapy, rarely necessitating
therapy discontinuation or dosage modification. The major therapy-limiting toxicities of systemically administered interferon are neuropsychiatric complications and bone marrow suppression.

**Nucleoside and nucleotide analogues**

Ribavirin (Rebetron) : Oral ribavirin has been coadministred with either interferon alpha or pegylated interferon for the treatment of HCV infections in adults. Current therapeutic regimens in adults result in long-term improvement of disease in approximately one third of adults treated. No consensus exists, however, on the treatment of children with chronic HCV infection. Efficacy using interferon plus ribavirin is greatest for non–type 1 genotypes.

Adefovir : Adefovir is an inhibitor of HBV viral replication. It also has in vitro activity against HIV, although it has not been shown to suppress HIV RNA in patients. Adefovir is indicated for the treatment of chronic HBV in adults with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases or histologically active disease. Oral bioavailability of adefovir is approximately 60%. Adefovir concentrations are not affected by administration with food. Persons with moderately or severely impaired renal function or persons on hemodialysis require adefovir dosage modification. Pharmacokinetic studies have not been performed in children. Lactic acidosis and severe hepatomegaly with steatosis have been reported with the use of nucleoside analogues alone or in combination with other antiretrovirals.

**Nucleoside reverse transcriptase inhibitors**

Lamivudine (Epivir, 3TC) : Lamivudine inhibits the reverse transcriptase of HIV and HBV. Lamivudine has been used for the treatment of chronic HBV infection in children and adults. Lamivudine-resistant HBV mutants occur in one third of subjects by the end of 1 year of therapy and in two thirds by the end of 4 years of treatment. Lamivudine resistance usually is manifest clinically as breakthrough infection, defined as reappearance of HBV DNA in serum after its initial disappearance.

**Antiviral agents used for treating HIV**

There are four classes of compounds currently are licensed for administration to patients with HIV infection: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease Inhibitors (PI), and, most recently, fusion inhibitors (FI). Among the protease inhibitors there are some which are used as boosted protease inhibitors in which a small dose of the PI ritonavir is used together resulting in a far higher concentration of the active drug. A further class of its integrase inhibitors are currently under development. The antiretrovirals commonly used in children are shown below.

**When to start HAART?**

Highly active anti-retroviral therapy (HAART) has been associated with a significant fall in mortality from HIV infection, in rate of progression to AIDS, and in incidence of opportunistic infection. There is no controversy that a child with AIDS should be started on HAART if available although there are issues of adherence, adverse reactions and drug interactions. There is no good evidence that starting all asymptomatic HIV infected children on HAART improves survival, and there is at least a theoretical risk that starting HAART early might increase the risk of emergence of resistant HIV strains. In asymptomatic children standard recommendations as to when to start HAART have been lacking largely due to conflicting results of meta analysis trying to pinpoint reliable indicators of disease progression. A large meta
analysis in children showed that CD4 T-cell percentage (CD4%) was found to be more reliable than viral load in predicting death or progression to AIDS. CD4% was more reliable than absolute CD4 count in younger children. The risk of death increased sharply when CD4% <10%. The risk of AIDS increased when CD4% was < 15% . Other meta analysis have shown children CD4 counts to be more reliable predictors of outcome than CD4% and viral load especially in the older children. Most experts recommend that it is reasonable not to start HAART for asymptomatic HIV infected children > 4 years old, unless the child develops a significant opportunistic infection or an AIDS defining illness or until the CD4 counts fall rapidly or falls below 300 cells/μL, or CD4% falls below 15%. In infants it is even more difficult to predict disease progression as HIV-1 RNA and CD4 count and percentage are poor predictors of disease progression and death during infancy. Currently most experts recommend starting antiretroviral therapy for all infected children in the first year of life.

The usual combination for initial anti-retroviral therapy is:

**Two NRTIs plus one NNRTI** OR **Two NRTIs plus one boosted PI**

The recommended doses of antiretrovirals are sometimes expressed by weight(dose/kg) and sometimes by surface area(dose/m²). This reflects the lack of pharmacokinetic data in children. As recommendations change frequently it is prudent to consult one of regularly updated web sites.9,10 In addition the web sites should be consulted for adverse drug reactions associated with each drug. It is imperative that antiretrovirals are not started or changed without expert opinion.
Summary

Antiviral agents are being increasingly developed against various viral pathogens. Most drugs have limited data in the pediatric age group and it is the clinician’s responsibility to optimize the use of these powerful but sometimes toxic drugs. Antiviral drugs are currently available for the treatment of herpesvirus infections (HSV, VZV, CMV), respiratory virus infections (influenza A, influenza B, RSV), hepatitis virus infections (HBV, HCV), HPV infections and HIV infections. A major challenge with increasing anti viral use would be the prevention of emerging resistance especially in the immunocompromised with prolonged use. Inspite of these concerns the future of antiviral therapeutics in children is bright but needs a rational and evidence based approach to avoid the problems which plague antibacterial chemotherapy.

Points to Remember

• **At present effective treatment and prophylactic antiviral therapy exist against herpes viruses, human immunodeficiency virus, respiratory syncytial virus, influenza A, influenza B, hepatitis B virus, hepatitis C virus, human papillomavirus and lassa virus.**

• **Most of these drugs don’t have pharmacokinetic data in the pediatric age group and thus needs caution and discretion before use.**

• **Emergence of resistance would be a major challenge in the future.**

• **Judicious and evidence based use of antiviral drugs are needed to prevent them from the problems which antibacterial therapy faces today.**

References


ALOPECIA AREATA

* Jayakar Thomas
** Parimalam Kumar

Abstract: Alopecia areata (AA) is a common dermatosis in children characterized by a chronic and unpredictable course. Treatment options aim at hair regrowth and control of remissions. The evaluation of the effectiveness of various existing therapeutic methods is confined by the lack of consensus on a grading system for AA, as well as the absence of a treating algorithm depending on the severity of AA. Therapeutic agents used in the treatment of AA include topical and systemic corticosteroids, minoxidil, anthralin, phototherapy and topical immunotherapy. Intralesional corticosteroid injections are widely used as therapy for patchy alopecia exhibiting good efficacy and tolerance by patients. Topical immunotherapy with the use of diphencyprone or squaric acid dibutylester has well-proven efficacy both in localized and extended disease. Other modalities, such as topical calcineurin inhibitors and biologic agents, have been used with limited success.

Keywords: Alopecia, Children, Therapy.

Alopecia areata (AA) is a relatively common dermatosis of autoimmune pathogenesis, characterized by nonscarring hair loss in an unpredictable course. It affects males and females equally, most commonly of young age and has a serious impact on social life and self-esteem of children and grown-ups alike. Consequently, AA represents an intriguing therapeutic challenge for dermatologists.

Clinical features

Alopecia areata usually manifests as a well-demarcated round or oval patch of hair loss that can be isolated or multiple (patchy AA). The skin of the affected area shows no visible signs of alteration and appears normal. The lesion usually expands in a circumferential way and the periphery may contain thick broken-off exclamation point hair easily observed through a hand lens. Hairs can be easily removed with a light pull in cases of an expanding lesion. A sign of remission is the white short vellus-type hair that may develop in the center of the patch. The scalp is the most common site affected by AA.

Patchy AA can be classified as localized or extensive according to the number and surface of lesional patches. A 25% total hair loss is recognized by some authors as an accepted borderline between those two forms in terms of management and prognosis. Alopecia totalis (AT) occurs when scalp and face hair such as eyebrows, eyelashes and beard are affected, while the term alopecia universalis (AU) refers to cases of entire body hair loss. Ophiasis pattern refers to AA extending along the posterior occipital and temporal regions of the scalp. Nail involvement
is present in about 20% of cases in features such as nail pitting, trachyonychia, Beau’s lines, koilonychia, onychomadesis, onychorrhexis and punctuate or transverse leukonychia.

**Histopathology**

Histopathology of AA is characterized mainly by follicular inflammatory infiltration. In the acute stage of AA the infiltration is predominant around an increased number of catagen and telogen follicles and the peribulbar lymphocytic accumulation has the characteristic pattern of ‘swarms of bees’. In the chronic stage, the main findings are the miniature type of hair follicles, with abnormal hair only reaching the infundibulum. Inflammatory infiltration may be absent in longstanding inactive AA. Trichoscopy is also useful in distinguishing between active and long standing AA. Characteristic trichoscopic features of AA are black dots, tapering hairs (exclamation mark hairs), broken hairs, yellow dots and short vellus hairs.

**Management**

Clinical classification has a significant impact on prognosis as ophiasis and AT and AU has significantly lower response rates. Patients presenting with active stage of AA benefit more of more aggressive treatment regimens.

Limited evidence-based knowledge harbors controversies in clinical treatment guidelines. Even though remarkable efforts in that direction have been made in the last few years, no general consensus has been achieved. Clinical guidelines are systematically developed statements in order to assist clinician and patient decisions about appropriate healthcare for specific clinical circumstances and should be based on high-quality evidence if available. Solid knowledge about the efficacy of a treatment can be verified by double-blind, placebo-controlled studies in a sufficient number of patients. In the case of AA, there is a variety of references from trial-based reviews to scarce reports and letters, showing that treatment of AA is mainly based on expert and experienced clinical opinion. This article summarizes the vast majority of different treatments available, topical or systemic, based mainly on published trials.

Therapies of AA in children most commonly include intraleisonal corticosteroid injections, corticosteroid creams with or without occlusion, systemic corticosteroids, minoxidil, anthralin, and topical immunotherapy though phototherapy. There is also a variety of agents that have been used with variable success in small groups of individuals. The choice of treatment always depends on patient’s age (children do not always tolerate side effects or painful and irritating therapies), extent of disease and both the physician’s and the patient’s personal preference.

**Topical corticosteroids**

Potent topical corticosteroids (mometasone/betamethasone) are widely used for the treatment of AA in children, even though their clinical efficacy is still controversial. It has been suggested that topical corticosteroids reduce the inflammatory response in AA.

**Intraleisonal corticosteroids**

Depot corticosteroids injected intraleisonally are preferred by many dermatologists in cases of AA involving less than 50% of the scalp. The basic concept of treatment is to maximize the corticosteroid effect on perifollicular inflammation by penetrating the epidermis barrier. Triamcinolone acetonide 5 mg/ml, is most commonly used by dermatologists. While the method is effective in localized AA, it has less applicability in more generalized types because of the dose of steroid needed and inefficiency in rapidly progressive AA.
Diphencyprone and squaric acid dibutylester

Diphencyprone (DPCP) represents a hallmark in AA treatment because its introduction produced reasonable aspirations for effective treatment of generalized AA. It has been described in the literature since 1972 as a potent contact allergen in both humans and animals. Even though topical immunotherapy with DPCP is considered as one of the most effective treatments of AA, success rates vary in different studies.

Like diphencyprone, squaric acid dibutylester (SADBE) is a nonmutagenic irritator, but a less stable one. Assessment of efficacy is based on various trials showing a similar treatment response in patients with moderate and serious AA.

Minoxidil

Minoxidil is an antihypertensive vasodilator also known for its ability to slow or stop hair loss and promote hair regrowth. The mechanism by which minoxidil promotes hair growth is not fully understood, although it has been widely used for almost 40 years as treatment for various types of alopecia. Topical minoxidil potentially shortens telogen phase, causing premature entry of resting hair follicles into anagen phase. The triggering effect of minoxidil has been attributed to the opening of potassium channels by minoxidil sulfate. In vitro effects of minoxidil include stimulation of cell proliferation, inhibition of collagen synthesis, stimulation of vascular endothelial growth factor and prostaglandin synthesis.

Calcineurin inhibitors

Tacrolimus (also known as FK-506) is a macroline immunosuppressive agent that inhibits calcineurin and thus reduces IL-2 production by T cells. It is used as a topical preparation in the treatment of severe atopic dermatitis and vitiligo. Despite initial encouraging results of topical tacrolimus in experimental bald animal models, no hair regrowth was achieved in children with AA.

Pimecrolimus is an ascomycin macrolactam product that exhibits both anti-inflammatory and immunomodulatory qualities. It prevents calcineurin-mediated dephosphorylation of the nuclear factor of activated T cells, which inhibits synthesis of Th1 and Th2 cytokines from T lymphocytes. Although during recent years the experimental use of pimecrolimus in AA in mice and rat models has given promising results, this has not been confirmed in clinical trials in human AA.

Imiquimod

Imiquimod is a potent immune response modifier and antiproliferative agent widely used in the treatment of skin cancers, genital warts and actinic keratoses. Early reports have been vague about its efficacy in terms of AA.

Systemic corticosteroids

Systemic corticosteroids have enjoyed a fair share of popularity in the treatment of AA because of their immunosuppressant properties. It is widely believed that long-term treatment with corticosteroids will produce regrowth of hair in some individuals, mostly those having localized AA rather than AU/AT. It is observed that in most children, continuous treatment is needed to maintain the achieved hair growth leading to side effects.

Cyclosporin

Cyclosporin A (CsA) is an immunosuppressant drug and a useful therapy in several pathologies where cellular immunity, especially CD4+ T lymphocytes, are causatively implicated.
One of known side effects of CsA is hypertrichosis. CsA efficacy in AA alone or in combination with other agents through uncontrolled studies in small groups of children shows varied results.

**Other forms of therapy**

These include photodynamic therapy (PDT), biologic agents, antidepressants, azathioprine, methotrexate, sulfasalazine, Excimer Laser, infrared irradiation, and hair transplantation.\(^9\,10\)

**Points to Remember**

- **Alopecia areata (AA) is a chronic disease with an unpredictable course. Pathogenesis is still under investigation, although an autoimmune mechanism has a key role.**

- **Lack of universal consensus in AA grading, small numbers of double-blind clinical trials and the considerable rate of spontaneous remissions, as well as simultaneous hair loss and hair growth in different regions of the same scalp in many cases, make evaluation of therapeutic results difficult.**

- **Diphencyprone seems to have efficacy both in localized and extensive AA. An evidence-based treatment schedule for maintenance of remissions must be pursued.**

- **Systemic corticosteroid administration can produce good results with minimal side effects in serious cases of AA. Topical or intralesional corticosteroids may be useful in milder forms of AA.**

- **Other forms of treatment include photodynamic therapy (PDT), biologic agents, antidepressants, azathioprine, methotrexate, sulfasalazine, Excimer Laser, infrared irradiation, and hair transplantation.**

**References**

Brain tumors are among the common malignancies in children and the posterior fossa is the most common region of the brain affected. The posterior fossa consists of the cerebellum and the brainstem. Superiorly it is bounded by the tentorium and inferiorly by the occipital bone. As such, the lack of space causes an early clinical presentation. About a quarter of posterior fossa masses are PNET (primitive neurectodermal tumors). In the posterior fossa location the tumor was formerly known as medulloblastoma. It is twice as common in male children. The site of origin is the ventricular roof or the cerebellar vermis immediately behind the ventricular roof. Consequently the medulloblastoma is a midline cerebellar mass. It is highly cellular and so appears as a hyperdense mass in plain CT. (Fig.1) shows a rounded homogenous midline lesion in the location of the fourth ventricle. In (Fig.2) it is brightly enhancing. There are no areas of hemorrhage or cyst formation and no calcification. These are features that help in differential diagnosis. Medulloblastoma can cause CSF dissemination and contrast CT helps to search for enhancement in the cisterns.

The other tumor in the posterior fossa that is equally common is the astrocytoma and here it is the juvenile pilocytic astrocytoma. This is a special type of astrocytoma that has a well circumscribed pattern of growth. It is not infiltrative. Therefore it presents with a well defined margin. It is usually partly cystic, sometimes entirely cystic with a small peripheral nodule. The solid nodule may show enhancement and calcification. (Fig.3) shows a cystic astrocytoma in the left cerebellar hemisphere. (Fig.4 and 5) shows another appearance of astrocytoma. The plain CT shows a vague mass lesion in the right cerebellar hemisphere with a solid peripheral calcific nodule on the right. On contrast examination (Fig.5) a well defined, enhancing thick wall is seen. (Fig.6) is a contrast enhanced image of a central mass but if you see carefully it is a little to the right of the midline. It is hypodense mass and shows multiple peripheral nodular calcifications. It shows enhancement that is not homogenous indicating areas of necrosis. Parasagittal location, hypodensity, inhomogenous appearance due to areas of degeneration, patchy enhancement, and the presence of calcification favour astrocytoma. Another tumor with cyst and nodule appearance in the posterior fossa is the hemangioblastoma. But these tumors present in middle age. Earlier presentation is associated with Von Hippel Lindau syndrome. Hemangioblastoma can also be complex with a heterogenous appearance in
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<th>Fig.1. Medulloblastoma-hyperdense midline cerebellar mass</th>
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<td>Fig.2. Medulloblastoma contrast CT. densely enhancing midline mass. Arrow points to 4th Ventricle</td>
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<td>Fig.3. Cystic astrocytoma in left cerebellar hemisphere</td>
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<td>Fig.4. Astrocytoma with calcific nodule(arrow)- plain CT</td>
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<td>Fig.5. Astrocytoma contrast CT (same patient as in Fig 4)</td>
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<td>Fig.6. Astrocytoma showing in homogenous enhancement and nodular calcifications</td>
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CT. In MR, there will be a heterogeneous solid intraaxial mass with multiple focal areas of hyperintensity due to blood products from small internal hemorrhages (methemoglobin) and multiple curvilinear hypointensities representing serpigenous vessels.

Children may also present with brainstem gliomas. These are also astrocytomas and typically arise from the pons and rarely in the medulla or the midbrain. Pontine astrocytomas, unlike the pilocytic astrocytoma, are typically diffusely infiltrating masses. They usually present with relatively minor symptoms since the infiltration is typically not accompanied by destruction of the structure of the brainstem. Cranial nerve findings, may be relatively minimal or absent. (Fig.7) shows a hypodense mass in the pons. The fourth ventricle is compressed posteriorly. The bright spot anterior to the pons is the basilar artery. On contrast administration, (Fig.8) the basilar artery is enhanced and brighter but the mass does not enhance. Pontine astrocytomas may either be low-grade tumors or high-grade tumors and the presence of contrast enhancement may suggest a higher grade lesion. (Fig.9) is the MRI picture showing hypointense
mass in a T1 weighted image. The fourth ventricle is displaced posteriorly. In T2 weighted images (Fig.10) the mass is hyperintense. The diagnosis of pontine gliomas is possible with imaging. PET imaging can also be used. Biopsy is not indicated.

Another tumor presenting in childhood and mostly in the posterior fossa is the ependymoma. These are benign glial tumors that arise from the ependymal lining within the fourth ventricle. In contrast to the other midline tumor (the medulloblastoma) the ependymoma typically arises from the ventral portion or floor of the fourth ventricle. Therefore, a more ventral or anterior location may suggest an ependymoma, whereas a more posterior location or a relationship to the ventricular roof, may favor the diagnosis of medulloblastoma. Another feature of the ependymoma is that it tends to assume the shape of the fourth ventricle, forming a cast of the dilated ventricular lumen. Medulloblastoma is often a more spherical mass. The ependymoma may also be infiltrative sending extensions or tongues of tissue out along the lateral foramina of Lushka or down through the midline foramen of Magendie. Ependymomas are midline like the medulloblastoma, but tend to be more heterogeneous than medulloblastomas in the posterior fossa. They often have several small cysts, and chunky calcification. Ependymomas also cause drop metastasis through the CSF to the spinal cord like the medulloblastoma.

Whenever a posterior fossa mass is encountered in children, the localization and appearance may give a likely diagnosis. If not, imaging can provide a broader differential diagnosis.

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**CLIPPINGS**


The majority of deaths in infants with hypoxic-ischemic encephalopathy (HIE) follow decisions to withdraw life-sustaining treatment. Clinicians use prognostic tests including MRI to help determine prognosis and decide whether to consider treatment withdrawal. A recently published meta-analysis provided valuable information on the prognostic utility of magnetic resonance (MR) biomarkers in HIE and suggested, in particular, that proton MR spectroscopy is the most accurate predictor of neurodevelopmental outcome. Reanalysis of published data reveals that severe abnormalities on conventional MRI in the first week have a sensitivity of 71% (95% confidence interval: 59%–91%) and specificity of 84% (95% confidence interval: 68%–93%) for very adverse outcome in infants with moderate encephalopathy. On current evidence, MR biomarkers alone are not sufficiently accurate to direct treatment-limitation decisions. Although there may be a role for using MRI or MR spectroscopy in combination with other prognostic markers to identify infants with very adverse outcome, it is not possible from meta-analysis to define this group clearly. There is an urgent need for improved prognostic research into HIE.
HEMINASAL AGNESIS (HEMIARHINIA) – A CASE REPORT

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** Chitra Ayyappan  
*** Nagarajan T

Abstract: Heminasal agenesis (hemiarhinia) is an extremely rare congenital malformation of unknown etiology. Around 70 cases have been studied in the past 35 years with either complete or hemiagenesis of nose and only one has been reported from India so far. A newborn male baby was admitted with respiratory distress, total absence of left side of nose (hemiarhinia), choanal atresia of right side and submucosal cleft palate. Ocular examination revealed iris and choroido retinal coloboma. Echo showed atrial septal defect (ASD). Surgical perforation of right choanal atresia was done and definitive soft tissue reconstruction of left nose was planned at a later stage.

Keywords: Heminasal agenesis, Hemiarhinia, Choanal atresia, Ocular malformations.

A 2 hours old term male baby, weighing 2.8 kg, born of non consanguinous parents presented with congenital absence of entire left side of nose, respiratory distress and feeding difficulty since birth. There was no history of aspiration, drooling of saliva or cyanosis. The antenatal period was uneventful. An elder sibling, 2 years old male, was alive and healthy. Clinical examination revealed normal anthropometric measurements with unilateral absence of left side nose (hemiarhinia), choanal atresia of right side and submucosal cleft palate. Ocular examination revealed normal right eye and left eye showed shortened palpebral fissure and telecanthus, vertically oval cornea with opacity at 11’o clock position, shallow anterior chamber and lacrimal duct stenosis. Baby had left iris coloboma with posterior synechiae and pupil not reacting to light. Fundus examination showed left choroido retinal coloboma involving optic disc (Fig.2). Both ears were normal and oto acostic emission study revealed normal hearing. Esophageal and anal patency were normal. No other congenital anomalies detected.

Opthalmological examination revealed normal right eye and left eye showed shortened palpebral fissure and telecanthus, vertically oval cornea with opacity at 11’o clock position, shallow anterior chamber and lacrimal duct stenosis. Baby had left iris coloboma with posterior synechiae and pupil not reacting to light. Fundus examination showed left choroido retinal coloboma involving optic disc (Fig.2). Both ears were normal and oto acostic emission study revealed normal hearing. Esophageal and anal patency were normal. No other congenital anomalies detected.

Routine blood investigations were normal. CT scan (Fig.3) showed absent nasal structures and hypoplasia of maxillary sinus on left side, DNS and membrano-osseous choanal atresia on right side and cleft palate. Echocardiogram detected ASD(OS) with left to right shunt. Abdominal ultrasound revealed no abnormality. Karyotyping was normal.

On admission, the oxygen saturation was 92%. Over the next 48 hours, child developed cyanosis and oxygen saturation gradually decreased to 70% in room air. Surgical opinion
was obtained and perforation of right choanal atresia was done. Intraoperatively there was no rudimentary structure on left side of nose—HEMINASAL AGENESIS. (A small rudimentary stub would have meant heminasal aplasia).

A stent was placed in the right choana. Following surgery respiratory distress subsided and oxygen saturation reached 98% in room air. Post operative period was uneventful. Stent was removed after 3 weeks.
Discussion

Hemi arhinia is a rare congenital malformation. This anomaly can occur either alone or with other craniofacial anomalies including meningocele and absent olfactory bulb.

Embryologically, the failure of the development of nasal placodes leads to congenital absence of nose. By 3rd to 4th week, the nasal placode appears and by 5th week the nasal pit deepens to form the median and lateral nasal process. The buccopharyngeal membrane which separates the nasal and oral cavity ruptures at 6th week. The two medial nasal processes fuse to form the nasal septum and philtrum and the lateral nasal processes develop into the external wall of the nose, the nasal bones, the nasal cartilages, the alae and the lateral crura of lower lateral cartilages. Failure of development of both nasal placodes results in complete nasal agenesis or arhinia, while failure of one nasal placode leads to heminasal agenesis or hemiarhinia. In heminasal aplasia, the nasal placode appears but fails to develop further leading on to rudimentary nasal structures. The failure of buccopharyngeal membrane to rupture results in choanal atresia. The adjacent structures that are developing during the same period of embryogenesis like the eye, palate and ear also may get affected leading on to other craniofacial malformations.

The congenital arhinia may be induced by chromosomal aberrations as some chromosomal change has been reported in several cases. The genetic analysis done in the affected children identified various abnormalities like large deletion involving 3q11-q11, translocation between chromosome 3 and 12, inversion of chromosome 9 and mosaic of chromosome 9.

Early surgical correction is thought to be better both from cosmetic and psychological point of view. A similar case report of heminasal agenesis reported from India by Bhandari.PS. show strikingly similar features as ours, where reconstruction of the heminose and internal nasal passage was done simultaneously by using expanded forehead tissue and a nasolabial flap. In our case, perforation of choanal atresia was done and reconstructive surgery was planned in two stages. Heminose reconstruction with a nasolabial flap to be done temporarily and once the growth of osteocartilagenous skeleton completed around 14 to 15 yrs of age, final reconstruction is aimed with cartilaginous graft.

References

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