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TOPIC OF INTEREST - "TOXICOLOGY - II"

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TOXICOLOGY - II

COMMON HOUSEHOLD POISONING

***Shruthi TK**
****Shuba S**

Abstract: *Poisoning in children may be accidental, non-accidental, iatrogenic or in older children deliberate. Accidental poisoning occurs in four-fifths of the cases and is predominantly seen in children less than 6 years. Substances consumed could be medicines, household products and plants. A variety of household agents which constitute about 44.1% of poisonings, include products such as cleaning agents, cosmetics, insect repellents and agents used for home remedies. Most of them are consumed in small amounts and hence non-toxic. In mild cases, symptoms are predominantly gastrointestinal. In severe cases manifestations may be neurological, cardiovascular or respiratory. Most of them recover with good supportive care even though no specific antidotes are available. Prevention is achieved by limiting access of these agents to children, which would reduce childhood mortality and morbidity due to poisonings.*

Keywords: *Poisoning, Household materials, Accidental poisoning.*

Poisoning during childhood is a universal problem. It may be accidental, non accidental and iatrogenic or suicidal. Data from National Poison Information Centre, New Delhi indicate that incidence of poisoning in children is 36.5%. The most vulnerable age was less than 6 years. Accidental mode of poisoning was about 79.7%, while intentional attempts were noted in 20.2% of children above 12 years of age.[1] Accidental poisoning in children is more seen in males, because children at this age become more curious in their newly acquired hand skills and mobility due to their exploratory, active and restless behaviours than the female children. Negligence or unawareness on the part of the parents and caretakers is one of the main factors in making the environment of the child favourable for poisoning. Majority of the poisoning takes place in small houses because of lack of space where chemicals or disinfectants or other house hold products would be kept within easy reach of children, which is considered as another reason for accidental poisoning in children.[2] Most commonly used agents are hydrocarbons, corrosive agents, cleaning agents, cosmetics, insect repellents and agents used for home remedies. Fortunately most of them are consumed in small amounts and hence non-toxic but can be fatal if ingested in large amounts. Most of the symptoms are nonspecific and may mimic other diseases, unless a history is forthcoming. Hence, there must be a strong index of suspicion in any unresponsive child as the diagnosis can be missed.

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Camphor

Camphor is an essential oil originally derived from the camphor tree, *Cinnamomum camphora*, but now primarily produced from turpentine.[3] It is a terpenoid, naturally occurring hydrocarbon. It is a colourless substance with a strong odour and pungent taste, available in solid and liquid forms. It is commonly seen in household items, including vaporized or topical cold preparations (e.g. Vicks Vaporub with 4.18% camphor and Tiger balm), topical musculoskeletal anaesthetic preparations (liniments), moth repellents, as part of rituals in religious ceremonies and in antimicrobial preparations.[4]

Pediatric overdose of camphor can cause refractory seizures. Despite this potential for serious toxicity, camphor-containing products remain widely available. Camphor content should not exceed 11% in camphor containing products [as per United States Food and Drug Administration (FDA)], but the concentration of camphor is not mentioned in the majority of the products.[5]

Pathophysiology

Camphor is absorbed rapidly from gut, hence there will be rapid action of toxic effects within 5-20 min after ingestion, with a peak effect occurring at 90 min. Camphor is a rapidly acting neurotoxin and can lead to excitation followed by depression of CNS. Major systemic

toxicity has not been reported with ingestion of up to 30 mg/kg of camphor. The neurotoxic dose of camphor is >50 mg/kg body weight, and the fatal dose is 500 mg/kg body weight.[6]

It is oxidised and conjugated by the liver and excreted through kidneys. Clinical toxicity typically resolves within 24 hours.

Clinical features

Children can develop generalised warmth, burning sensation in pharynx, epigastric pain and vomiting. The breath gives a strong pungent smell. It can lead to change in mental status, restlessness, confusion, delirium and hallucinations. Camphor ingestion can cause muscle twitching, myoclonus, hyperreflexia, fasciculations and seizures. Seizures are the most common reported symptom after camphor ingestion. Seizure may be the first sign of systemic toxicity and may occur soon after ingestion without any preceding symptoms.[6] Seizures can occur after gastrointestinal, dermal or inhalational exposures to camphor. Camphor can also lead to hepatic and renal injury. Mortality usually occurs due to seizures or respiratory failure.[5]

Management: Treatment of camphor poisoning is primarily supportive with special attention to management of seizures.

Decontamination - Any camphor-containing medicine that is on the skin should be removed using soap and lukewarm water. Hot water should not be used as it causes local vasodilatation and increased absorption.

Because camphor has the potential to cause sudden deterioration in mental status and seizures, it is suggested that children who ingest camphor should not receive activated charcoal and inducing emesis with syrup of ipecac is contraindicated.

Asymptomatic: The greatest risk for seizures is within the first two hours after ingestion. Patients who remain asymptomatic at four to six hours after exposure can be discharged home.

Seizures: Children who develop seizures after camphor exposure warrant hospitalization. Once initial seizures are controlled, most children fully recover and do not require seizure prophylaxis. Benzodiazepines (e.g., midazolam, lorazepam) are the first line treatment with repeat doses as necessary. If seizures are not controlled by appropriate doses of benzodiazepines, a second anticonvulsant agent such as phenobarbital should be administered. Other second-line agents, such as phenytoin or fosphenytoin, are unlikely to be effective in toxin-induced seizures.

Hemodialysis is unlikely to remove a significant amount of camphor given its high volume of distribution and degree of protein binding. Most of the occasions, camphor induced seizures gets controlled with one or two doses of benzodiazepines.

Detergents

Accidental powder or liquid-based detergent ingestion has been well documented in previous literatures among pediatric population.[7] Most ingestions by children are accidental and the amount ingested tend to be small. Alkalis tend to cause significant injuries at a pH>11. Common cleaning products include laundry and dishwasher detergents and cleaning agents with sodium phosphate, sodium carbonate and ammonia.

Clinical features

The most common symptom of caustic ingestion is dysphagia, which can occur even without severe esophageal injury. Patients may also present with drooling, retrosternal or abdominal pain, hematemesis, and features suggesting upper airway injury. Esophageal burns account for most of the serious injuries and chronic complications of caustic ingestion. Injury to the lips, oropharynx, upper airway and stomach also may occur.

Esophageal injury grading scheme is widely used in adults, although few studies have examined its validity[8] (Box 1).

Box 1. Grading of esophageal injury

Grade 0 - Normal mucosa

Grade 1 (superficial) - Mucosal edema and hyperemia

Grade 2 (transmucosal) - Friability, hemorrhages, erosions, blisters, whitish membranes and superficial ulcerations

- Grade 2A - No deep focal or circumferential ulcers
- Grade 2B - With deep focal or circumferential ulcers

Grade 3 - Areas of multiple ulceration and areas of brown-black or greyish discoloration suggesting necrosis

- Grade 3A - Small scattered areas of focal necrosis
- Grade 3B - Extensive necrosis

Although grade 1 esophageal injuries do not progress to stricture, 15 to 30% of all grade 2 burns and up to 75% of circumferential grade 2 injuries of the esophagus develop strictures. With full-thickness third-degree burns (grade 3), up to 90% result in stricture.[8] Following the initial necrosis, additional destruction takes place over the first week and the risk for esophageal perforation peaks at this stage.

Management

Patients should have vigorous intravenous fluid resuscitation. Attempts to neutralize the ingested corrosive with weak acids can cause possible thermal reactions and worsen the injury. Induction of emesis, administration of activated charcoal, and performance of gastric lavage are not indicated. Chest radiography should be done to rule out pulmonary complications. Early endoscopy permits early grading of injuries and helps to determine treatment plan, disposition and nutritional support. Thoraco abdominal computed tomography, ultrasonography and serial lactic acid or C-reactive protein measurement can be useful in evaluation and follow up of GI injuries after ingestion of caustic.[8]

Asymptomatic patients: Patients who are asymptomatic (no evidence of oral lesions, and no dysphagia, vomiting, or other symptoms), should be observed for several hours to monitor fluid intake and overall status.

Symptomatic patients: Symptomatic patients should be treated with a proton pump inhibitor for approximately one week. The use of corticosteroids for caustic esophageal injury is controversial. Giving prophylactic antibiotics to patients with severe esophageal burns is common practice.[9]

Mosquito repellents

Hydrocarbons are amongst the most common toxic exposures, not only in India, but also in the developed world. In India, accidental ingestion of kerosene is common, especially in rural households; however, a disturbing shift in hydrocarbon poisoning has been noticed to middle and higher socio-economic urban households due to accidental ingestion of liquid mosquito repellents.[10,11] The commercial mosquito repellents are marketed in various forms including creams, lotions, mats, coils, aerosol sprays and liquid vaporizers. The liquid formulations currently available in India contain synthetic pyrethroids like transfluthrin or prallethrin as the active insecticide component (~1%), and deodorized kerosene as a solvent (~97%), thus making them an important source of hydrocarbons in urban household. The attractive containers, colourful indicator lights, and advertisements on mass media heighten the curiosity and exploratory behaviour of young children. This coupled with inadequate seal of containers, improper storage, and easy accessibility increases the risk of accidental ingestion due to mouthing behaviour, especially in the 1-2 year old children.

DEET (N, N - diethyl - m-toluamide) is one of the most potent mosquito repellent, but cannot be used on damaged skin and in children, as accidental ingestion can cause poisoning.

Products are available in varying concentration from 7.5%-95%. Only products containing lower concentration of DEET (< 15%) should be used in children formulated with ethyl or isopropyl alcohol.

Toxicity

- Generally well tolerated on external application.
- Extrapolated animal studies have demonstrated the potential fatality of 50ml of 100% DEET, though doses as low as 21mg/kg/day have developed toxic encephalopathy.
- DEET is efficiently absorbed through the skin and gut.
- If small amounts are ingested - only gastrointestinal symptoms such as nausea, vomiting, diarrhea and abdominal pain occur.
- Chemical pneumonitis, ARDS has been reported.
- Ingestion of large amounts of DEET (concentrations of 40 to 95%) provoke coma, hypotension, abnormal hypertonic movements, tremors and convulsions within 0.5 to 6 hours.
- Eye contact causes irritant conjunctivitis.
- Can produce mild tingling on external application. Dermatitis with erythema and bullous reaction or urticaria may occur after prolonged or repeated exposure to highly concentrated formulations.

Treatment

- Vomiting should not be induced for minimal ingestion. Gastric aspiration and/or lavage should be performed only in cases of ingestion of large amounts of concentrated product, after airway protection.
- If large amounts of a highly concentrated DEET formulation have been ingested, the stomach should be aspirated, and a slurry of activated charcoal should be administered, followed by sorbitol or saline cathartics.

- In case of recent excessive cutaneous exposure, the skin should be washed with non-irritant soap and water.
- Eye contamination should be removed by prolonged flushing of eyes with copious amount of clean water or saline.
- Topical steroids and oral antihistamine can be prescribed for dermatitis
- Haemodialysis and charcoal haemoperfusion have been tried
- Seizures should be treated with anticonvulsants.

Prognosis

Following DEET poisoning, children usually recover within 36 hours, but death has been reported in children with ornithyl-carbarmoyltransferase deficiency.

Silica gel

Silica gel is a form of silicon dioxide, a mineral found in quartz, the mineral is a desiccant, which means it is a "super-soaker" because it can absorb up to 40% of its weight in water. Commonly included in the packaging of new items as small, white packets. They are commonly found in leather goods, such as shoes and purses, as well as in electronics and display cases. Commonly included in the packaging of new items, they are usually small, white packets. A person may mistake silica gel packets for sugar or salt and consume them, which can have adverse effects, especially choking in children.[12] These packets are frequently ingested by young children, accounting for 2.1% of the annual calls to poison control centers.[13] Fortunately, a vast majority of silica ingestion causes no symptoms, while occasionally resulting in self-limiting mouth and throat discomfort.[13]

Silica gel is usually nontoxic and the body eliminates the substance. But eating a large amount of the substance could cause an upset stomach in both humans and animals.

Sometimes, manufacturers add a substance called cobalt chloride to the silica gel which indicates humidity, by it's colour changes on exposure to moisture and cobalt chloride can be inherently toxic. Silica gel has been known to rarely cause silicosis, a fibrotic lung disease that develops due to occupational exposure of respirable silica, with a death rate of 0.74 per one million in the year 2010.[14]

Eucalyptus oil

Eucalyptus oil is obtained by extracting the oil distilled from leaves of various species of eucalyptus. Major active ingredient is cineole. Medicinal eucalyptus oil contains not less than 70% w/w of cineole.[15]

Uses

- Inhalation as decongestant.
- Orally for catarrh and cough.
- Topically as rubefacient (0.5-3%)
- Flavouring agent and cleaning solvent.
- Not recommended for children

Toxic Dose

0.05 - 0.5 ml / kg.

Well absorbed orally.

Toxicity

- Toxic effects are rapid in onset and extensive.
- Gastrointestinal tract (GIT) symptoms such as abdominal pain, vomiting, diarrhea occur initially followed by loss of consciousness.
- CNS - features are loss of consciousness, hypoventilation, depression of reflexes and convulsions. Onset of coma may be from several minutes upto 2 hours. Coma lasts for ½ hour to 30 days. Convulsions may be prominent in children.

  Miosis or mydriasis (miosis more common)

  Muscle weakness and ataxia
- Respiratory - respiratory depression, dysphonia, pneumonitis, bronchospasm. Aspiration is a major risk following vomiting. Inhalation of eucalyptus oil may result in pneumonia
- CVS - tachycardia and weak irregular pulse
- Nephritis
- Prolonged prothrombin time and irritation to skin and eyes are other features.

Management

- Assessment and support of the ABC and neurological status
- Symptomatic and supportive management of the patient.
- Attempts to induce vomiting and aggressive gastrointestinal decontamination are to be avoided.
- Asymptomatic patient has to be observed for 6 hours and X-ray to be taken after 6 hours.

- Close observation alone is required for minimal or moderate poisoning.
- In cases of large ingestion, gastric lavage and administration of charcoal can be performed after securing the airway.
- Routine use of peritoneal dialysis or hemodialysis is not established.

No specific antidote is available.

Naphthalene

Naphthalene ($C_{10}H_8$) is a natural component of fossil fuels such as petroleum, diesel and coal. The common household products made from naphthalene are moth repellents, in the form of mothballs or crystals and toilet deodorant blocks.[16]

Naphthalene itself is a strong oxidizing agent, leading to formation of free oxygen radicals, which in turn causes erythrocyte membrane damage. It also leads to depletion of glutathione, a major reducing agent which protects erythrocytes from damaging effects of various oxidants.

Major toxic effects of naphthalene are due to precipitation of acute intravascular hemolysis.

It is used in dusting powder, lavatory deodorant discs, wood preservatives, fungicides, moth balls and insecticides.

Lethal dose: Mean lethal dose in adult is between 5 - 15gms.

- Among G6PD deficient individuals, even miniscule doses cause dangerous reactions.
- In children absorption occurs rapidly; even ingestion of 2 gm may be fatal.
- Newborns are more susceptible; thinner skin and application of baby oil increase dermal absorption.
- The newborns are unable to conjugate naphthalene metabolites effectively. Glucose-6-phosphate dehydrogenase (G6PD) levels decide the severity of hemolysis with disastrous consequences in patients with G6PD deficiency

Toxicity

- Occurs mostly in children who suck or chew moth balls.
- Transplacental transfer has been reported.
- Ingestion leads to formation of epoxide metabolite, probably responsible for hemolysis.
- Hemolysis occurs in G6PD deficiency due to instability of erythrocyte glutathione.
- Ocular toxicity occurs due to oxidative stress and lipid peroxidation.
- Newborns have increased susceptibility due to inability to conjugate both naphthalene and bilirubin resulting in kernicterus. Erythema and dermatitis, hemolysis and jaundice have occurred after dressing infants in clothing stored with naphthalene moth balls.

Acute Toxicity

- Acute intravascular hemolysis is the most characteristic sign, particularly in persons with red cell glucose-6-phosphate dehydrogenase deficiency;
- This is accompanied by anaemia, leucocytosis, fever, haemoglobinuria, jaundice, renal insufficiency and sometimes disturbances in liver function
- Headache, abdominal pain, nausea, vomiting, diarrhea, fever and profuse sweating.
- Methemoglobinemia and cyanosis
- Irritation of the urinary bladder causes urgency, dysuria and the passage of brown or black urine with or without albumin and casts.
- Optic neuritis
- Liver necrosis
- Severe poisoning leads to irritability, coma, convulsion, acute renal failure in older children and adults or kernicterus in young infants.
- Inhalation results in respiratory failure and pulmonary edema. Moth ball abuse by inhalation has been described.
- Dermatitis occurs following industrial exposure.
- Usually 1 day after exposure, intravascular hemolysis can occur leading to sharp fall in haemoglobin.[17]
- Patients may develop acute oliguric renal failure due to hemoglobinuria and dehydration.[18]
- Neurological complications usually occur within 3-4 days and are due to cerebral hypoxia

Chronic abuse can result in peripheral neuropathy, chronic renal failure.

Clinical features: Common toxicity[16] of naphlalene are as follows:

Gastrointestinal: Nausea, vomiting, abdominal pain, diarrhea

Renal: Increased creatinine level, increased serum urea nitrogen level, hematuria, renal tubular acidosis

Respiratory: Congestion, acute respiratory distress syndrome (ARDS) (noted at 2 ppm).

Neurological: Confusion, lethargy, vertigo, fasciculations, convulsions, cerebral edema, coma (coma is noted at 0.05 mg/kg per day)

Hepatic: Jaundice, hepatomegaly, elevated liver enzyme levels (noted at 0.02 mg/kg per day)

Ocular: Optic atrophy, bilateral cataract with chronic exposure

Investigations

- Hemoglobin, reticulocyte count, RBC count, hematocrit
- Methemoglobin levels
- Serum: bilirubin, plasma hemoglobin, peripheral smear
- Urine: hemoglobin, alpha naphthol

Investigations show a rapid fall in RBC count, hemoglobin and hematocrit followed by temporary increase in reticulocyte count and normoblasts in peripheral blood. During hemolytic crisis, the fragility of remaining cells is increased. In the peripheral smear, RBCs contain Heinz bodies and cells may be fragmented showing anisocytosis and poikilocytosis.

Management

- Flush contaminated skin or eyes with lukewarm running water for 20 minutes.
- In case of inhalation. remove from source of contamination.
- In case of ingestion, lavage may not be effective after 2 hours.
- Activated charcoal – 1gm /kg upto 50 gms should be given as a slurry with water.
- Milk or fatty meals should be avoided for 2 – 3 hours, as they promote absorption.
- Supportive care.

Symptomatic treatment

- Repeated blood transfusion till Hb is 60 - 80% of normal.
- Corticosteroid is useful in cases of hemolysis.
- Kernicterus - hemodialysis / exchange transfusion.
- Convulsions - Diazepam
- Sodium bicarbonate - 5gm orally q 4H or as necessary to maintain alkaline urine.
- Fluids - 15ml / kg / hr with frusemide 1mg / kg to produce maximum diuresis.
- Methemoglobinemia >30% - IV methylene blue.[17]

Neem Oil / Margosa Oil

Neem oil is obtained from tree *Azadirachta indica.*

Uses

- As insecticide and insect repellent. Oral dentifrice (a substance used earlier for cleaning the teeth, which, now is replaced by fluoride)
- In traditional medicine, to treat malaria, diabetes, worm infestation, cardiovascular and skin diseases.
- As contraceptive, anti-ulcer, anti-secretory and fungicidal agents.
- Home remedy for respiratory problems
- Contains neutral oils such as palmitic and stearic acids. Active ingredients are terpenoids such as azadirachtin, nimbin, picrin and sialin. Also contains aflatoxin in very low concentrations. Seed kernels comprise primarily of glyceride azadirachtin which is the most active insecticidal component of neem.
- Most often neem oil is mixed with other oils. Sometimes neem leaves are mixed with other leaves and given as a decoction.[19]

Mechanism of toxicity: Azadirachtin (C35H44O16) manifests its toxicity possibly by interfering with mitochondrial bioenergetics. Acute poisoning with inhibitors of electron transporting complexes causes symptoms such as muscle weakness, easy fatigability, hypotension, headache, facial flushing, nausea, confusion, and seizures. The inability to utilize oxygen is manifested as a cytotoxic hypoxia which causes metabolic acidosis and hyperpnea.

In animal models, neem acts rapidly within 30 minutes on nuclei of hepatocytes, followed by mitochondrial injury, loss of ribosomes, loss of liver glycogen and presence of lipid droplets in the hyaloplasm.

Toxicity

- Toxin not identified but possibly a long chain monosaturated free fatty acid
- Toxic dose not known, but symptoms seem to be dose related

- Toxic encephalopathy - Reye's like illness.
- Metabolic acidosis, tachypnoea vomiting
- Recurrent seizures, drowsiness, coma and rarely optic neuritis.
- Investigations show polymorphonuclear leucocytosis and elevated transaminases.
- Small case series by Lai et al., showed 22 infants who were administered few drops to < 5ml recovered well after developing hepatic toxicity, encephalopathy and metabolic acidosis.[20]
- In another series by Sundaravalli et al., 12 children who were given 20 to 60ml of neem oil developed features of acidosis and encephalopathy and 10 children out of them died.[21]

Treatment

- Gastric lavage not recommended.
- Supportive management is done by stabilizing ABCs, control of seizures with benzodiazepines, fosphenytoin, levetiracetam and other anticonvusants, if child develops status epilepticus.

Match stick head poisoning

Ingestion of few match heads may not be harmful. It is generally accidental and manifestations may vary from mild gastric irritation to severe hemolysis, liver failure and renal failure.[22] The toxicity is primarily due potassium chlorate in the match head. Potassium chlorate is a powerful oxidant. Case reports of acute renal failure in children and adults requiring peritoneal or hemodialysis have been reported. There has been a case report of neonatal hyperbilirubinemia within 24 hours of life due to chronic ingestion of match sticks by mother in the antenatal period.[23] The newborn presented with loss of consciousness and MRI changes of symmetric abnormal signal intensity within the deep gray matter and medial temporal lobes, suggestive of potassium chlorate poisoning.[24] It was treated with hyperbaric oxygen.

Vacha/Vasambu/Sweetflag

It is the dried rhizome of the plant *Acorus calamus* commonly used in native medicine. Giving vasambu is a harmful child rearing practice.[25]

Constituents: Volatile oil acorin, a bitter principle acoretin, calamine starch, mucilage

Root is a stimulant and aromatic, expectorant, antispasmodic and nervine sedative

Toxic dose is unknown.

Uses: Antidote to several poisons, counter irritant; root is burnt and mixed with coconut oil or castor oil and smeared over the abdomen as antiflatulant, also used as insecticide.

Side effects

Calamus oil causes hypothermia, generalized CNS depression, sedation, hypothermia, hypotension, depression of respiration, diarrhea.

Points to Remember

- ***Poisoning due to household agents is common in children. They are mainly accidental in those less than 6 years of age and intentional in children above 12 years. Accidental ingestion is more common in boys.***
- ***Fortunately most of the household agents are taken in small doses and hence do not cause toxicity. When exposed to larger doses they exhibit signs of poisoning and occasionally can be fatal.***
- ***Mostly, the commercially available agents are heterogeneous and compositions are variable. The toxicity may be due to one or more substances. Most symptoms are nonspecific and may mimic other diseases. unless a history is forthcoming. Hence, there must be a strong index of suspicion in any unresponsive child as the diagnosis can be missed.***
- ***For most agents, gastric lavage is avoided unless airway is protected. The mainstay of management is good supportive care, as no specific antidote is available.***
- ***Implementation of good safety measures at home will bring down morbidity and mortality due to poisonings.***

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CLIPPINGS

Fab fragments in the treatment of digoxin overdose: Pediatric considerations

Serious digoxin toxicity due to accidental or deliberate overdose is uncommon, but more than half of the cases reported involved children. Toxicity can occur acutely, as with accidental overdose, or with long-term maintenance dosing. In children it is almost always acute. Conventional treatment includes gastric lavage or ipecac-induced emesis, and activated charcoal or nonabsorbable resins and cathartics to reduce absorption. Although children appear to tolerate massive ingestions without specific therapy, serum digoxin levels must be reduced quickly and safely when conventional measures have failed. Fab fragments of digoxin-specific antibodies have been successfully used to treat refractory digoxin toxicity. Indications for use should be limited to life-threatening digoxin toxicity when conventional therapy has failed.

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TOXICOLOGY - II

HYDROCARBONS POISONING

***Vinod H. Ratageri**

Abstract: *Hydrocarbon exposure is a common cause of accidental poisoning in children. Volatile hydrocarbons can be aspirated and cause chemical pneumonitis. Respiratory and central nervous system are most commonly affected. Clinical effects can be predicted by substance, route of exposure and dose. Kerosene is the most common chemical agent. Close monitoring and supportive care are the key to successful management. There is no documented role for prophylactic antibiotics and steroids. Ninety percent of hospitalized children with pneumonitis have benign clinical course and their symptoms improve within 72 hours. Fatality rate is low.*

Keywords: *Hydrocarbon, Poisoning, Kerosene, Pneumonitis, Accidental ingestion.*

Despite many innovations and inventions in the field of science and technology, hydrocarbons are still the chief components in many fuels used in industries such as heating, lighting and transportation. It also forms the base for common utility products like mosquito repellants. Humans are exposed to these hydrocarbons mainly either by inhaled or ingested route. Hydrocarbons are the commonest cause of accidental poisoning in children (under five) especially in developing countries like India.[1] Kerosene is the commonest chemical agent followed by turpentine.

Incidence

Worldwide, hydrocarbons poisoning constitute 5% of accidental poisoning and 25% of deaths in under five children.[2,3] Hydrocarbon poisoning occurs in young children, often accidently. The probable reasons include, storage of these products in inappropriate containers, such as opened water bottles and in attractive colors.[4] Physical properties of the hydrocarbons such as low viscosity, high volatility and surface tension of kerosene increases the risk of aspiration into lung.

Box 1. Various classes of hydrocarbons

- Aliphatics: Most commonly derived from petroleum distillates (e.g. gasoline, kerosene, n-hexane)
- Aromatics: e.g. benzene, naphthalene, toluene
- Halogenated compounds: e.g. methylene chloride, chloroform, carbon tetrachloride
- Terpenes: e.g. turpentine, pine oil, menthol, camphor

Classification

Hydrocarbons are classified based on structure into following four classes (Box 1).[4]

Routes of exposure

- Ingestion: Common in young children, though large volume ingestions are uncommon due to unpleasant taste. Commonly ingested hydrocarbons are gasoline, lubricating oil, motor oil, mineral spirits, lighter fluid naphthalene, lamp oil and kerosene.
- Inhalation: “Sniffing”, “huffing” , “bagging” - abuse is common in young adolescents and polysubstance users.
- Dermal and ocular exposures: Skin and eye irritation may occur, although dermal absorption is insignificant for aliphatic hydrocarbons.

Pathophysiology

The toxicity of hydrocarbons depends on physicochemical properties such as viscosity, volatility and surface tension. Viscosity determines the extent of penetration into distal airways, while volatility explains the tendencies of liquid to vaporise. Low viscosity and high volatility pose high risk for toxicity. Thus hydrocarbons like kerosene and gasoline with high volatility, low viscosity and low surface tension are more likely to get aspirated and cause lung injury.[5] For children, it is difficult to estimate the exact amount of hydrocarbon ingestion. In a study, it has been found that ingested amount could vary anywhere between 30 to 90 ml.[6] The effects of hydrocarbons on different systems are described below.

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Pulmonary system: Occurs due to aspiration or by inhalation. The necrotizing pneumonia following hydrocarbon poisoning is due to aspiration and not due to gastrointestinal absorption. Not all chemical pneumonitis occur by aspiration; sometimes, mere presence of hydrocarbons in hypopharynx is also found to cause pneumonitis due to contiguous spread in the airway. Hydrocarbons cause lung injury by lowering the alveolar surfactant, impairing gas exchange and diffusion and disrupting the lipid membranes of microvasculature.

CNS: The exact mechanism is unknown, but may be secondary to hypoxia and acidosis. Hydrocarbons affect N-methyl D aspartate (NMDA), dopamine and gamma aminibutyric acid (GABA) receptors; causes demylination and axonal loss.

Cardiac toxicity: Hydrocarbons (halogenated) sensitize the myocardium to catecholamines and predisposes the cells to tachyarrhythmias and sometimes cause sudden cardiac arrest (Sudden Sniffing Death Syndrome).

Renal toxicity: Metabolic acidosis leads to renal tubular acidosis, glomerulonephritis, hyperchloremia and hyponatremia.

Gastrointestinal toxicity: Gastric irritation leading to erosion of mucosa. Animal studies revealed direct toxicity on hepatocytes through oxidation system.

Clinical features

Exposure to hydrocarbons can present in many different ways. Table I shows various clinical features of hydrocarbon poisoning. The two most common system affected by hydrocarbon poisoning are lungs and CNS. Many studies reported from India on hydrocarbon poisoning in children, showed common manifestation in the form of respiratory distress, altered sensorium, vomiting, fever and seizures.[7]

Pulmonary manifestations[8]: They can present with asthma like reactive airway syndrome as well as chemical pneumonitis. Because of low surface tension and low viscosity, they can cause severe necrotizing pneumonia. Symptoms typically present as cough/or shortness of breath. The clinical symptoms may develop within 6 hours or may be delayed upto 48 hours. Destruction of surfactant, leads to inflammation of airway epithelium and atelectasis. Fever can occur within 30 minutes of exposure. The severity of fever correlates well with extent of lung damage.

CNS[9]: Generalized depression with slurred speech, disorientation, hallucinations, seizures.

Cardiac manifestations[10,11]: Arrhythmias are commonly seen with halogenated hydrocarbons. They occur due to sensitization of the myocardium to catecholamines.

Table I. Clinical manifestations of hydrocarbon exposure in children

System	Clinical features
Vital signs	Fever (38^0c to 40^oc), persistence of fever more than 48 hours suggests bacterial superinfection, decreased oxygen saturation on pulse oximetry
Respiratory system	Coughing, choking, cyanosis, tachypnea, nasal flaring, retractions and occasionally hemoptysis
Central nervous system	Somnolence, dizziness, weakness, ataxia, fatigue, lethargy, seizures, coma, euphoria, headache, visual disturbances and impaired level of consciousness
Gastrointestinal system	Nausea, vomiting, pain abdomen, diarrhea, constipation and melena
Cardiac system	Dysarrhythmias, pulmonary hypertension
Renal system	Metabolic acidosis, renal tubular acidosis, urinary calculi, glomerulonephritis, hyperchloremia and hypokelemia
Skin manifestations	Mild irritation, burns, bullae, blistering
Hematology	Leukocytosis, hemolysis, hemoglobinuria, rarely DIC

Gastro intestinal manifestatations[12]: Ingestion may cause breakdown of epithelium leading to nausea, vomiting, abdominal pain and hematemesis.

Approach to hydrocarbon exposure

A detailed history of incident is needed to detect the nature of hydrocarbon exposure.In unresponsive children, there is a need to question caregivers, bystanders in order to get complete picture of exposure. If possible, try to obtain the container or bottle to determine the exact chemical exposure. The initial physical examination should focus on inhalation/aspiration. The physical examination includes evaluation of vitals, thorough examination of respiratory, cardiovascular, neurological systems and skin. Diagnosis is typically deducted clinically based on kerosene smell in the breath,distressing cough, history and physical examination.

Management

Investigations

Radiology: A chest X ray (CXR) is indicated in all cases of hydrocarbon exposure irrespective of symptomatology. Children with signs of pulmonary aspiration should have a chest X ray within 4-6 hours of exposure. Eighty eight percent (88%) of children had evidence within 2 hours of exposure and by 12 hours in 98%. Radiographic abnormalities are more pronounced between 2-8 hours after aspiration.[13] The CXR abnormalities include fine, with punctuate mottled densities in perihilar areas and mid lung fields. Box.2 provides other common abnormalities. There exists is a poor correlation between clinical symptoms and chest X-ray findings. Resolution of radiographic abnormalities varies from 2 weeks to several weeks or months. In one study, persistent abnormality was found even at 10 years after ingestion.[14]

Box 2. Chest X-ray abnormalities

i) Unilateral or bilateral interstitial alveolar infiltrate (Fig.1)
ii) Consolidation
iii) Atelectasis
iv) Pleural effusion
v) Pneumatoceles
vi) Pneumothorax
vii) Hydropneumothorax
viii) Acute respiratory distress syndrome (ARDS) like picture (Fig.2)

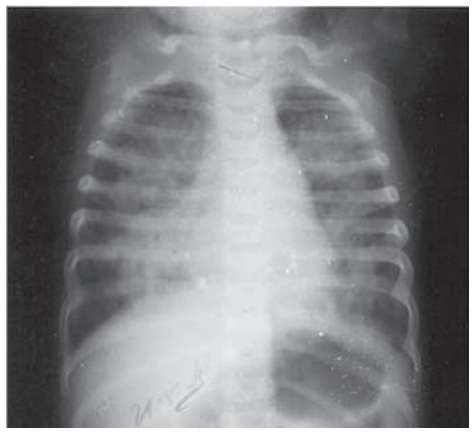

Fig.1. Aspiration pneumonia following kerosene ingestion

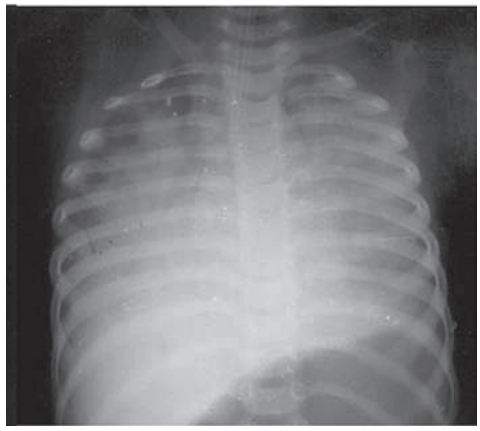

Fig.2. ARDS like picture following massive aspiration

Hematological: Leucocytosis is seen in many children and occasionally hemolytic anemia was found as an unusual feature.[15] The other laboratory tests may not be of much help.

Arterial blood gas: Hypoxia,hypercarbia and metabolic acidosis are observed.

Treatment (Fig.3)

There are no published clinical trials on standard treatment of hydrocarbon poisoning. Treatment is mainly supportive care.It includes close monitoring, symptomatic treatment, monitoring for complications and managing them appropriately.

At emergency room: Gastric lavage/or induction of emesis is contra indicated as it may predispose further aspiration. However,when it is contaminated by pesticides, heavy metals or other toxins, gastric lavage is recommended after intubation with cuffed endotracheal tube.[16]

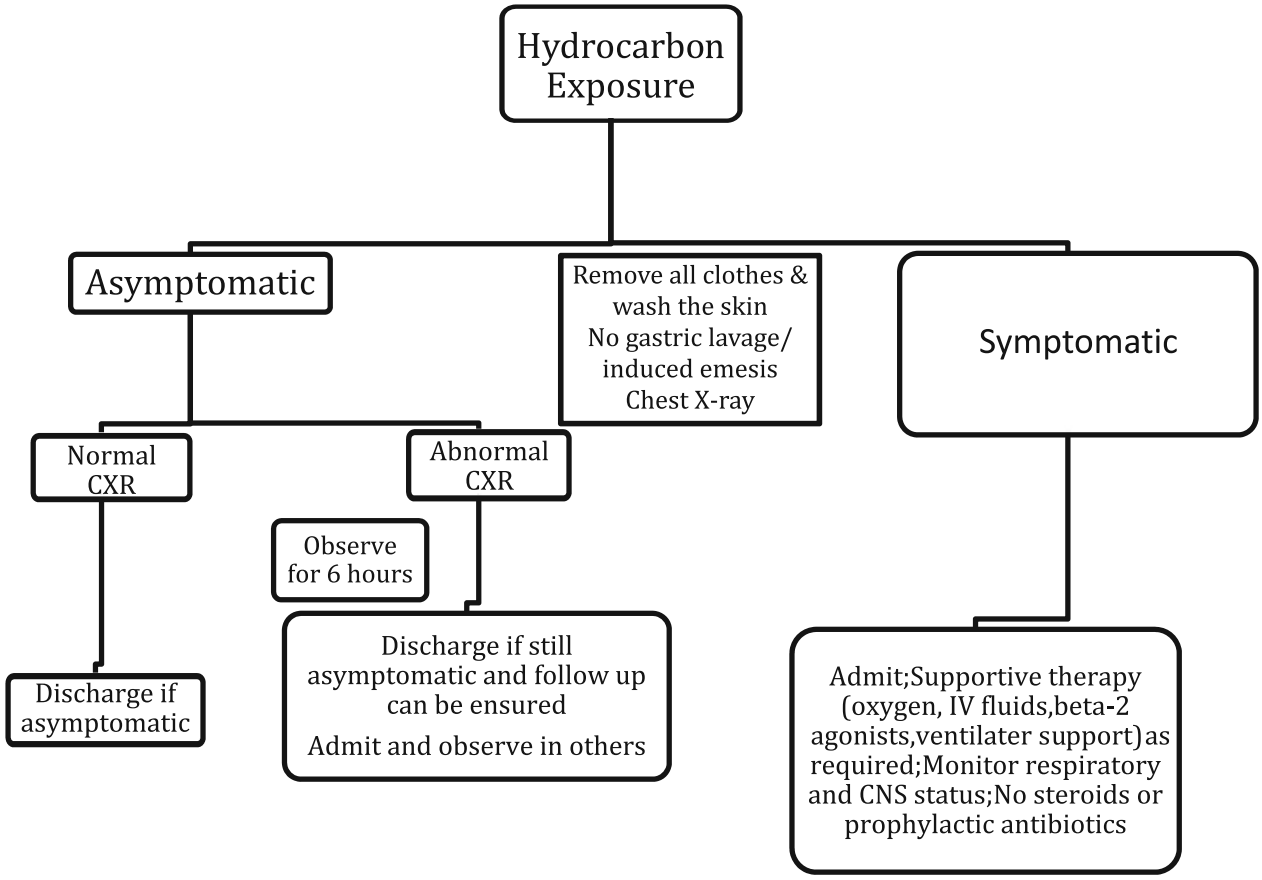

Fig.3. Management protocol of hydrocarbon poisoning[22]

All children should be observed for 6 hours irrespective of their clinical status. A CXR should be done for all children. Symptomatic as well as asymptomatic children with X-ray abnormality should be admitted.[17] Management protocol for hydrocarbon exposure is shown in Fig.3. Treatment of symptomatic children includes oxygen and IV fluids and beta2 agonists. Very rarely, children with respiratory failure may need non invasive or invasive respiratory support. Antibiotics may be indicated when secondary infection is suspected, but there is no role for steroid.[18,19] All these children need close monitoring.

Recent developments in the management are surfactant and ECMO. Surfactant is an adjunct therapy for serious cases with complications. It is a, safe option but timing of administration is highly variable. In two case reports, marked improvement has been documented in oxygen index following surfactant addition.[20] Extracorporeal membrane oxygenation is used as a life saving measure.[21]

Complications: Potential complications have been enumerated in Box 3. Children with severe pneumonitis requiring ventilator support are at greatest risk of worst complications.[8, 23]

Box 3. Complications hydrocarbon poisoning

Non severe pneumonitis

Bacterial superinfection

Pneumatoceles –infection

- Rupture
- Pnematocele under tension

Severe Pnemonitis

Pneumatocele

Airleak syndrome

Ventilator associated pneumonia

Subcutaneous Emphysema, pnemomediastinum

Pneumothorax

Empyema

Prognosis

Fatality is low (<1%) and usually results from severe pneumonitis.Most children survive without complications/

sequelae.However, in few children, abnormal lung function has been observed during long term follow-up, probably secondary to small airway injury.[24]

Points to Remember

- ***Kerosene ingestion is the most common cause of hydrocarbon poisoning in children followed by gasolene.***
- ***Kerosene and gasoline with high volatility, low viscosity and low surface tension are more likely to get aspirated and cause lung injury.***
- ***Affects the respiratory, CNS, gastrointestinal,renal, skin and hematological system.***
- ***Chest X-ray taken shows changes within 2 to 8 hours after ingestion.***
- ***Treatment of symptomatic children includes oxygen, IV fluids, beta2 agonists and if require, positive pressure ventilation.***
- ***There is no role for steroids or prophylactic antibiotics.***

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TOXICOLOGY - II

CORROSIVE INGESTION

*Arun Kumar
**Ebor Jacob James

Abstract: *Ingestion of caustic agents leading to corrosive esophageal and gastric injury, is a common situation faced in the pediatric emergency department. The nature of the agent ingested (acid/alkali), the physical form (liquid/solid) and the quantity consumed determine the extent of the injury. Liquid agents cause diffuse injuries, whereas solid agents lead to focal injuries secondary to prolonged contact time. Majority of the the ingestions occur at home as the causative agents are stored in bottles used for drinking water, soft drinks etc., and other containers without child proof seals, kept within the reach of children. Management involves a good history of caustic ingestion, whether symptomatic or not and if there is ingestion of a substance with a high caustic index then upper gastrointestinal endoscopy is done within 12 to 48 hours of ingestion for grading the injury. This is followed by nasogastric tube insertion, antibiotics and follow up. If found sick with evidence of perforation emergency sugery must be done. Radiological imaging is very useful for diagnosing perforation, aspiration pneumonia, long term sequalae and also in button battery ingestion which can result in mucosal injury within one hour and also if the diameter is more than 20mm. Endoscopic removal is preferred but in cases of tight impaction, thoracoscopic removal with oesophageal reconstruction may be needed.*

Keywords: *Corrosive injuries, Acid, Alkali, Button battery.*

Ingestion of caustic agents leading to corrosive oesophageal and gastric injury is a common situation faced in the pediatric emergency department. It is one of the most typical causes of upper gastrointestinal strictures, especially in children, who account for 80% of all corrosive ingestion cases.[1] The reported incidence is 5 - 518 events per 100,000 population per year.[2] However, it remains a significant public health issue in our country, with the actual prevalence not known due to limited data. The ingestion is usually accidental in children compared to deliberate attempts at suicide seen in adolescents and adults.[3]

Table I. Commonly ingested caustic substances

Alkali	Available household product
Sodium Hydroxide	Drain cleaners, oven cleaners, oil removers
Sodium hypochlorite	Household bleaches
Potassium hydroxide	Washing powders
Sodium carbonate	Soaps, fruit drying
Hydrogen peroxide	Surface cleaners
Acid	
Hydrochloric acid	Toilet and drain cleaners
Sulfuric acid	Batteries, cleaning agents
Acetic acid	Pickling, vinegar spirit

The risk factors identified in children include male gender, attention-deficit / hyperactivity disorder, lower socio-economic status and lack of adequate supervision.[4] Commonly ingested corrosives can be broadly classified as acids and alkalis.

Alkaline oxidizing agents like sodium hydroxide and chlorine bleaches are the most commonly implicated agents (Table.I). In India, acids are commonly used as toilet cleaners and contribute to a higher ratio of cases.[5] Sodium hydroxide causes a third of oesophageal strictures, with reports of 10 - 75% of children ingesting it developing strictures. In contrast, acid ingestion has a reported lower stricture formation rate of 3 - 16% only.[6]

Pathophysiology

The nature of the agent ingested (acid/alkali), the physical form (liquid/solid) and the quantity consumed determine the extent of the injury. The quantity consumed

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can be challenging to assess accurately from history. Acidic agents have a sour taste limiting their accidental intake compared to alkaline agents, which are tasteless and odourless.[7] Liquid agents cause diffuse injuries, whereas solid agents lead to focal injuries secondary to prolonged contact time.

Alkaline agents with pH above 11.5 to 12.5 tend to cause esophageal injury by liquefaction necrosis. Disruption of proteins and fats leads to mucosal disintegration, deeper penetration and eventually perforation. In contrast, acidic agents with a pH below two cause coagulative necrosis. There is eschar formation due to protein coagulation which protects against deeper tissue involvement.[8] The general dictum is that alkali cause esophageal injuries while gastric injuries are more by acids as they trigger pyloric spasm, leading to acid pooling in the antrum.[9]

Most household alkaline agents used for bleaching or cleaning purposes have a pH of 11 or lower and large quantities must be consumed for significant injury.[10] Solid caustic materials like batteries can adhere to mucosa and cause rapid injury to the esophagus and surrounding structures. Upper airway injuries are also more common in acid ingestion.[9]

There are three phases of tissue injury following corrosive ingestion. Acute necrotic phase lasting 24-72 hours, ulceration and granulation phase over the next 3-12 days and finally cicatrization and scarring phase starting three weeks after injury. The esophagus is most susceptible to perforation during the ulceration phase and invasive procedures are contra-indicated in that period.[11]

Clinical features

History of observed ingestion of a known caustic substance is the most common presentation. Nearly two-thirds of children are asymptomatic after the incident. Symptoms of esophageal injury manifest after 24-48 hours, and it is preferable to keep children under observation

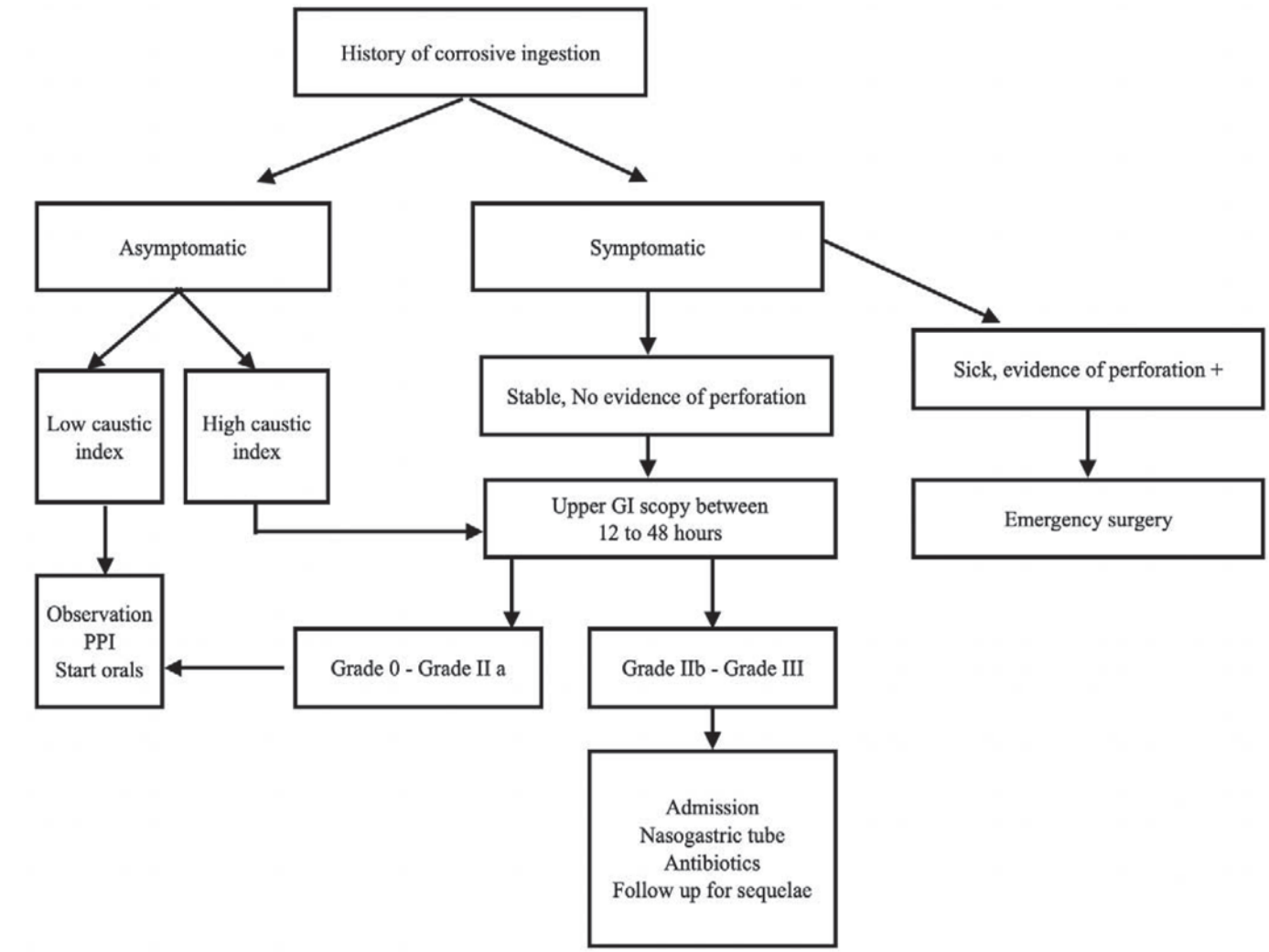


Fig.1. Management of corrosive ingestion in acute phase

during that period. Drooling, inability to swallow and food refusal are the most common symptoms in children with significant injury warrant further investigation.[12] Severe retrosternal pain or abdominal pain with fever and tachycardia may indicate the more sinister finding of esophageal or gastric necrosis and perforation.[13]

Airway injury can happen in 6-18 % of patients. Extensive oropharyngeal burns and oedema leading to hoarseness, stridor and dyspnea may develop. Severe injuries to the epiglottis can require emergency tracheotomy or intubation.[12]

Management

Primary prevention: About 90% of accidental ingestion occurs in the home environment and is attributed to these substances being stored in unmarked containers without childproof seals and within reach of children.[14] Parental education and awareness can reduce the incidence. Legislation to stop the sale of caustics in unlabeled containers and make them childproof is necessary, especially in developing countries.

Acute phase management : An algorithm for managing any child brought with a history of caustic ingestion is shown in Fig.1.

The initial question to answer is whether the child is symptomatic or not. In asymptomatic children with normal swallowing and the suspected substance is identified as an agent of low causticity, observation for 12 - 48 hours is sufficient. No further investigations are indicated, and the child can be started orally.[15] Ingestion of a known substance of high causticity requires close monitoring and early endoscopic evaluation, even if asymptomatic.[16] Symptomatic patients are kept nil orally and on intravenous maintenance fluid until further investigations have been performed.

Contraindications in the acute phase

Vomiting should never be induced as it can increase caustic exposure. Gastric lavage also should be avoided. Using neutralising fluids is not recommended as the exothermic chemical reaction can potentially worsen the tissue damage.[17] Activated charcoal is contraindicated in corrosive ingestion. The focus is on supportive care than specific antidotes.

Table II. Endoscopic grading of corrosive injuries to esophagus (Zargar classification)

Grade 0	Normal Examination
Grade 1 (Superficial)	Edema and hyperemia of mucosa
Grade 2 (Transmural)	Friability, hemorrhages, erosions, blisters, whitish membranes, superficial ulcerations
Grade 2a	No deep focal or circumferential ulcers
Grade 2b	With deep focal or circumferential ulcers
Grade 3	Areas of multiple ulceration and areas of brown-black or greyish discolouration
Grade 3a	Small scattered areas of focal necrosis
Grade 3b	Extensive necrosis

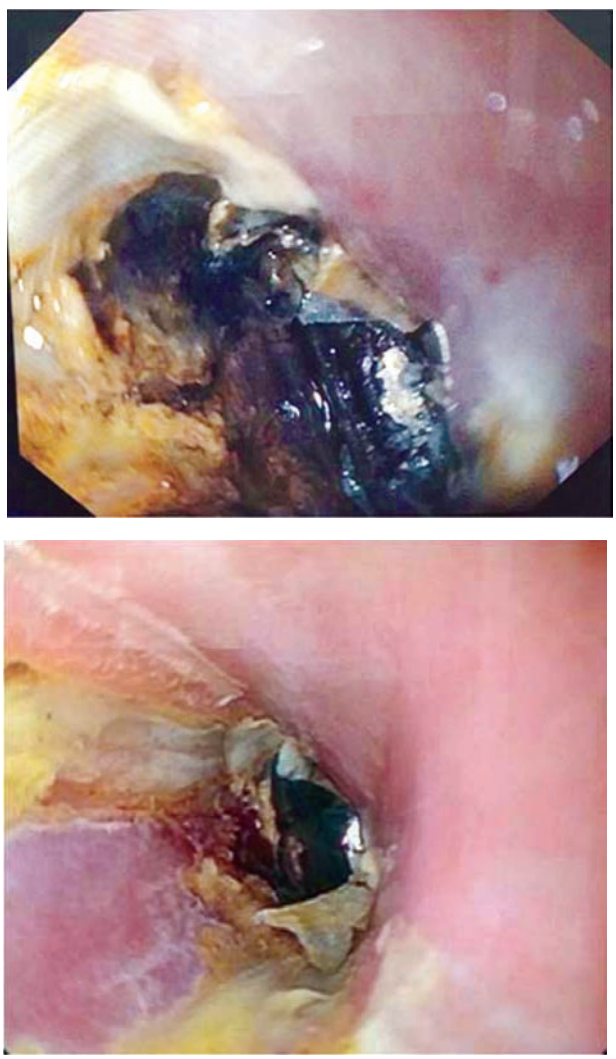


Fig.2a & 2b. Endoscopic findings of corrosive injury following ingestion of battery. Extensive mucosal sloughing and necrosis involving all four quadrants

Role of endoscopy (Fig. 2a & 2b)

Early esophago-gastroduodenoscopy is the gold standard in establishing esophageal injury and estimating the injury grade. The procedure should be done under general anesthesia after 12 hrs to prevent underestimation of injury and before 48 hours to reduce the risk of perforation.[18] The grading of injury in endoscopy is shown in Table.II which aids in prognosticating stricture formation. Grade 0 to Grade IIa can be started on oral feeds and discharged if tolerating. Grade IIb and Grade III injuries require admission and further management (Fig.2a & 2b). Initiation of oral intake may be delayed and a quarter of patients tolerated only nasogastric feeds for the first 2 - 4 weeks.[19]

Role of imaging (Fig. 3a & 3b)

An erect chest X-ray can show free mediastinal or subdiaphragmatic air in esophageal or gastric perforation. Signs of pneumonitis or aspiration pneumonia can also be seen. Technetium labelled sucralfate scan is the only non-invasive investigation to determine the esophageal injury. It adheres to injured or inflamed mucosa and is detected by nuclear scintigraphy.[20] Some recent studies have reported that contrast-enhanced computed tomography performed 3-6 hours after corrosive ingestion is superior to endoscopy to detect transmural injuries of the esophagus or stomach.[21]

Role of pharmacotherapy

Broad spectrum antibiotics are routinely prescribed in the acute phase, but studies have shown no benefit and

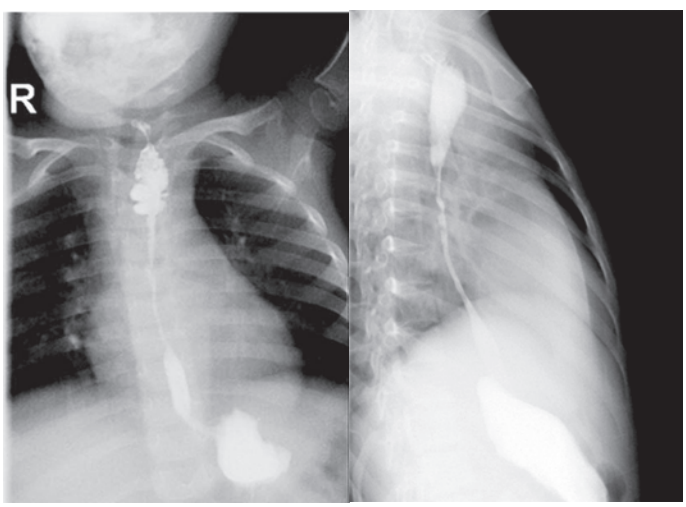


Fig.3a & 3b. Upper gastrointestinal contrast study showing long segment stricture of the thoracic esophagus - six weeks after corrosive ingestion

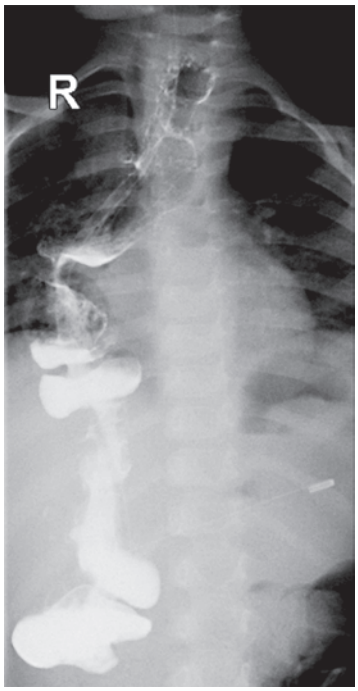


Fig.4. Post operative upper gastrointestinal contrast study of colonic pull up for stricture oesophagus due to corrosive ingestion

are not recommended except for high-grade injuries and sick patients.[21] Proton pump inhibitors are recommended to minimise gastric mucosal damage and to prevent exacerbation of esophageal injury by reflux. However, there is no consensus on the duration of therapy, with four weeks being the arbitrary period followed by most physicians.[22] Steroids have been proven to give no added benefit in preventing strictures and are prescribed only in children with significant upper airway injury.[23]

Role of nasogastric tube

Nasogastric tubes can be introduced under endoscopic guidance to maintain luminal patency and start early enteral feeds. However, there are reports of nasogastric tubes facilitating more significant acidic reflux, delaying mucosal healing and causing long strictures.[24]

Role of emergency surgery: Surgery is indicated in children with perforation and complete transmural necrosis. The aim is to damage limitation and reduce the risk of sepsis. Primary repair may not be feasible and diversionary procedures in the form of esophagostomy and gastrostomy are preferred. In addition, adjunct feeding procedures can be done in the same sitting.

Long-term sequelae

Esophageal strictures: A contrast esophagogram done 3 - 6 weeks after the injury aids in the early identification

of esophageal strictures (Fig.3a & b). Some children can present with persistent dysphagia. Post-corrosive esophageal strictures are managed by serial dilatation done by endoscopy. The dilatation is usually done using balloon dilators or bougies (Guilliard-Savary). Multiple sessions over a year may even be required.[25]

Adjunct measures are available to prevent restricturing and reduce the number or frequency of sessions. Gastro-esophagal reflux can lead to additional fibrosis and cicatrisation. Long-term acid suppression can aid successful endoscopic dilatation in this group of patients.[24]

Mitomycin is an inhibitor of fibroblast proliferation, and direct injection after dilatation is reported to reduce recurrent stricture formation.[26] Steroids have also been used for a similar purpose.

Role of surgery: Recalcitrant patients with persistent stricture after dilatation, multiple level strictures or extended length of stricture will require surgical correction. Esophageal substitution procedures are done. The stomach and colon are the most common substitutes used (Fig.4).

Esophageal carcinoma: Adenocarcinoma is reported in 1 - 2% of patients after caustic ingestion, representing a 1000-fold increased risk of esophageal cancer. Overall, 1% of squamous cell carcinoma of the esophagus has also been associated with past caustic ingestion.[27]

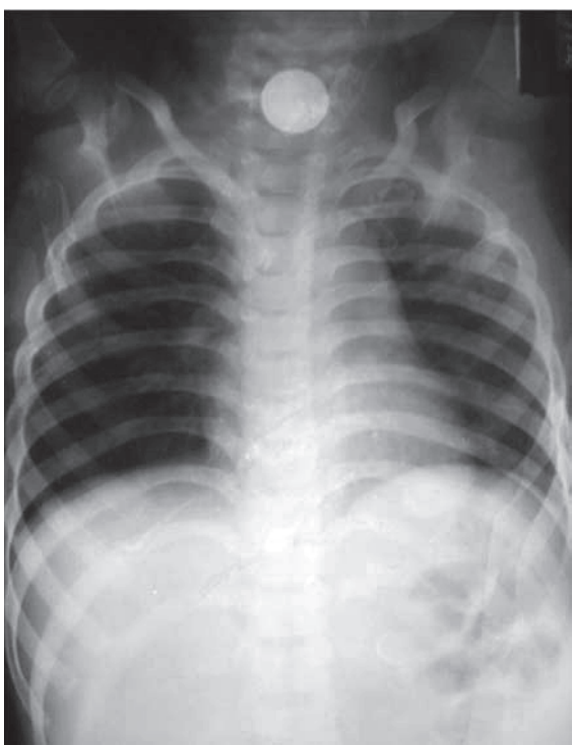


Fig.5a Round coin like foreign body in cricopharynx

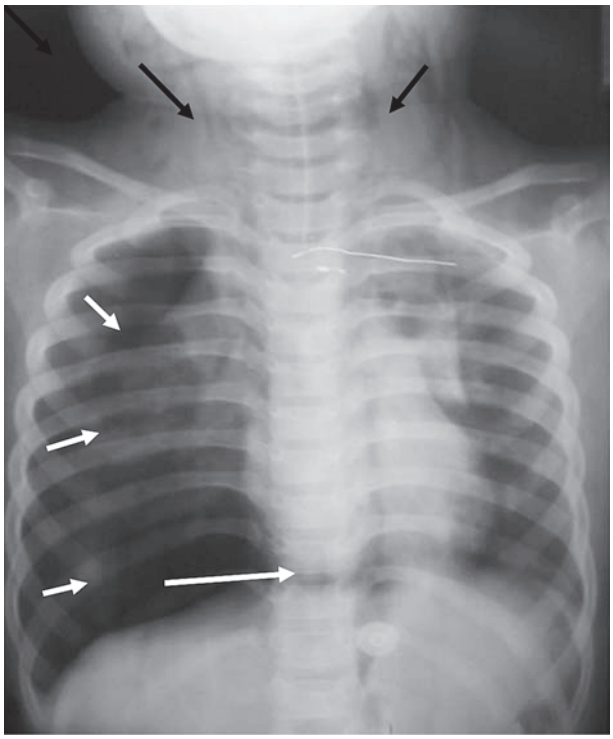
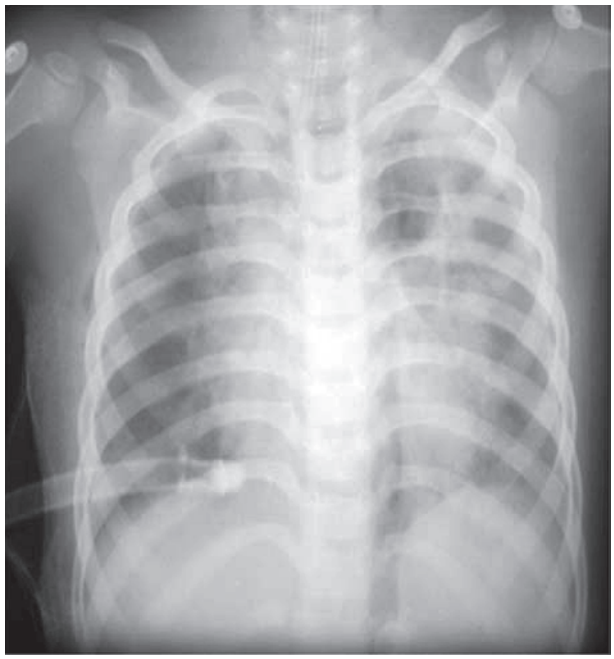


Fig. 5b Button battery was removed, 12 hours after ingestion. X-ray showing right pneumothorax and pneumomediastinum. Three white arrows - Pneumothorax; two black arrows - SC emphyesema in the neck; Horizontal long white arrow – pneumomediastinum

Button battery (BB) ingestions[28-32]

Impaction of battery in esophagus causes significant morbidity due to a combination of pressure necrosis, release of low voltage electric current and leakage of alkaline solution. Ingestion of button batteries is more common than cylindrical batteries in young children. Radiological imaging can be misleading at times as they appear as round, smooth objects and often misdiagnosed as coins (Fig.5a). As Clinicians should carefully look at the X-ray and use magnification to "zoom in" and assess for the classic "double ring" or "halo" sign in the AP view. Mucosal injury happens as early as one hour after impaction and immediate removal is warranted. Battery diameter > 20 mm has been associated with potential for greater damage. Endoscopic removal is preferred but in cases of tight impaction, thoracoscopic removal with esophageal reconstruction may be needed. If facilities for emergency endoscopy is unavailable, oral honey 10 ml every 10 minutes up to six doses is recommended while the child is shifted to a higher centre BB ingestion requires the clinician to act quickly for diagnosis and intervention. Serious mucosal injury can occur in as quickly as 2 hours, leading to pneumothorax



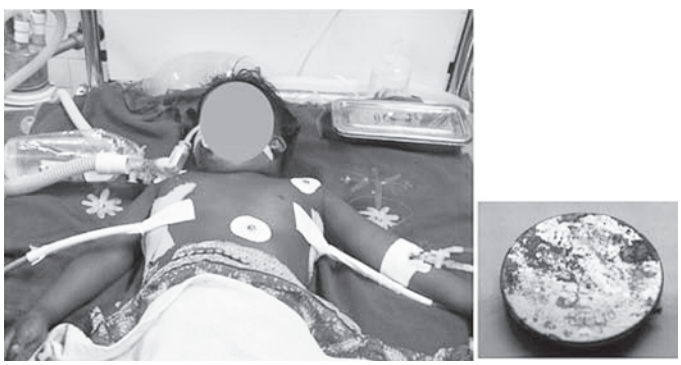


Fig.6a. ICD tube in situ right side, 6b.Child with bilateral ICD tubes 6c. Button battery removed from the patient

(Fig.5b, 6a, 6b, 6c) there exists only a small window for a child to present to the emergency department, undergo diagnosis, be transported to the operating room (OR) for BB removal.

Russel, et al demonstrated that the use of a trauma triage activation led to significantly shorter times to evaluation and BB removal for patients with suspected BB ingestion. The mean time from arrival in emergency room to battery removal was 183 minutes in standard emergency room triage (ST) group (n=4) and 33 minutes in Trauma triage (TT) group (n=7) (p=0.04). One patient in ST group developed a tracheoesophageal fistula. There were no complications in the TT group. Exsanguinating hemorrhage secondary to esophago-aortic fistula is life threatening complication specific to battery impaction in esophagus.

Conclusion

Ingestion of caustic substances is a typical pediatric emergency which leads to significant complications. It is a preventable problem, and the focus should be on primary prevention. Early recognition of airway compromise and perforation is essential. It is advisable to avoid blind nasogastric tube insertion, lavage, emesis, charcoal and milk after acute corrosive injury. Early esophagogastroduodenoscopy is indicated in all children with CI to estimate grade of esophageal injury and to reduce the risk of perforation. Despite ideal management, morbidity in the form of long-term therapy affects the quality of life. Large volume studies from developing countries are needed to determine the extent of the problem and devise effective safety mechanisms. Further studies must also evaluate the development of adjunct therapies to reduce the formation of strictures and the need for surgery.

Points to Remember

- ***Accidental ingestion of corrosive acid or alkali results in gastric or esophageal injury.***
- ***Alkaline agents with pH above 11.5 to 12.5 tend to cause injury by liquefaction necrosis, disruption of proteins and fats leads to mucosal disintegration, deeper penetration and eventually perforation of esophagus.***
- ***Acidic agents with a pH below two cause coagulative necrosis, eschar formation due to protein coagulation which protects against deeper tissue involvement.***
- ***Inducing vomiting, gastric lavage, neutralizing fluids and activated charcoal not indicated in corrosive ingestion.***
- ***Esophago-gastroduodenoscopy is the gold standard in establishing oesophageal injury.***
- ***Serious mucosal injury can occur in as quickly as 2 hours following button battery ingestion.***
- ***Oral honey 10 ml every 10 minutes up to six doses is recommended while the child is shifted to a higher centre for emergency endoscopic removal and of course it cannot replace removal of button battery.***

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TOXICOLOGY - II

SEDATIVES, ANXIOLYTICS AND ANTIPSYCHOTICS POISONING

**** Siva Vayasam***
***** Arun Bansal***

Abstract: *Poisonings due to drug ingestion are becoming more frequent and poisoning due to sedative-hypnotics can result in cardiorespiratory depression. Good supportive care can save most children. Propofol can be used for procedural sedation, however continuous infusion has a risk of propofol infusion syndrome. Dexmedetomidine infusion can cause hypotension and bradycardia. Antipsychotics can result in toxicity due to overdose. Clinical effects of all antipsychotics occur quickly after acute ingestion. Selective serotonin reuptake inibitors can cause serotonin toxicity, where early identification and close monitoring with supportive management are the mainstay of therapy. Hand sanitizers are widely used all over the world, particularly since COVID-19 pandemic, which contain 60-70% alcohol; toxicity can occur even with small amounts. Every child presenting to the emergency with acute confusion or ataxia should be evaluated for alcohol ingestion.*

Keywords: *Poisoning, Sedative-Hypnotics, Propofol, Dexmedetomidine, Antipsychotics, Selective serotonin reuptake inibitors, Ethyl alcohol, Sanitizer.*

Sedative-hypnotics[1]

In pediatric ingestions, common sedative-hypnotic agents include barbiturates, benzodiazepines, chloral hydrate and opioids.

1. **Opioids:** Acute ingestion results in a coma, pinpoint pupils and paralytic ileus. Respiratory depression, bradycardia, hypotension and a depressed sensorium can occur. Significant histamine release may cause orthostatic hypotension.
2. **Benzodiazepines:** The majority of obtunded patients can be aroused in 12 to 36 hours. Hypotension or hypothermia is uncommon. With oral ingestion, respiratory depression is usually minimal and death occurs in patients who have combined ingestion with other drugs.
3. **Chloral hydrate**: About 30 minutes after ingestion, acute poisoning causes stupor and coma. Irritation of the skin and mucous membranes is possible. Nausea, vomiting, and gastritis can occur, which can progress to hemorrhagic perforation. There is also direct hepatic toxicity with jaundice. Atrial and ventricular dysrhythmias are common. Persistent ventricular dysrhythmias are a common cause of death.

Pathophysiology

All the drugs listed above reduce activity, produce calmness, and aid in sleep. Analgesia, euphoria and sedation are all side effects of opioids. Following acute ingestion, these agents cause varying degrees of CNS depression. Some are directly toxic to organs, such as liver. Toxic effects usually appear at 10-15 times the therapeutic dose, though individual differences are common.

Barbiturates inhibit neurotransmission at synapses, resulting in generalized neuronal activity depression. Large doses cause hypotension due to decreased central sympathetic tone and direct myocardial depression. Short-acting barbiturates are more toxic than long-acting compounds because of their high lipid-solubility. The use of forced alkaline diuresis is justified by significant renal excretion of phenobarbital and its relatively low pKa.

Toxic effects

Poisoning can occur as a result of the cumulative toxicity of anticonvulsant medication (such as phenobarbital) or as a result of accidental single-drug ingestion. Polypharmacy ingestions may occur in adolescents with suicidal tendencies.

a. CNS: The onset of symptoms is determined by the drug and route of poisoning. Drowsiness is frequently the first symptom of intoxication. Slurred speech,

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nystagmus and ataxia are symptoms of mild to moderate toxicity. Initially, pupils may be small, but as coma progresses, they may become dilated and non-responsive.

b. Respiratory and circulatory: More severe toxicity manifests as stupor or coma and can lead to respiratory arrest, hypotension, and cardiovascular collapse due to decreased myocardial contractility and sympathetic vasomotor tone.

Investigations

To rule out metabolic causes of altered mental status, serum electrolytes, glucose, BUN and creatinine are tested. Barbiturate levels do not correlate with patient's clinical status, particularly in those who are tolerant to the drug. The therapeutic range of phenobarbital in serum is 15-40 mcg/mL. Toxic levels range from 60 to 80 mcg/mL. Serum phenobarbital levels are useful for diagnosis because alkaline diuresis is a therapeutic option. Coma is commonly associated with short-acting barbiturates with serum levels of more than 20-30 mcg/mL.

Management

Therapy is aimed at supporting vital organ functions and improving medication elimination.

a. ABCs

i) If protective reflexes are suppressed, intubation and/or assisted ventilation may be required.

ii) The depressant effects of single or multiple drugs on the heart can result in hypotension, arrhythmias, or decreased contractility.

iii) IV fluids, inotropic agents, or antiarrhythmics depending on clinical condition of the child.

b. Decontamination / Elimination

i) Consider gastric lavage if the child is brought within 4 - 8 hours of ingestion. Administer 1g/kg activated charcoal via nasogastric tube or orally. Repeat charcoal doses of 0.5 g/kg should be administered every 2 to 4 hours until sensorium improves.

ii) For extremely large ingestions of medication, failure to respond to aggressive supportive therapy, or coma, hemodialysis, or charcoal hemoperfusion are indicated to improve elimination.

iii) Urine alkalinization is beneficial in the treatment of phenobarbital poisoning but not in the treatment of other barbiturates. Use sodium bicarbonate to alkalinize urine: 1-2 mEq/kg IV initially, then 50-100 mEq/L intravenous fluid to maintain serum pH 7.45-7.50 and urine pH 7-8.

c. Antidote and supportive therapy

i) Inotropic support of cardiac output and blood pressure may be required. Excessive fluids should be avoided to prevent pulmonary edema.

ii) Naloxone is a narcotic antagonist used for known or suspected opioid overdose. Dose: 0.01 mg/kg, IM or IV repeated every 3-10 minutes if no response occurs.

iii) To treat isolated benzodiazepine overdoses, flumazenil is useful.[2] It is given in a dose of 0.01 mg/kg, IV over 30 seconds and repeated as necessary every 30 seconds to a maximum dose of 1 mg in children. As the duration of action is 30-60 minutes, one should monitor for re-sedation.

iv) In chloral hydrate intoxication, adequate glucose must be provided to prevent hypoglycemia associated with liver injury.

v) Continuous cardiopulmonary and oxygen saturation monitoring are to be carried out for all significant ingestions. Arrhythmias may develop with chloral hydrate and meprobamate (Table 1).

Propofol

Propofol is a postsynaptic GABA sedative-hypnotic with a rapid onset of action. Propofol is also an N-methyl-D-aspartate (NMDA) receptor antagonist. Propofol is used in the induction or maintenance of general anaesthesia, as well as for procedural sedation. Because it is highly lipid soluble, it rapidly crosses the blood-brain barrier. Because of its rapid redistribution from the CNS, the duration of action after short-term dosing is typically less than 8 minutes. Intravenous induction dose is around 2 mg/kg and an infusion of 0.2 mg/kg/min will usually maintain anaesthesia.[3]

Toxic effects

a. Acutely, propofol causes dose-related respiratory depression. Propofol has the potential to lower systemic vascular resistance and depress myocardial function. A myoclonic syndrome characterized by opisthotonus, myoclonus, and occasionally myoclonic seizure-like activity is linked to the short-term use of propofol in the perioperative setting.[4]

b. Propofol infusion syndrome (PIS), which includes metabolic acidosis, cardiac dysrhythmias, and skeletal muscle injury, is linked with prolonged propofol infusions lasting more than 48 hours at rates of

4-5 mg/kg/h or higher.[5] Young age, significant brain injury (particularly following trauma), respiratory compromise, concomitant exogenous injection of catecholamines or glucocorticoids, inadequate carbohydrate intake, and undiagnosed mitochondrial myopathy are risk factors for developing PIS.

c. According to some theories, propofol may cause disruptions in the usage and metabolism of mitochondrial-free fatty acids, leading to a state of energy imbalance and myonecrosis that is similar to other mitochondrial myopathies. Prolonged propofol infusions should be administered with caution in any patient, especially youngsters, as they may have an undetected myopathy that puts them at risk for PIS.

d. Multiple adverse events have been linked to the unique nature of propofol's carrier base, a milky soybean emulsion formulation. Many organisms thrive in it, including enterococcal, pseudomonas, staphylococcal, streptococcal and candidal strains.

Dexmedetomidine

Dexmedetomidine is a central α2 adrenergic agonist that inhibits presynaptic catecholamine release in the locus coeruleus. It has a terminal half-life of 1.8 hours and a distribution volume of less than 1 L/kg. It is also used in children with iatrogenic withdrawal syndrome.[6,7] It's also used for procedural sedation in contexts such as interventional radiology and awake fibreoptic intubations.

Pathophysiology

Unlike other sedative-hypnotics, dexmedetomidine has little action on the GABA receptor and does not cause considerable respiratory depression. The usual infusion dose is 0.3-0.7mcg/kg/hr. Dexmedetomidine is claimed to cause "cooperative sedation," in which a patient is asleep yet still awake enough to communicate with health workers. Dexmedetomidine might act as an analgesic.[8]

Toxic effects

a. Rebound hypertension and tachycardia following discontinuing dexmedetomidine have not been observed, in contrast to clonidine. Dexmedetomidine reduces cerebral sympathetic outflow, hence it should be avoided in patients whose clinical stability is dependent on high resting sympathetic tone.

b. Nausea, dry mouth, bradycardia and various blood pressure consequences are the most frequent side effects that result from its use (usually hypertension followed by hypotension). Slowing the continuous infusion may help to avoid or mitigate hypotensive symptoms.[8]

Antipsychotics[9,10]

Antipsychotics are primarily divided into two categories: Typical (traditional, conventional) and atypical, based on their structure, pharmacological profile and other factors (novel, second-generation). Antipsychotics are a structurally diverse group of heterocyclic compounds. Several of these medications work as dopamine receptor antagonists.

Most antipsychotics in use today cause sedation and suppress extrapyramidal movement disorders. They are also known as classical neuroleptics or major tranquilizers. Commonly used antipsychotic drugs are listed in Box 1. In pediatric patients, the safety and efficacy for most antipsychotics have not been established.

Pathophysiology

The aliphatic and piperidine phenothiazines, such as chlorpromazine and thioridazine, have an immediate negative inotropic effect and an effect on the heart that is similar to quinidine's (type IA) antiarrhythmic properties. These substances bind to potassium channels that cause membrane repolarization and rapid sodium channels that are inactivated and responsible for membrane depolarization. Most typically, drugs that prolong cardiac repolarization do so by inhibiting the delayed rectifier, voltage-gated potassium channel encoded by hERG (human ether-a-go-go-related gene). With pimozide, thioridazine and sertindole as well as with many other antipsychotics, this mechanism has been shown in vitro and clinically linked to QT prolongation.

Antipsychotics cause dose-related electroencephalographic (EEG) changes in epileptic patients and are thought to lower the threshold for new-onset and recurrent seizures.

Box 1. Commonly used antipsychotic drugs

1. Phenothiazines
   a. Aliphatic: chlorpromazine, triflupromazine.
   b. Piperazine: trifluoperazine, prochlorperazine, perphenazine, fluphenazine.
   c. Piperidine: thioridazine, mesoridazine.
2. Thioxanthines: Chlorprothixene, clopenthixol, flupenthixol, pifluthixol, thiothixene, zuclopenthixol.
3. Butyrophenones: Droperidol, haloperidol, benperidol.
4. Dibenzodiazepines: Clozapine, fluperlapine, olanzapine.
5. Benzisoxazoles: Risperidone.

Clozapine, loxapine and chlorpromazine are the most commonly associated antipsychotics with seizures after therapeutic doses and overdose.

By blocking nigrostriatal D2-receptors, all antipsychotics appear to cause extrapyramidal symptoms (EPS). This blockade causes striatal cholinergic excess as well as EPS signs and symptoms.

Akathisia may be a symptom of mesocortical D2-receptor blockade. Acute dystonic reactions (DRs), like parkinsonism, can be caused by decreased dorsal striatal dopaminergic activity.

Children may be more sensitive to the CNS and respiratory depressant effects of these drugs than adults. Additionally, compared to other age groups, children have a higher risk of developing an acute DR.

Pharmacokinetics

The majority of antipsychotics are lipophilic, have a wide volume of distribution and are often well absorbed, while some antipsychotics may take longer to take effect due to anticholinergic effects. Following a therapeutic dose, serum concentrations typically peak in 2 to 3 hours; however, after an overdose, this can take longer. Numerous isoenzymes of the hepatic cytochrome P450 (CYP) enzyme system are substrates for the majority of antipsychotics. Antipsychotics are largely excreted through the kidney, therefore patients with renal impairment typically do not require dose adjustment. These medicines are metabolised by children faster than adults.

Toxic effects

a. Cardiovascular: Tachycardia, hypotension (orthostatic or resting), myocardial depression, electrocardiographic QRS complex widening, QT interval prolongation, Torsade's de pointes, nonspecific repolarization changes

b. Central nervous system: Somnolence, coma, respiratory depression, hyperthermia, seizures. Extrapyramidal syndromes, central anticholinergic syndrome

c. Endocrine: Amenorrhea, oligomenorrhea, or metrorrhagia, breast tenderness, galactorrhea

d. Ophthalmic: Mydriasis or miosis, visual blurring

e. Dermatologic: Impaired sweat production, cutaneous vasodilation

f. Gastrointestinal: Impaired peristalsis, dry mouth

g. Genitourinary: Urinary retention, ejaculatory dysfunction, priapism

Diagnosis : A history of ingestion, suggestive physical examination findings of CNS or respiratory depression, anticholinergic symptoms, miosis, sinus tachycardia, hypotension, and extra pyramidal symptoms (EPS) and supporting data from ECG that displays repolarization abnormalities (e.g., nonspecific ST-T alterations, QT interval lengthening), laboratory testing using gas chromatography-mass spectrometry or high-performance liquid chromatography may be done when necessary and other ancillary tests are used to establish the diagnosis of antipsychotic poisoning.

Management

1. ABCs

a. Children with significant CNS or respiratory depression should undergo endotracheal intubation and assisted ventilation. ECG should be performed, and cardiac and respiratory function should be monitored continuously.

b. Children who are experiencing seizures or a coma should be evaluated for serum glucose levels and given naloxone, oxygen, or thiamine. For children with seizures, hyperthermia, or severe toxicity, arterial blood gas, urinalysis, and serum creatine phosphokinase, calcium and magnesium measurements should be obtained.

c. Rapid intravenous crystalloid infusion should be used to treat hypotension at first. Inotropes or vasopressors should be used to treat refractory hypotension. Norepinephrine or epinephrine infusions are preferred first-line vasopressors because their direct alpha-adrenergic agonist effects can overcome the alpha-adrenergic antagonist effects of many antipsychotics.

2. Decontamination: Although activated charcoal effectively adsorbs antipsychotic agents, its efficacy in altering the clinical course or outcome in these patients is unknown. If given an hour after ingestion, it is unlikely to affect drug absorption. Gastric lavage is not recommended. It is not advised to use multiple doses of activated charcoal as there is no clinically shown benefit. Hemodialysis, hemoperfusion, forced diuresis, or urinary alkalinization procedures do not improve the clearance of antipsychotics because of their widespread distribution, high protein binding, and predominant liver metabolism.

3. Control of arrythmia*:* Supraventricular tachycardias and ventricular tachycardia can be managed using standard advanced cardiac life-support protocols.

4. **Management of seizure:** Seizures are typically treated with benzodiazepines followed by barbiturates as needed. The efficacy and safety of phenytoin for antipsychotic-associated seizures have not been established, and it is not recommended.
5. **Management of dystonia:** Supplemental oxygen and assisted ventilation may be required in the treatment of acute dystonic responses (DRs) in individuals with respiratory distress caused by laryngeal and pharyngeal dystonia. Diphenhydramine (1mg/kg) can be administered intramuscularly or slowly intravenously during a 2-minute period. A repeat dose could be required to completely resolve acute DRs. Diazepam (0.1 mg/kg intravenously) or lorazepam (0.05-0.1mg/kg intravenously) may be used to treat resistant cases.
6. **Antidote:** In patients with significant anticholinergic toxicity, physostigmine may be used to control agitation and reverse delirium. It is administered intravenously over 2 minutes at a rate of 0.02 mg/kg (max:2mg) in children. Because its duration of action is less than 1 hour, repeat dosing may be required. Caution is advised if the ECG reveals cardiac conduction delays.
7. **Indications for PICU admission:** Children with moderate-to-severe CNS or respiratory depression, hypotension, seizures, significant agitation, acid-base disturbances, arrhythmias other than mild sinus tachycardia, and cardiac conduction disturbances should be admitted to a PICU for aggressive supportive care (Table 1).

Selective serotonin reuptake inhibitors (SSRIs)[11]

Antidepressants work by modifying the activity of serotonin and norepinephrine. Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline are examples of selective serotonin reuptake inhibitors (SSRIs). Along with treating various medical and psychological conditions, SSRIs are also used to treat alcoholism, obesity, panic disorders, obsessive-compulsive disorders, and panic attacks.

Pathophysiology

Serotonin neurons are almost entirely found in the brainstem's median raphe nucleus, where they extend into and are close to norepinephrine neurons, which are mostly found in the locus coeruleus. The structurally related p-trifluoromethyl or p-fluoro substitution found in many of these drugs contributes to the selectivity of SSRIs for serotonin reuptake.

SSRIs are a diverse group of lipid-soluble compounds. Their primary mode of elimination is hepatic, primarily via cytochrome P450. The half-life of all SSRIs is less than 2 days at a steady state. All SSRIs would probably exhibit nonlinear elimination kinetics during an overdose.

Toxic effects

The most frequent adverse effect is serotonin syndrome, which is directly related to how much serotonin reuptake is inhibited. The mild clinical manifestations, are specifically brisk reflexes and poorly sustained clonus.

Cardiovascular: SSRIs have been found to inhibit the repolarization of cardiac cells by blocking the potassium efflux channels encoded by the hERG (human ether-a-go-go-related gene) gene, increasing the risk of QT prolongation and Torsades de Pointes. The risk of QT prolongation is substantially higher for citalopram and escitalopram ingestions; hence it is important to evaluate all patients for this condition. Overall, there is little chance that taking a single SSRI will cause mortality or serious morbidity.

Diagnosis

Hunter Serotonin Toxicity Criteria are used to diagnose the condition. These criteria require the presence of one of the following classical symptoms or combinations of features: spontaneous clonus, ocular clonus with agitation or diaphoresis, inducible clonus with agitation or diaphoresis, temperature above 100.4°F (38° C), ocular or inducible clonus and tremor and hyperreflexia, or hypertonia,

Management

Majority of serotonin syndrome cases are mild, and they can be managed with supportive care and the removal of the offending drug. Agitation and tremor can both be treated with benzodiazepines. As an antidote, cyproheptadine can be used. Hospitalization is necessary for serotonin syndrome patients who have moderate to severe cases.

1. **Decontamination:** Administering activated charcoal up to 4 hours after ingesting either citalopram or escitalopram lowers the risk of QT prolongation. Children who meet the criteria for ICU admission, especially those who have taken multiple serotonergic synergistic medicines, should be given consideration for decontamination.
2. **QT prolongation:** In children with QT interval prolongation, correction of hypocalcemia, hypokalemia and hypomagnesemia is recommended.

Table I. Outline of the clinical features and management of sedatives-hypnotics, antipsychotics and SSRIs

Class of drugs	Common features	Specific features	Common management	Specific management
Sedative / Hypnotics	Respiratory failure Hypotension	CNS depression	Take care of ABCs Consider gastric lavage	Naloxone-Opioid poisoning Flumazenil-Benzodiazepine poisoning
Antipsychotics	CNS, Respiratory depression	Anticholinergic toxicity- Extrapyramidal symptoms	Stabilization of ABCs, decontamination, seizure control, arrythmia, dystonia management	Physostigmine for anticholinergic toxicity
SSRI	Cardio vascular - Long QT syndrome	Serotonin syndrome	Activated charcoal, ECG monitoring, Correction of electrolytes	Cyproheptadine

3. **Indications for PICU admission:** Severe serotonin toxicity, shown as fever, spontaneous persistent clonus, and respiratory failure. Patients who are in critical condition might need neuromuscular paralysis, sedation, and intubation (Table I).

The prognosis is favourable if serotonin syndrome is recognized early and complications are appropriately managed.

Sanitizer poisoning

The use of hand sanitizers has increased as a result of the COVID-19 pandemic. Sanitizers based on ethyl alcohol/ isopropyl alcohol are available for clinical use. Some products may contain isopropyl alcohol (isopropanol), methanol, or methylated spirits, which are extremely toxic when consumed orally. We will discuss ethyl alcohol-based sanitizer poisoning in this review because it is more commonly used. Children are inherently curious. Ethanol can be found in a variety of alcoholic beverages, as well as in concentrations ranging from 60-95% in some household products (e.g., vanilla extract, mouthwash, perfume, cologne or hand sanitizers)[12]. Swallowing even a small amount of hand sanitizer containing high levels of alcohol can result in alcohol poisoning in children, which can lead to complications such as low blood sugar levels, seizures, coma and death[13].

Pathophysiology

Ethanol is easily absorbed from the GI tract, with approximately 20% absorbed from the stomach and the remaining amount from the small intestine. 80 to 90% of an ingested dose is completely absorbed in 60 minutes when absorption conditions are ideal. 5%-10% of ethanol is excreted unchanged by the kidneys, lungs and sweat and the majority of ethanol is eliminated by the liver. Ethanol is metabolised via at least three distinct pathways: alcohol dehydrogenase (ADH) pathway, which is found in the cytosol of hepatocytes, the microsomal ethanol oxidising system (MEOS; CYP2E1), which is found on the endoplasmic reticulum and the peroxidase-catalase system, which is found in hepatic peroxisomes.

Toxic effects

Children with ethanol-associated hypoglycemia typically exhibit altered consciousness 2 to 10 hours after consuming ethanol. Hypothermia and tachypnea are two other physical findings. When approaching a child with sudden onset confusion and unsteadiness, it is critical to rule out other medical conditions as well as screen for toxins such as alcohol.[14]

Widmark's formula can be used to calculate how much hand sanitizer was consumed. (Alcohol intake in grams/ Body weight in grams X R) x100 (R is the gender constant: R = 0.55 for females; R = 0.68 for males).

When 1 g of ethanol per kg is consumed, the peak serum ethanol concentration is approximately 100 mg/dL (22 mmol/L). Blood ethanol level as low as 100 mg/dL (22 mmol/L) have been linked to fatal hypoglycemia in young children.[15] Because ethanol is rapidly absorbed, early effects such as dose-related CNS depression, nausea and vomiting may occur.

Management

1. A positive blood ethanol concentration, ketonuria without glucosuria, and mild acidosis are common laboratory findings in addition to hypoglycemia. If isolated ethanol ingestion is confirmed, the clinician must determine whether infants or young children have

consumed enough ethanol to produce a peak serum level of 0.05% (11 mmol/L).

2. Key interventions to ensure a better outcome are treatment of respiratory failure, hypoglycemia, hypovolemia, hypothermia, acid-base disturbances, and electrolyte imbalances.

Parental education and increased child supervision are recommended preventive measures for unintended alcohol poisoning, particularly during the COVID-19 pandemic.

Points to Remember

- ***Toxic effects are frequently an exaggeration of pharmacological effects.***
- ***Poisoning due to sedative hypnotics can result in cardiorespiratory depression. Good supportive care can save most of the children.***
- ***Propofol can be used for procedural sedation and continuous infusion has a risk of propofol infusion syndrome.***
- ***Dexmedetomidine infusion can cause hypotension and bradycardia.***
- ***Clinical effects of all antipsychotics occur quickly (within a few hours) after acute ingestion.***
- ***Presence of central nervous system and respiratory depression, anticholinergic toxicity, miosis, sinus tachycardia, hypotension and extrapyramidal side effects should indicate antipsychotic poisoning. All symptomatic children should have an electrocardiogram and cardiac monitoring.***
- ***For serotonin toxicity of SSRIs, early identification and close monitoring with supportive management is the mainstay of therapy.***
- ***Every child presenting to emergency with acute confusion or ataxia should be evaluated for alcohol ingestion, including hand sanitizer. Toxicity can occur even with small amounts.***

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TOXICOLOGY - II

PLANT POISONING

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Abstract: *Poisoning is a major cause of morbidity and mortality in India. Common poisons encountered are chemicals, household substances or drugs. Envenomation, poisoning due to ingestion or exposure of toxic plants or plant parts also constitute a substantial proportion. Children usually become victims of these toxic plants due to accidental ingestion, whereas adolescents consume these products for suicidal purpose. Plant poisons vary in their mechanism of toxicity, fatal dose, fatality and fatal period. This article reviews plant poisons which are commonly encountered in pediatric and adolescent age groups.*

Keywords: *Plant poisoning, Children, Datura, Strychnine, Abrus, Mushroom.*

India being a tropical country is a host to a rich variety of flora encompassing thousands of plants; while most are non-poisonous, a significant few possess toxic properties of varying degrees. Cases of accidental poisoning related to these plants due to mistaken identity or exploratory behaviour among children are not infrequent, while deliberate consumption in the form of suicidal attempts are also reported in adolescent population. In India, the overall percentage of plant poisoning ranges from 6% to 15%, but if only rural population is taken into account, this goes up to as high as 63%.[1] Common culprits being datura, cannabis, strychnine, arbus precatorius, semicarpus anacardium, calotropis, croton tiglium, mushroom, etc.

Datura

Name in different languages: Omathangai in Tamil; Kariumatta in Kannada: Unmeta in Telugu; Sada Dhatura in Hindi.

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Fig.1. Datura fruit

Datura fastuosa grows on waste places all over India. The fruits are spherical and have sharp spines (thorn-apple) and contain up to 500 yellowish brown seeds (Fig.1.). The flowers are bell-shaped. Datura stramonium grows at high altitudes in Himalayas. All parts of these plants including nectar (honey) are poisonous, especially the seeds and the fruit. They contain 0.2 to 1.4% of hyoscine (scopolamine), hyoscyamine and traces of atropine. Alkaloid form is available in market as drugs like atropine and hyoscyamine.

Action: The alkaloids atropine, hyoscyamine and hyoscine stimulate the higher centres of brain first and later cause depression and paralysis, especially respiratory and vasomotor centres in medulla. All symptoms and signs are because of anticholinergic action of the alkaloids.

Clinical features: After ingestion of whole seeds, symptoms manifest within 30 minutes, whereas if alkaloid form is used symptoms appear immediately. Dryness of mouth and throat, hoarseness of voice, dysphagia, burning sensation in the stomach and vomiting are seen initially. Facial flushing, conjunctival congestion, dilated pupil with loss of near vision, photophobia and diplopia are observed after sometime. Light reflex is initially sluggish and later absent.

Patient becomes agitated, deliriant and appears as if drunk. Urinary retention is a common feature. The skin will be dry and hot. Tachypnea, tachycardia with bounding pulse appears initially, which later becomes weak and irregular. Raised temperature by 2 or 3 degrees due to atropine. A scarlantiform rash may be observed. The patient is usually aggressive. Visual and auditory hallucinations and delusions may occur and are also reported in pediatric age group.[2] As time advances, patient passes into deep sleep or coma after 1 to 2 hrs. The patient may remain in this condition for 2 to 3 days but usually gets better within 24 hours. Death may result from respiratory paralysis. One of the most important challenges in datura poisoning is the delay in making diagnosis and hence, it should be suspected in all adolescents presenting with altered mental state, hallucination and anticholinergic features.[3]

8 D's: Dryness of mouth, dysphagia, dilated pupils, dry hot skin, drunken gait, delirium, drowsiness, death due to respiratory failure are cardinal feature of datura poisoning.

Fatal dose: 0.6 to 1 gm. (100 to 125 seeds). Fatal Period: 24 hours.

Treatment: 1. Vital monitoring (HR, BP, and respiration) and stabilization of the ABCs should be done in the ED.

2. Gut decontamination (lavage) followed by activated charcoal administration is recommended. Decreased gastrointestinal motility is common and gastric decontamination may be useful even several hours after exposure.

3.Physostigmine in children used in Intramuscular or Intravenous route: Start at 0.02 mg/kg, with a maximum dose of 0.5 mg/dose, 2 mg total; repeated every 5 to 10 minutes if symptoms persist and are severe, with the absence of cholinergic signs. Infuse at a rate no faster than 0.5 mg/minute. in the pediatric population. Atropine should be kept available for any severe cholinergic symptoms when dosing/administering physostigmine, as serious reactions like bradyarrythmia leading to arrest and ventricular fibrillation has been reported.

4. For agitation or delirium, adults can be sedated with IV diazepam (0.1-0.3 mg/kg); whereas in children, sedation is not recommended.

5. Dantrolene may be considered where there is muscular hyperactivity (1mg/kg IV to a maximum of 10 mg/kg).

6. In patients with hyperpyrexia, renal function and creatine kinase activity must be monitored.

7. Adequate hydration and careful monitoring of urine output must be undertaken.

Fig.2a. Cannabis plant and leaf.

Wikimedia Commons, the free media repository.https:// commons.wikimedia.org/wiki File:Cannabis_leaf.svg. Accessed on 2022,November 6.

Fig. 2b. Cannabis available as chocolates and cakes.

In Wikipedia. https://en.wikipedia.org/wiki/Cannabis_ consumption. Assessed on 2022, November 6.

8. Easily digestible food and laxatives given for 3 to 4 days to remove the seeds increase intestinal motility.

Cannabis Indica

Alternative names: *Ganja* in Tamil

The plant grows all over India, but its cultivation is restricted by law. The active principles are contained in its resin. The principal constituent of the resin are cannabinol, which on exposure to heat, is partly converted to the very active isomeric tetrahydrocannabinols (THC). All parts of the plant contain the active material, except stem, root and seeds (Fig.2a). It is a CNS stimulant. Alternative names of cannabis are pot, grass, dope, weed, hash, marijuana, hashish or bhang. It is one of the commonest substance

abuse in adolescents. Rarely unintentional cannabis intoxication cases are also reported in children.[4] Consumed as smoke, or ingestion as chocolates, brownies, space cakes and majoun are popular methods - which are usually called edibles (Fig.2b).

Clinical features: They appear soon after smoking and last for one to two hours, and within half-an-hour after swallowing and last for 2 to 3 hours. Taken in small dose, the effects are very slight, which usually include euphoria, passivity, heightening of subjective experiences and disorientation. With moderate doses these effects are intensified by impaired immediate memory function, disturbed thought patterns, lapses of attention and a subjective feeling of unfamiliarity. High doses produce changes in body image, depersonalisation and marked sensory distortion.

Symptoms of intoxication: (a) Psychiatric: Feelings of detachment, disinhibition, depersonalisation, euphoria, elation, relaxation, well-being, dreaminess, sleepiness, laughing, silliness, rapidly changing emotions. (b) Speech changes: rapid, impaired, talkative with poor immediate memory.

Physical signs: Increased appetite and thirst, slight nausea, heaviness and pressure in the head, dizziness, dysesthesias, somnolence, paresthesia, restlessness, ataxia, tremors, dry mouth, tachycardia, urinary frequency, injected conjunctivae. The characteristic odour of cannabis may be perceived if the drug has been smoked, but not if it has been ingested.

The victim becomes drowsy and passes into deep sleep, and wakes with exhaustion and impaired mental function, and recovery occurs in about six hours. Deaths occur with extreme rarity due to respiratory failure. Clinicians should suspect cannabis toxicity in any child with sudden onset of lethargy or ataxia.[4]

Fatal dose: Charas 2 g.; ganja 8 g.; bhang 10gm/kg body weight. THC 30mg/kg.

Fatal period: Several days.

Treatment: (1) Stomach wash or emesis, activated charcoal and cathartic. (2) 100 mg thiamine IV should be given along with IV glucose (3) Naloxone is given as 0.01 mg/kg IV at 2 to 3 minute intervals to the desired degree of reversal (4) diazepam as 0.2 to 0.5 mg/kg/dose IV, if the patient is violent or aggressive. Can be repeated at 3 to 5 mins interval (5) Assurance of recovery. (6) If flashbacks occur give anti-anxiety and if necessary anti-psychotic drugs, such as haloperidol. (7) Psychotherapy and de-addiction in case of chronic consumption.

Strychnos nux vomica

Alternative names: *Etti* in Tamil

Strychnine (Kuchila) is a powerful alkaloid obtained from the seeds of strychnos nux vomica,which are found in the jungles in India. Fruit is round, hard, slightly rough, glossyorange, 4 to 5 cm. wide, with jelly-like white or pale yellow pulp. It has 3 to 5 seeds. The seeds of nux vomica contained in the ripe fruit are poisonous. The seeds contain two principal alkaloids; strychnine and brucine 1.5% each. Strychnine is available as alkaloid in market only as rat poison.

Action: Strychnine competitively blocks ventral horn motor neurone postganglionic receptor sites in the spinal cord and brainstem and prevents the effects of glycine (the presumed inhibitory transmitter). Widespread inhibition in the spinal cord results in 'release' excitation. The action is particularly noted in the anterior horn cells.

Clinical features: Symptoms appear faster with consumption of crushed seeds than swallowed as a whole. If the alkaloid alone is swallowed, the symptoms occur very rapidly, usually within five to fifteen minutes. Bitter taste in the mouth, sense of uneasiness and restlessness, breathing difficulty and dysphagia occur initially. The convulsions are most marked in anti-gravity muscles, so that the body typically arches in hyperextension (opisthotonos). Sensorium remain intact and the patient has fear of impending death. Even minimal stimulation, like sudden noise, triggers convulsion. It is usually considered as a differential diagnosis for tetanus or refractory status epilepticus.

In fatal cases, seizures gradually become continuous. The patient develops severe breathing difficulty because of full contraction of the diaphragm and thoracic muscles resulting in hypoxia causing medullary paralysis and death. Profound lactic acidosis secondary to the violent motor activity during seizures may occur. Rhabdomyolysis and hyperthermia from the extreme muscular activity during convulsions can lead to myoglobinuria and acute renal failure. Prognosis for survival is good if the patient survives beyond 5 hours.[5]

Fatal dose: 50 to 100 mg; one crushed seed. Fatal Period: One to two hours.

Treatment: (1) The first step is the effective control of convulsions. The patient should be kept in a dark room, free from noise and disturbance. Convulsions may be controlled initially with diazepam 0.1 to 0.5 mg/kg IV slowly, and then phenobarbital IV. If these prove

ineffective, consider general anesthesia and/or muscle relaxants.

(2) Adequate oxygenation and ventilation are of paramount importance, as most fatalities are secondary to respiratory compromise. Prophylactic intubation should be strongly considered in significant acute ingestions

(3) Gastric lavage is indicated in recent, acute, or symptomatic ingestions, but requires airway and seizure control first. Activated charcoal is of proven benefit which can absorb strychnine.

(4) Acidifying the urine will increase excretion of strychnine. It is usually done by giving ammonium chloride orally @100 mg/kg/dose 12 hrly to maintain the urine pH below 7. But dangers of acidosis and hyperammonaemia outweigh the benefits

(5) Intravenous fluid sufficient to maintain hydration and good urine output should be given to treat rhabdomyolysis.[6]

(6) If Metabolic acidosis persists despite the administration of oxygen and fluids, then sodium bicarbonate should be given intravenously.[7]

Calotropis

Alternative names: *Erukku* in Tamil, *Arkagida* in Kannada, *Jilledu* in Telegu, in Hindi, in Bengali

Calotropis gigantea (akdo, madar) (Fig.3) has purple flowers and calotropis procera has white flowers. They grow wild throughout India. The active principles are uscharin, calotoxin, calactin and calotropin (glycoside). The milky juice in addition contains trypsin. The leaves and stem when incised yield thick acrid, milky juice. Most ingestions are for suicidal purpose in adolescent and young adults.

Clinical features : Applied to the skin, it causes redness and vesication. Abdominal pain is the commonest presenting symptom of calotropis poisoning.[8]

Fig.3 Calotropis gigantea

Other symptoms after ingestion of calotropis are burning pain in throat and stomach, salivation, stomatitis, vomiting, diarrhea, dilated pupils, tetanic convulsions, collapse and death. Accidental application of milky juice to eye can lead to loss of vision.

Fatal Dose: Uncertain. Fatal period: 6 to 12 hours.

Treatment: Stomach wash, demulcents and symptomatic.

Semecarpus anacardium

Alternative names in different languages: Chengottai in Tamil, Aginimukki in Kannada; Nallajeedi in Telugu; Alakkucheru in Malayalam, Bhilawa in Hindi

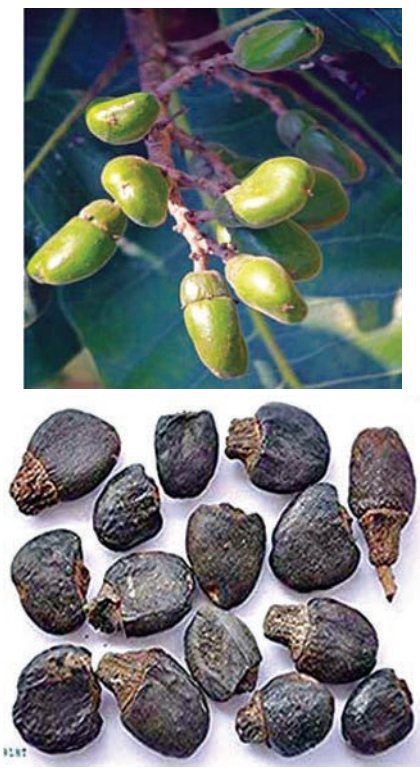

Fig.4. Semecarpus anacardium plant and seeds

Marking nuts (Dhobi nut) are black, heart-shaped with rough projection at the base (Fig.4.). They have a thick, cellular pericarp, which contains an irritant juice which is brownish, oily and acrid but turns black on exposure to air. The active principles are semecarpol (0.1%) and bhilawanol (15 to 17%).

Clinical features: Applied externally, the juice causes irritation and a painful blister which contains acrid serum, and produces eczematous eruptions of the neighbouring skin with which it comes into contact, and there is itching. The lesion resembles a bruise. Later, an ulcer is produced

and there may be sloughing. Taken by mouth, the juice causes less irritant action. In large dose, it produces blisters on throat and severe gastrointestinal irritation, dyspnoea, tachycardia, hypotension, cyanosis, absence of reflexes, delirium, coma and death. Acute renal failure can also occur.[9]

Fatal dose: 5 to 10g. Fatal period: 12 to 24 hours.

Treatment: (1) Gastric lavage. (2) Demulcent drinks. (3) When applied externally wash with lukewarm water containing antiseptic.

Abrus precatorius

Names in different languages: Kundumani in Tamil, Gulakanji in Kannada, Guruvinda ginja in Telugu, Kunni Kuru in Malayalam, Raththi in Hindi.

It is a slender, twining climbing plant, woody at base and is found all over India. The seeds are egg shaped, bright scarlet colour with a large black spot at one end which are poisonous. (Fig.5.) The seeds contain an active principle abrin, a toxalbumen, which is similar to viper snake venom.

Fig.5. Abrus precatorius seeds

Seeds are tasteless and odourless. Abrin inhibits protein synthesis and causes cell death. Ingestion usually done for suicidal purpose but accidental ingestion in a small infant leading to severe gastrointestinal symptoms is also reported.[10]

Clinical features: Symptoms may be delayed from a few hours to two or three days when taken by mouth. They include severe irritation of upper G.I. tract, abdominal pain, nausea, vomiting, bloody diarrhea, weakness, cold perspiration, trembling of the hands, weak rapid pulse, miosis and rectal bleeding. Delayed cytotoxic effects occur in the CNS, liver, kidneys and adrenal glands 2 to 5 days after exposure. Case of a 22-year-old developing acute disseminated encephalomyelitis (ADEM) after ingestion of arbus seeds for suicide is reported.[11] Ingestion of seeds or extract can cause hemorrhagic gastritis. There is faintness, vertigo, vomiting, dyspnea, and general prostration. Convulsions may precede death from cardiac failure

Fatal dose: 90 to 120 mg. (one to 2 seeds) by injection. Subcutaneously abrin is 100 times as toxic as by the oral route. Fatal period: 3 to 5 days.

Treatment: (1) Gastric lavage. (2) Activated charcoal (3) Purgative (5) IV fluids (4) Sodium bicarbonate 10 g. orally per day helps in maintaining alkalinity of urine and prevents agglutination of red cells.

Croton tiglium

Names in different languages: Nervalavithu in Tamil, Katalavanakku in Malayalam, Nepalamu in Telugu, Byaribittu in Kannada, Jamalgota in Hindi

The seeds of croton contain crotin, a toxalbumen. Seeds are oval, dark brown with longitudinal lines (Fig.6). They have no smell. Crotonoside, a glycoside, which is less poisonous is also present.

Fig.6. Croton tiglium

Clinical features: There is hot burning pain from mouth to stomach, salivation, vomiting, purging, vertigo, prostration, collapse and death. Applied to the skin, the oil produces burning, redness and vesication.

Fatal Dose: 4 to 5 seeds; one to two ml. oil. Fatal period: Six hours to three days. **Treatment**: Stomach wash, demulcent drink and symptomatic

Fig.7. Ricinus communis fruit and seeds

Ricinus communis

Names in different languages: Aamanakku in Tamil, Oudla in Kannada, Chittamankku in Malayalam, in Telugu, Arandi in Hindi

The castor plant grows all over India. Entire plant is poisonous, though seeds are most poisonous, containing toxalbumen ricin, a water-soluble glycoprotein (highest level in the seeds) and a powerful allergen (Fig.7).

Action: Ricin blocks protein synthesis through the inhibition of RNA polymerase. Ricin has a special binding protein that allows it to gain access to the endoplasmic reticulum in gastrointestinal mucosal cells causing severe diarrhea. Ricin is said to be 6000 times more powerful than cyanide.[12] It can be absorbed through inhalation, ingestion, injection and through skin contact.

Clinical features : Include burning in mouth, throat and stomach. Burning of the oral mucosa appears similar to an alkali burn. Salivation, nausea, vomiting, bloody diarrhea, severe abdominal pain, thirst, impaired sight, weak rapid pulse, cramps in calves and abdominal muscles, hemolysis, drowsiness, delirium, convulsions, shallow breathing, uremia, jaundice, collapse and death. It is poorly absorbed, with its full effect taking up to 5 days.

Fatal Dose: 5 to 10 seeds; Fatal period: Two to five days.

Treatment: Gastric lavage; activated charcoal, demulcents, cathartics and symptomatic

Mushrooms

Amanita phalloides and Amanita muscaria are the common varieties of poisonous fungi. Poisonous mushrooms usually have a bitter, astringent, acid or salt taste. On section and exposure change colour; a brown, green or blue colour developing on the cut surface. (Fig.8). Amanita muscarina grows singly in sandy soil and is of large size. It contains an alkaloid muscarine, the action of which resembles stimulation of parasympathetic post-ganglionic nerves. Amanita phalloides is also called the deadly agaric or death cap. The fungus is a powerful poison and contains phalloidin, phallon, B amanatin, which are cyclopeptides and virotoxins. They are powerful inhibitors of cellular protein synthesis.

Clinical features: In some cases, irritant symptoms may be present, and in others neurological a combination of both. The irritant symptoms are delayed for 6 to 12 hours. There is constriction of the throat, burning pain in the stomach, nausea, vomiting and diarrhea followed by cyanosis, slow pulse, laboured respirations, convulsions, sweating, collapse and death. The neurologic symptoms

Fig.8. Amanita muscaria

are giddiness, headache, delirium, diplopia, constriction of pupils, cramps, twitching of the limbs, convulsions, salivation, bradycardia and coma. Hepatic and sometimes renal toxicity occurs between 3 to 6 days. Factors associated with poor prognosis include lab features: low sodium and high urea, AST, ALT, total bilirubin, PT, APTT, international normalized ratio, and lactate dehydrogenase. Studies have reported 6.9% mortality in children with mushroom poisoning.[13]

Fatal Dose: Two to 3 mushrooms. Fatal period: Usually 2 hours.

Treatment: (1) General management include correcting water and electrolytes imbalance, coagulation abnormalities and maintaining adequate hydration (2) Stomach wash with potassium permanganate. (3) Activated charcoal. (4) Forced diuresis. (5) Benzyl penicillin (crystalline penicillin) 3 lakhs to one million units daily. (6) Atropine sulphate. (7) Hemodialysis.

Hydro cyanic acid (HCN) containing plant (tapioca/ cassava) and fruitseeds (apple, apricot)

HCN is a vegetable acid found in nature in many fruits seeds like apricot, apple, almond etc. where it exists in the form of a glucoside amygdalin, a naturally aromatic

cyanogenic compound which generates hydrocyanic acid on hydrolysis.[14] Amygdalin is converted to cyanide in the small intestine by bacteria in the presence of the enzyme emulsin. All parts of cassava (Tapioca) plant contain cyanide which is a worldwide staple food consumed by over 800 million people, mostly in Africa (Nigeria, Mozambique). The normal range of cyanogen content of cassava tubers falls between 15 and 400 mg HCN/kg fresh weight.[15] Finely crushed or chewed apple seeds of 1 gm contains 0.06-0.24 mg of cyanide. Fatal dose is 0.5 to 3.5 mg of cyanide per kg for which 200 grinded apple seeds (around a full cup) has to be ingested to cause significant toxicity which is highly unlike situation especially in children. Accidental ingestion of seeds in toto is harmless as the seeds have tough outer coating which protects the amygdalin inside them and also resistant to digestive juices.

Mechanism of toxicity: Cyanide's main effect is that it inhibits oxidative phosphorylation, (a process of generation of ATP) by binding to the enzyme cytochrome C oxidase and thus blocks the mitochondrial transport chain. After that, cellular hypoxia and the depletion of ATP occur, leading to metabolic acidosis leading to impair of vital functions.[16]

Clinical features: Intravenous and inhalation of cyanide produce a more rapid onset of signs and symptoms than exposure via the oral or transdermal route. If consumed in large quantities, the symptoms can occur instantly including, seizures, shortness of breath, trembling, spasm, increased heart rate, respiratory failure, hypotension and death. Lower amount of cyanide can lead to problems like nausea, headache, vomiting, stomach cramps, dizziness, confusion and weakness.

Treatment: (1) Patient should be kept under observation for 24 to 48 hours, as cyanide toxicity may recur. (2) Ventilate with 100% oxygen by maintaining the airway. (3) Gastric lavage is also done on those who have ingested cyanide using activated charcoal. (4) Drug of choice is inj. sodium nitrite followed by inj sodium thiosulphate. The principle of the treatment is to reverse the cyanide-cytochrome combination. This is achieved by converting hemoglobin to methemoglobin by giving nitrites which by virtue of its more affinity for cyanide, removes cyanide from the cytochrome oxidase. Cyanides combine with methemoglobin to form cyanmethemoglobin which in turn in the presence of rhodanase and sulphate donors, such as thiosulphate, converts cyanide to thiocyanate which is excreted in the urine. by complexing with hydroxocobalamin (Vit B12 A). (5) Another effective antidote is inj hydoxycobalamine which converts cyanide to cyanocobalamin (Vit B 12).

Points to Remember

- ***In India, plant poisoning is common in rural population, which include datura, cannabis, strychnine, arbus precatorius, semicarpus anacardium, calotropis, croton tiglium, mushroom, etc.***
- ***Datura poisoning causes dryness of mouth, dysphagia, dilated pupils, dry hot skin, drunken gait, delirium and drowsiness.***
- ***Cannabis is consumed as smoke or by ingestion as chocolates, brownies, space cakes and majoun, which are usually called edibles. Clinicians should suspect cannabis toxicity in any child with sudden onset of lethargy or ataxia.***
- ***Nux vomica seeds poisoning is a differential diagnosis for tetanus and refractory status epilepticus.***
- ***Semecarpus anacardium in large dose, produces blisters in throat and severe gastrointestinal irritation, dyspnea, tachycardia, hypotension, cyanosis, absence of reflexes, delirium, coma and death. Acute renal failure can also occur.***
- ***Ingestion of Abrus precatorius seeds or extract can cause hemorrhagic gastritis, fainting, vertigo, vomiting, dyspnea, convulsions, cardiac failure and prostration.***
- ***Finely crushed or chewed apple seeds or improperly cooked tapioca can lead to cyanide poisoning. Ingestion of seeds in toto is harmless as the seeds have tough outer coating which protects the amygdalin inside them and also resistant to digestive juices.***

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CLIPPINGS

An epidemiological study of poisoning cases reported to the national poisons information centre, All India Institute of Medical Sciences, New Delhi

A retrospective analysis of poisoning calls received by the National Poisons Information Centre showed a total of 2719 calls over a period of three years (April 1999-March 2002).

The age ranged from less than 1 to 70 years, with the highest incidence in the range of 14-40 years, with males (57%) outnumbering females (43%). The most common mode of poisoning was suicidal (53%), followed by accidental (47%). The route of exposure was mainly oral (88%). Dermal (5%), inhalation and ocular exposure contributed 7% to the total. The highest incidence of poisoning was due to household agents (44.1%) followed by drugs (18.8%), agricultural pesticides (12.8%), industrial chemicals (8.9%), animals bites and stings (4.7%), plants (1.7%), unknown (2.9%) and miscellaneous groups (5.6%).

Household products mainly comprised of pyrethroids, rodenticides, carbamates, phenyl, detergents, corrosives etc. Drugs implicated included benzodiazepines, anticonvulsants, analgesics, antihistamines, tricyclic antidepressants, thyroid hormones and oral contraceptives. Among the agricultural pesticides, aluminium phosphide was the most commonly consumed followed by organochlorines, organophosphates, ethylene dibromide, herbicides and fungicides. Copper sulphate and nitrobenzene were common among industrial chemicals. The bites and stings group comprised of snake bites, scorpion, wasp and bee stings. Poisoning due to plants was low, but datura was the most commonly ingested.

An alarming feature of the study was the high incidence of poisoning in children (36.5%). The age ranged from less than 1 to 18 years and the most vulnerable age group included children from less than 1 year to 6 years. Accidental mode was the most common (79.7%). Intentional attempts were also noticed (20.2%) in the age group above 12 years.

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TOXICOLOGY - II

ROLE OF ANALYTICAL TOXICOLOGY IN THE MANAGEMENT OF POISONING

**** Pillay VV***

Abstract: *Earliest milestones in the identification of a poison in body tissues and fluids centred around arsenic as it was commonly used as a homicidal poison in the Middle Ages. In the presence of altered mental status without any obvious cause, a clinician must consider investigations to identify toxicants such as CNS depressants or drugs of abuse. For a potentially suicidal patient, paracetamol, lithium, theophylline, iron, salicylates and digoxin tests can be requested as suggested by history, physical signs or bedside tests. Toxicological assays may be qualitative or quantitative. Radio-immunoassay is a slow and expensive method of detecting drugs in the blood, but is highly accurate, which is useful in the detection of drugs in extremely low blood concentrations such as cannabis, digoxin, LSD, paraquat, etc. Enzyme mediated immuno assay technique is preferred over other immuno assay methods in the emergency situation because of its simplicity and speed in providing information on toxic drug concentrations. In a majority of cases, non-toxicological routine metabolic tests such as urea, glucose, electrolytes, and arterial or venous blood gases may be more useful than toxicologic assays. But toxicological assays are useful in suspected poisoning to confirm or exclude such a suspicion. They are particularly useful with regard to digoxin, ethylene glycol, lithium, methanol, paracetamol, salicylates or theophylline where toxicity correlates with serum levels, and specific drug therapy can be instituted. They are also useful in chronic poisoning involving heavy metals and other chemicals or drugs.*

Keywords: *Analytical toxicology, Toxicology assay, Bedside toxicology.*

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Scientific methods of analysis for poisons have only recently been developed. Until the 19th century, doctors and scientists had faulty notions about the effect of poisons on the human body.[1] It was believed that if a dead body was black or blue or spotted in places or "smelled bad", the cause of death was a poison. Other fallacious ideas were that the heart of a poisoned person could not be destroyed by fire and that the body of a person dying from arsenic poisoning would not decay. The first person to suggest a method for detecting poisons in tissues was the Dutch physician Hermann Boerhoave who theorized that various poisons in hot vaporous condition yielded typical odours. He placed substances suspected of containing poisons on hot coals and tested their smells.

Owing to the widespread use of arsenic as a homicidal poison in the middle ages, it is small wonder that the first milestone in the chemical isolation and identification of a poison in body tissues and fluids centred around arsenic.

In 1775, Karl Wilhelm Scheele, the famous Swedish chemist, discovered that white arsenic (arsenic trioxide) was converted to arsenious acid by chlorine water, and the addition of metallic zinc reduced the arsenious acid to arsine gas. Gently heating the ensuing gas led to deposition of metallic arsenic on the surface of a cold vessel. In 1821, Sevillas utilised the decomposition of arsine for the detection of small quantities of arsenic in stomach contents and urine in poisoning cases.

In 1836, James Marsh, a London chemist developed the first reliable method to determine an absorbed poison (arsenic) in body tissues and fluids such as liver, kidney, and blood.

Since then, mankind has come a long way to the present era of sophisticated analytical techniques which can detect even micrograms of virtually any poison in almost any kind of biological specimen. Today, an analytical (toxicology) laboratory has become a vital adjunct to the proper management of poisoned patients. However it is to be noted that the cornerstone of the management of such patient's intensive supportive therapy is mostly independent of the kind of poison implicated, and hence routine employment of expensive analytical techniques may be avoided.[2] The attending physician must be judicious in calling for

necessary investigations, and exercise discretion in the choice of tests to be done.[3]

At the time when the IV catheter is inserted, blood samples for glucose, electrolytes, BUN, CBC and any indicated toxicologic analysis can be drawn. If the patient has an altered mental status, the attending physician may be tempted to send blood and urine specimens to identify any CNS depressants or drugs of abuse, along with other medications, but the indiscriminate ordering of these tests rarely provides clinically useful information. For the potentially suicidal patient, a paracetamol concentration should be routinely requested, along with tests affecting the management of any specific xenobiotic such as carbon monoxide, lithium, theophylline, iron, salicylates and digoxin (or other cardioactive steroids), as suggested by history, physical examination, or bedside diagnostic tests. In the vast majority of cases, the blood tests that are most useful in diagnosing toxicologic emergencies are not the toxicologic assays but the "non-toxicological" routine metabolic profile tests such as BUN, glucose, electrolytes, and ABGs or venous blood gases (VBGs).

Mahoney and associates have categorised treatment of a poisoning cases into 4 groups with respect to toxicological evaluations (Box 1).[4]

In fact, most poisoned patients can be treated successfully without any contribution from the laboratory other than routine clinical biochemistry and hematology. This is particularly true when there is no doubt about the poison involved and when the results of a quantitative analysis would not significantly affect therapy. In those cases where an analytical toxicological investigation is deemed beneficial, an orderly progression is desirable in the performance of necessary tests and their interpretation.

Box 1. Evaluation of drug toxicity

1. Toxicity correlates very well with serum levels, and specific drug therapy can be instituted: e.g., Digoxin, ethylene glycol, lithium, methanol, paracetamol, salicylates, theophylline
2. Toxicity correlates closely with serum level, but only non-specific care is required: e.g., barbiturates, ethanol, phenytoin
3. Toxicologic testing only serves to confirm fairly clear-cut clinical parameters of poisoning: e.g., Cyanide, narcotics, organophosphates, tricyclics.
4. Toxicity correlates poorly with serum level and only non-specific care is required: e.g., Amphetamines, benzodiazepines, cocaine, neuroleptics.

Box 2. Common analytical methods in toxicology

I. Qualitative assays

1) Bedside tests

A. Color tests B. Other tests

2) Thin layer chromatography (TLC)

II. Quantitative assays

1) Ultraviolet spectrophotometry
2) Gas chromatography (GC)
3) High performance liquid chromatography (HPLC)
4) Mass spectrometry (MS)
5) Radio-immunoassay (RIA)
6) Enzyme mediated immuno assay technique (EMIT)
7) Atomic absorption spectrophotometry
8) Inductively coupled plasma atomic emission spectroscopy (ICP-AES)

Analytical methods used

Toxicology laboratories use several methods to screen for poisons/drugs, since there is no single, accurate, inexpensive method for this purpose. Each method differs in cost, accuracy, complexity, speed and specificity. The actual equipment required depends on the size of the laboratory and the kind of testing done.

In a given case of poisoning it may be sufficient to know just the nature of poison (qualitative analysis) or there may be a need for identification as well as estimation of its concentration in the body (quantitative analysis). They are further categorized and listed in Box 2.

I. Qualitative tests

1A. Bedside tests - Colour tests

1. Trinder's test: Done on urine or gastric aspirate sample for detection of salicylates (salicylic acid, salicylamide and methyl salicylic acid). The test has a sensitivity of 94% and a specificity of 74% for identifying patients whose salicylate concentrations are greater than 30 mg/dL (2.17 mmol/L).
2. Ferric chloride test: Done on urine for detection of phenol, phenothiazines, phenylbutazone, oxyphenbutazone or salicylates.
3. FPN ('FPN' reagent is a combination of ferric chloride, perchloric acid and nitric acid) test, on urine or

stomach contents for detection of phenothiazines and tricyclic antidepressants.

4. O-cresol test: Done on urine or stomach contents for detection of paracetamol or phenacetin.
5. Dichromate test: Done on urine sample for the detection of ethanol.
6. Marquis test: Done on gastric fluid for the detection of opium or its derivatives.
7. Lee Jones test: Done on gastric fluid for the detection of cyanide or salicylates.
8. Reinsch test: Done on stomach contents or urine in heavy metal poisoning (mercury, arsenic, bismuth or antimony).
9. Qualitative desferrioxamine colour test (QDCT): Done on gastric fluid to detect toxic levels of iron. A variation of this test is the Desferrioxamine challenge test (DCT), in which 25 to 50 mg/kg of desferrioxamine is administered by intramuscular injection. Iron poisoning is indicated if the urine which is voided subsequently is pinkish in colour (vin rose¢ urine).
10. Meixner test: Done on stool or gastric sample to detect the presence of amatoxin (present in most toxic mushrooms).
11. Fujiwara test: Useful to detect the presence of trichloro compounds such as chloral hydrate, chloroform, and trichloro ethylene.

1B. Bedside tests - Others

1. Isonitrile test: Done on gastric contents to detect the presence of carbon tetrachloride, chloral hydrate, chloroform, methyl bromide or any other chlorinated hydrocarbon.
2. Tensilon test (Edrophonium challenge test): When 10 mg edrophonium is given intravenously in a case of sudden paralysis, there will be dramatic recovery if it is due to myasthenia gravis, while a case of poisoning (e.g., botulism) will not show any improvement.
3. Melzer's test: This is a test done to confirm whether a given mushroom is toxic (especially *Amanita phalloides*). However, a negative reaction does not necessarily mean that the mushroom is non-toxic.

2. Thin layer chromatography(TLC)

This is a qualitative technique which involves the movement by capillary action of a liquid phase (usually an organic solvent) through a thin, uniform layer of stationary phase (usually silica gel) held on a rigid support (usually a glass, aluminium, or plastic sheet). Compounds are separated by partition between the mobile and stationary phases.

TLC is a simple, inexpensive technique which is widely used.[5] It takes only about 2 hours for completion. It is also a very versatile method since the order of separation of compounds can be altered simply by changing the nature of the developing agent. However, interpretation of the plates can prove difficult and calls for a trained eye with considerable experience in recognising colours, spot shapes and metabolite patterns.

It is also well known that TLC can produce false positive results because of interference between xenobiotics.[6] It is always desirable to confirm results by more sophisticated methods, especially in forensic cases.

II. Quantitative assays

1. Ultraviolet spectrophotometry[7]

This technique is based on the principle that many drugs when in solution will absorb UV radiation. The degree of absorption depends on the chemical structure of the drug, its concentration in the solution and the wavelength of the UVR. This technique is ideal to quantitate blood levels of paracetamol and salicylates, as well as urine levels of phenothiazines.

A major disadvantage of UVS is the possibility of interference in multiple drug overdose. In such a case, UV scanning can produce a composite spectrum of bewildering complexity from which neither qualitative nor quantitative information can be derived. Conventional spectrophotometric methods are known for producing false positive results which can be disastrous in medicolegal cases.[8]

2. Gas chromatography (GC)

This is a more sophisticated system of quantitative analysis and has found great favour with analytical toxicologists since it offers a way of simultaneously separating, identifying and measuring drugs and other organic poisons. GC(Gas chromatography - specifically gas-liquid chromatography) involves a sample being vapourised and injected onto the head of the chromatographic column. The sample is transported through the column by the flow of inert, gaseous mobile phase. The column itself contains a liquid stationary phase which is adsorbed onto the surface of an inert solid.

The liquid or solid specimen dissolved in a solvent is injected into the chromatograph. The specimen is vapourised by heat and is carried through a column by an inert carrier gas (usually nitrogen). The column is packed with a substance like carbowax or adiponitrile which is capable of changing the migration time of the specimen as it traverses the column. The sample vapourises to form a mixture of carrier gas, vapourised solvent and vapourised solutes. A proportion of this mixture passes onto the column, but most exits through the split outlet.

A detector recognises the presence of the chemical and graphically plots its emergence as a function of time. The retention time and peak area for a chemical compared to known standards are used to identify and to quantitate its presence. There are many detectors which can be used in gas chromatography. Different detectors will give different types of selectivity.

GC is most commonly employed to quantitate blood levels of volatile liquids such as ethanol, ethylene glycol, and methanol.

3. High performance liquid chromatography (HPLC)

This is similar to GC, except that it is not restricted to volatile compounds. A high pressure (1000 to 6000 pound per square inch) pump facilitates movement of the specimen through the columns packed with chromatographic adsorbents e.g., silica gel and alumina. The effluent stream passes through a detector, usually an ultraviolet spectrophotometer and the appearance of a drug in the solvent is signalled by a recorder peak in the same way as in GC. Again, the size of the peak is proportional to the concentration of drug in the sample. HPLC can be used to separate and analyse complex mixtures.

4. Mass Spectrometry (MS)

This is usually combined with gas chromatography (GC-MS), and is considered to be the best technique for quantitative analysis of a wide variety of chemicals, but its expense (capital as well as operational costs) greatly restricts its use.[9]

In the simplest terms the GC/MS instrument represents a device that separates chemical mixtures (the GC component) and a very sensitive detector (the MS component) with a data collector (the computer component).

A mass spectrometer can also be connected to a liquid chromatograph (LC-MS) for detection of non-volatile compounds. Tandem mass spectrometry consists of double mass spectrometers connected to gas chromatograph (GC-MS-MS) or liquid chromatograph (LC-MS-MS). These are very costly and sophisticated instruments that can refine chemical analysis to almost flawless degree.

5. Radio-immunoassay (RIA)[10]

It is a slow and expensive method of detecting drugs in the blood, but is highly accurate. It involves mixing known quantities of drug specific antibody with known amount of radioactively labelled drug which allows analysis of the precipitate with a gamma counter. The amount of emittance inversely correlates with the presence of assayed drug. This test is excellent for detection of drugs in extremely low blood concentrations (cannabis, digoxin, Lysergic acid diethylamide (LSD), paraquat, etc).

6. Enzyme mediated immuno assay technique (EMIT)[11]

This is a fast, expensive method with good accuracy, which works on the principle that the amount of drug present is proportional to the inhibition of an enzyme-substrate reaction. A known quantity of a drug is labelled by chemical attachment to an enzyme. Drug specific antibodies added to the specimen bind the drug-enzyme complex thereby reducing enzyme activity. Free drug in the specimen competes with enzyme labelled drug and limits the antibody-induced enzyme inactivation. Enzyme activity correlates with drug concentration in the specimen as measured by absorbance change resulting from the enzyme catalytic action on a substrate.

EMIT is preferred over other radio-immuno assay methods in the emergency situation because of its simplicity and speed in providing information on toxic drug concentrations (approximately one sample per minute). It eliminates the complex separation phase necessary in RIA.

7. Atomic absorption spectrophotometry (AAS) [12]

This is the best method for detecting inorganic elements (arsenic, lead, mercury, thallium, etc). However, it requires a large sample of blood for accurate analysis. The blood sample is introduced into a high temperature oxyacetylene flame situated in the path of a beam of radiation. The organic matrix is combusted and the metal forms a cloud of atoms which absorbs a fraction of the radiation in proportion to the concentration of metal in the sample. This method is very sensitive and it can measure trace elements down to the part per million level, as well as being able to measure elements present in minor and major amounts.

Table I. Comparison of analytical methods used in toxicology

Method	Specificity	Sensitivity	Speed
Thin-Layer Chromatography	+ +	+ +	+ +
Gas-Liquid Chromatography	+ + +	+ + +	+
High Performance Liquid Chromatography	+ + +	+ + +	+
Spectrophotometry	+	+ +	+ + +
Gas Chromatography-Mass Spectrometry	+ + + +	+ + + +	+
Immunology	+ + +	+ + +	+ + + +

8. Inductively coupled plasma atomic emission spectroscopy (ICP-AES) is a new development that allows simultaneous multi-element analysis. Seventeen elements can be measured from a single sample : aluminium, barium, cadmium, chromium, copper, iron, lanthanum, lead, manganese, molybdenum, nickel, platinum, silver, strontium, tin, titanium and zinc.

Table 1 gives the comparative status of efficiency of the commonly used laboratory techniques in toxicology.

Points to Remember

- ***Sophisticated analytical techniques are available, which can detect even micrograms of any poison in almost any kind of biological specimen***.
- ***Analytical methods include qualitative tests and quantitave analysis***.
- ***Qualitaive tests include bedside color tests and thin layer chromatography which take a few minutes to hours, but may require training to interpret them***.
- ***Quantitative tests include ultraviolet spectrophotometry, gas chromatography, high performance liquid chromatography, mass spectrometry, atomic absorption spectrophotometry, radio immunoassay and enzyme mediated immunoassay technique.***
- ***Inductively coupled plasma atomic emission spectroscopy (ICP-AES) is a new method that allows simultaneous multi-element analysis and several elements (mostly heavy metals) can be measured from a single sample.***

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TOXICOLOGY - II

RECENT DEVELOPMENTS IN THE MANAGEMENT OF POISONING

***Ravikumar T**

Abstract: *Management of the child with poisoning begins with recognition of the agent(s) involved, identification of the signs of toxicity and assessing the severity. Therapy involves the provision of supportive care, prevention of poison absorption and when appropriate, the use of antidotes and other interventions to enhance elimination of the toxin. Extracorporeal treatment is considered if the manifestations are severe and the poison is dialyzable. Extracorporeal treatment, modalities include hemodialysis, ccontinuous renal replacement therapy, peritoneal dialysis, hemoperfusion, therapeutic plasma exchange, albumin dialysis*

Keywords: *Extracorporeal treatment, Poisoning, Children.*

Acute poisoning in children is a clinical emergency, and ranks fourth among the causes of morbidity and mortality in children. Prompt and effective treatment is critical for life-threatening poisoning. Most substances are non- or minimally toxic in pediatric poisonings, rarely a few are severely toxic. Management of the poisoned child begins with recognition, identification of the agent(s) involved, the signs of toxicity and stratification of the severity. Therapy involves the provision of supportive care, prevention of poison absorption and when appropriate, the use of antidotes and other interventions to enhance elimination of the poison. Majority of exposures due to poisonous substances need supportive care only.

When the patient has developed life-threatening manifestations of poisoning, and alternative treatments are not available, timely consideration of extracorporeal treatment is indicated if the poison is considered dialyzable. Extracorporeal treatments are required only in 0.1% of intoxications. Conventional treatments must be performed promptly and completely in each case before extracorporeal treatment is initiated. The first successful in vivo experiment with hemodialysis was carried out for the removal of salicylates from poisoned animals in 1913, even after so many years the application of extracorporeal treatment in the management of poisoned patients remains debatable.

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Extracorporeal treatment (ECTR)

Most substances are nontoxic or minimally toxic in pediatric poisonings, rarely a few are severely toxic. Severe poisoning is defined as exposure to a poison causing a significant clinical effect that can be lethal, may cause irreversible tissue damage, or may cause major end-organ damage.[1] The goal of ECTR is to maximize elimination of poison and harmful metabolites from the body by diffusion, convection, adsorption and centrifugation. ECTR includes hemodialysis (HD), continuous renal replacement therapy (CRRT), peritoneal dialysis (PD), hemoperfusion (HP), therapeutic plasma exchange (TPE) and albumin dialysis.

A basic understanding of the following 4 critical determinants will permit the clinician to determine whether ECTR may successfully enhance poison removal[2] (Table I).

(1) Molecular weight of the poison

The molecular weight (MW) of a substance strongly influences its likelihood to be cleared by ECTR especially in HD. Majority of poisons have a MW in the 100-1000 Dalton range, and are therefore amenable to removal by intermittent HD, provided other determinants are not limiting factor e.g lithium used for bipolar diseases has a molecular weight of 74 Da with no other determinant limitation can be easily removed by HD. The Table I describes the capability of different modes of ECTR.

(2) Protein binding of the poison

Albumin is responsible for the majority of nonspecific binding of drugs and poisons (albumin-poison complex is >67,000 Da), it cannot be removed by HD/HF. Only the free, unbound form of the poison in the plasma can be removed by them. Poisons that have a protein binding (PB) of 80% or more are usually not

Table I. Pharmacokinetic properties of the poison to assess its potential for ECTR removal

	HD	HF	HP	Albumin dialysis	TPE	ET	PD
Mechanism of removal	Diffusion	Convection	Adsorption	Diffusion/ convection	Centrifugation / separation/ convection	Separation	Diffusion
Molecular weight	1000 - 10000 Da	10000 - 40000 Da	5000 - 10000 Da	60000 - 100000 Da	130000 Da	No restriction	< 500 Da
Protein bound	<80 %	<80%	<90-95%	Highly likely	No restriction		Low
Volume distribution	Low VD (<1-2 litre /Kg)						Low VD

considered amenable to removal by either HD or HF, exception are saturable binding in overdoses or drugs with equilibrium to dissociate from protein binding e.g salicylates and valproic acid.

(3) Endogenous clearance of the poison:

Lower the poison's endogenous clearance, the higher the potential for ECTR to have a toxico kinetic impact. For medicines that undergo extensive and rapid enzymatic (e.g.,hepatic) clearance, endogenous clearance may exceed 2000 mL/minute (e.g., labetalol, cocaine, verapamil, toluene) so the contribution of ECTR for such poisons will be minor. In poisoned patients with acute kidney injury (AKI) or organ failure reducing endogenous clearance ECTR will be also useful.

(4) Volume of distribution of the poison

ECTR only removes poison located in the blood compartment. As the volume of distribution (VD) increases, the usefulness of any ECTR decreases substantially, a VD >1-2 L/kg is usually a deterrent to extracorporeal removal. Substances with rapid diffusion from tissue to plasma (concentration gradient) are dialysable but those with slow diffusion from tissue to plasma may cause rebound effect after dialysis is stopped e.g. lithium, methotrexate, metformin, dabigatran etc.

Indications for ECTR

- Exposure to the poison is likely to cause serious morbidity and mortality
- Toxicity unlikely to be prevented or reversed by an antidote

All abbreviations are listed in Box 1

Box 1. Expansions for abbreviations

CRRT - Continuous renal replacement therapy

HD - Hemodialysis

HF - Hemofiltration

HP - Hemoperfusion

TPE - Therapeutic plasma exchange

ET - Exchange transfusion

ECTR - Extracorporeal treatment

ECLS - Extracorporeal life support

ECMO - Extracorporeal membrane oxygenation

SLED - Sustained low efficiency dialysis

IHD - Intermittent hemodialysis

PD - Peritoneal dialysis

- Toxicity unlikely to be minimized by treatments that prevent absorption and/or enhance elimination
- Poison's endogenous clearance is <4 mL/min/kg
- Volume of distribution is <1 to 2 L/kg
- Patients who demonstrate progressive clinical deterioration despite appropriate clinical management, presenting with intractable hypotension, hypoventilation, heart failure, seizures, metabolic acidosis or dysrhythmias.
- Patients whose normal route of elimination of the intoxicant is impaired (liver or kidney dysfunction)

When these situations occur or appear likely to occur, ECTR should be taken into consideration as soon as possible. Characteristics of group of xenobiotics and role of ECTR is given in Table II.

Modalities of extracorporeal therapy for poisoning

Hemodialysis (HD)

In intermittent hemodialysis (IHD), the movement of particles (solutes) is driven by diffusion, i.e. a concentration gradient from one compartment to another through a semi permeable membrane. Factors determining solute clearance are the magnitude of the concentration gradient (blood and dialysate flow rates), duration of therapy and the filter composition. Majority of poisons are less than 500-2000 Da in molecular weight which favours HD as best modality for clearance. Targeting a Qd (dialysate flow rate)/Qb (blood flow rate) ratio >2.5:1 may be ensured so that clearance of small molecules is not restricted by dialysate flow. Countercurrent direction of dialysate flow

Table II. Characteristics of group of xenobiotics and role of ECTR[3]

	Class of drug/poison	Pharmacokinetic properties	Agents amenable to ECTR	Agents not amenable to ECTR
1	Antiarrhythmic	Lipophilic, increase Vd, protein bound	Sotalol (HD)	Amiodarone, flecainide, lidocaine
2	Anti-diabetic	Varied	Metformin (HD)	Insulin, sulphonylureas
3	Antidepressants and antipsychotics	Lipophilic, increase Vd, protein bound	Lithium (HD, CRRT)	Tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors
4	Antiepileptics	Varied, moderately lipophilic	Barbiturates, carbamazepine, phenytoin, valproic acid (HD)	Benzodiazepines, lamotrigine
5	Antimicrobials	Varied	Cefepime, vancomycin (HD)	Amphotericin
6	Beta blockers	Varied	Atenolol, metoprolol	Carvedilol, labetalol, propranolol
7	Calcium channel blockers	Lipophilic, increase Vd, protein bound	None	All
8	Cardiac glycosides	Lipophilic, increase Vd, protein bound	None	All
9	Chemotherapeutic drugs	varied	Methotrexate (HD), rituximab,cisplatin (plasma exchange)	Vincristine, doxorubicin
10	Methylxanthine	Hydrophilic, low Vd, low protein bound	All	None
11	Anticoagulant	Lipophilic, increase Vd, protein bound	Dabigatran (HD) protein bound	Apixaban, rivaroxaban, warfarin
12	Sympathomimetics	Lipophilic, increase Vd, protein bound	None	Cocaine, amphetamines, syntheticcathinones
13	Alcohol	Hydrophilic, low Vd, low protein bound	Methanol, ethylene glycol (HD)	None
14	Non opioid analgesia		Salicylates, acetaminophen	None

provides 20%–30% better clearances for small molecules than a concurrent direction of flow. Augmenting Qd increases clearance by approximately 10%-20% for small molecular weight (MW) molecules but does not affect the clearance of larger molecules. There is an improved clearance of larger MW solutes relative to small MW solutes with high flux membranes. The simultaneous use of more than one filter, or even two distinct circuits, can increase clearance by approximately by 5-7%.

Albumin dialysis

Albumin dialysis may facilitate the clearance of highly protein bound toxins because the unbound fraction diffuses into the dialysate side where it binds to albumin and is trapped. There will be a protein binding disequilibrium on the blood side and more drug would become unbound and cross the membrane to be cleared which has been observed with poisoning due to diazepam, valproic acid and carbamazepine.

Intermittent hemodialysis (IHD)

IHD is frequently available, least expensive with fewer complications, Ability to treat concomitant metabolic disorders and its significant clearance capacity for a wide spectrum of toxic substance and quickest to implement when compared to other ECTRs makes IHD the most common modality used in poisoning.

Hemofiltration (HF)

In HF, poison and solvent are simultaneously removed by convection (solvent drag) and replaced by a physiological solution. Convection allows removal of poisons as large as 25,000 Da. As the large majority of known poisons have a low MW (<2000 Da), HF would not seem to be more advantageous than HD in the majority of poisonings. Factors influencing solute clearance during convection include blood flow rate (Qb), ultrafiltration rate (QUF), the site of fluid replacement and the type of hemofilter (size of membranes pores).

Continuous renal replacement therapy (CRRT) / Sustained low efficiency dialysis (SLED)

Poison clearance with CRRT is 50%-80% less than that obtained with intermittent modalities because of lower blood and/or effluent flow rates. CRRT as modality will not be the best extracorporeal treatment as the slow rate of blood flow and dialysate flow does not rapidly remove elimination of poison, but has a role when there is hemodynamic instability or poison with slow movement from tissue to blood or more lipophilic poison such as lithium. Opioids and other sedative-hypnotic agents causing shock, sympathomimetics (e.g. cocaine) causing rhabdomyolysis and AKI and severe acetaminophen poisonings (which may result in AKI and multiorgan failure) are some of the more common non dialyzable toxins receiving dialysis; it is likely that CRRT is often the therapy used in such cases.

Sustained low efficiency dialysis (SLED) is a hybrid technique usually provided as a prolonged treatment using both reduced Qd (compared to HD) and Qb and differs from CRRT in three areas - shorter duration, higher Qd than CRRT(dialysate flow rate is more as follows HD>SLED>CRRT) and can be administered using standard IHD equipment. Clearance of middle and large solutes during CRRT is greater than that during SLED due to extended duration and addition convective clearance in CRRT. When poison removal is urgent, SLED and CRRT are not the treatments of choice unless no other method is available or ultrafiltration is needed in an unstable patient.

Peritoneal dialysis (PD)

In PD clearance of toxins is very slow; it should only be used if all other extracorporeal modalities are unavailable in resource-limited settings.

Hemoperfusion (HP)

HP works on the principle of adsorption of particles from blood to the surface of the column (charcoal coated). Clearance is variable and pronounced for middle and large MW molecules. HP requires greater systemic anticoagulation than do other ECTRs. HP also non selectively adsorbs platelets, white blood cells, calcium, and glucose, charcoal cartridge are very costly and needs frequent change (<2 hr based on saturability of the surface). This modality is becoming less used due to its cost, expertise required for its use and the comfort of use of other methods.

Therapeutic plasma exchange (TPE)

TPE works on the principle of centrifugation which separates the whole blood into various components according to their specific gravity. The most important factor influencing clearance with centrifugation is the total volume of plasma exchanged per session which is usually one to two volumes of plasma per day until clinical improvement or as long as the toxin is released from tissue. TPE is useful for clearance of substances which are highly protein bound (>95%) or with MW more than 50000 Da. There is some support for it in exposures to the mushroom Amanita phalloides, thyroxine, vincristine, and cisplatin.

Box 2. Extracorporeal treatment options based on percentage of protein bound and molecular weight

- >95% of poison is protein bound at current concentration - **Therapeutic plasma exchange**
- 80% to 95% of poison is protein bound - **Hemoperfusion**
- <80% of poison is protein bound based on molecular weight (MW):
- Poison's MW 1500 Da - **High flux HD**
- Poison's MW 1500 to 20,000 Da - **Hemofiltration**
- Poison's MW 20,000 to 50,000 Da - **High cut off/ middle cut off - HD, hemofiltration**
- Poison's MW >50,000 Da Therapeutic plasma exchange

Exchange transfusion

Exchange transfusion is seldom used but has been described in poisoning due to substances highly bound to erythrocytes such as cyclosporine or tacrolimus and to treat methemoglobinemia induced by a toxic exposure (e.g. propranolol, aniline, dapsone, and sodium nitrite). Exchange transfusion has the advantage of being simpler to use in infants and has been tried in them or poisonings due to salicylates, theophylline, and barbiturates. Exchange transfusion and therapeutic plasma exchange have been utilized for rare poisonings not otherwise amenable to extracorporeal removal, such as snake envenomation, iatrogenic poisoning with monoclonal antibodies, arsine gas and amanita phalloides.

Extracorporeal life support

Extracorporeal life support includes extracorporeal membrane oxygenation (ECMO), emergency cardiopulmonary bypass, intra-aortic balloon pumps and left ventricular assist devices. ECMO is increasingly used as a bridge to recovery in clinically refractory patients with cardiovascular and/or pulmonary failure not responding to conventional medical therapies. Extracorporeal liver assist devices remain occasionally used to support liver function in poison induced hepatotoxicity such as amanita poisoning.

ECTR prescription for poisoning: The dialysis prescriptions to maximize extracorporeal elimination are higher blood flow, higher dialysate flow, higher ultrafiltration rate, post filter replacement with HF, larger filter or kidney (surface area and flux), and longer duration.[4]

The extracorporeal treatment options are given in the Box 2.

EXTRIP (Extracorporeal treatment in poisoning) Workgroup is a group of experts who have given guidelines after reviewing literature and expert opinion on indications to initiate ECTR as therapeutic or prophylactic, based of concentration levels. They have also provided when to cease ECTR. Other recommendations include the preferred type of ECTR for every reviewed poison (favoring intermittent HD in all circumstances) and specific miscellaneous recommendations regarding anticoagulation, special populations and antidotal dose. The executive summaries of all EXTRIP recommendations are published at http://www.extripworkgroup.org/recommendations.[3]

Intravenous lipid emulsion

Intravenous lipid acts as antidote for local anesthetic severe/systemic toxicity (LAST) especially when cardiovascular or neurologic toxicity features present following LA administration. The exact mechanism of action of intravenous lipid emulsion (ILE) for rescue therapy is not clearly understood, the strongest evidence supports the lipid sink/sponge mechanism. Once in circulation, the emulsion acts as a sink/sponge, extracting lipophilic drug molecules. This reduces drug distribution to tissue and enhances redistribution from the tissue to the nonaqueous part of the plasma. ILE may be considered for patients with hemodynamic instability, or status epilepticus, after ingestion of a lipid-soluble substance in whom maximal treatment with standard resuscitation methods has failed. Possible benefit of ILE has been suggested for cyclic antidepressant, bupropion, lipophilic beta blockers and calcium channel blockers. However, the quality of evidence for its use for non-local anaesthetic poisoning is low and results are variable. The dose is 20% ILE 1.5 mL/kg (lean body weight) IV bolus over one minute, followed by an infusion of 20% ILE 0.25-0.5 mL/kg/min IV given over 30-60 minutes. ILE can be used in children although guidance on optimal dosing and safety is needed.

Conclusion

Poisoning is a medical emergency and in severe cases, extracorporeal treatment may be urgently required to prevent or reverse major toxicity in very small proportion. The different options include IHD, intermittent HF, HDF, CRRT, hemoperfusion, TPE, exchange transfusion, and PD. Though the use of extracorporeal treatment started in 1913 it has not grown to its full potentials. The concepts are evolving as more evidences may increase the scope of this field.

Points to Remember

- ***Extracorporeal treatment is required only in 0.1% of intoxications, when the patient has developed life-threatening manifestations of poisoning and alternative treatment is not available.***
- ***Conventional treatment must be performed promptly and completely in each case before extracorporeal treatment is initiated.***
- ***The goal of ECTR is to maximize poison elimination or harmful metabolites from the body by diffusion, convection, adsorption and centrifugation.***
- ***Various methods of ECTR include hemodialysis, continuous renal replacement therapy, peritoneal dialysis, hemoperfusion, therapeutic plasma exchange and albumin dialysis.***
- ***Four critical determinants will decide whether ECTR may successfully enhance poison removal like molecular weight of the poison, protein binding, endogenous clearance and volume of distribution of the poison.***
- ***Intravenous lipid emulsion acts as antidote for local anesthetic severe/systemic toxicity, which acts as a sink/sponge, extracting lipophilic drug molecules.***
- ***EXTRIP (Extracorporeal treatment in poisoning) is a group of experts who have given guidelines and expert opinion on indications to initiate either therapeutic or prophylactic measures, based of concentration levels, preferred modality and also when to cease ECTR.***

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CLIPPINGS

A survey of antidote knowledge and availability among physicians in a South Indian district.

A survey was designed to identify the knowledge of emergency medicine practitioners, on antidotes for common poisonings, along with queries on antidotes and decontamination measures available within each hospital.

A total of 232 people replied to the poll (77.33 % response rate). In general, data of antidotes are not found higher but differed based upon the antidote. Physicians who work in tertiary hospitals and more bedded hospitals appreciably served well. Merely 42.24 % of the 16 antidotes are accessible at each reporting hospitals on average; 18.1 % could acquire them from adjacent hospitals and 20.26 % could acquire them from a local distributor. Only 19.4 % of people can acquire an antidote within 2 h. The most common decontamination therapy is gastric lavage, while extracorporeal decontamination procedures 42.24 % and 36.64 % respectively are available in varying degrees.

Knowledge of specific antidotes was shown to be connected to the size, type and location of the hospital in the East Godavari district, rather than individual physician characteristics. In roughly half of the hospitals assessed, significant antidotes are still unavailable or available within 2 h, even though all key acute decontamination therapies and procedures appear to be widely used.

Kirubakaran JJ, Dachuru RSR, Magharla DD. Antidote Mastery: A Survey of Antidote Knowledge and Availability among Physicians in a South Indian District. Indian J Pharm Sci 2022; 84(3):598-603. DOI: 10.36468/pharmaceutical-sciences.955.

TOXICOLOGY - II

ANTIDOTES FOR COMMON POISONS

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	Toxin	Antidote	Dose	Remarks
1.	Cyanide gas	Hydroxycobalamin - preferred	70 mg/kg (adults: 5 g) given over 15 min (IV)	Removal from the source of exposure, rapid administration of oxygen
		Cyanide kit		
		1. Amyl nitrate	1 crushable ampule; inhale 30 sec of each min	Both these drugs induce methemoglobinemia, which reversibly bind to cyanide to form cyanomethhemoglobin
		2. Sodium nitrate	0.33 mL/kg of 3% solution if hemoglobin level is not known; otherwise, based on tables with product (IV)	
		3. Sodium thiosulphate	1.6 mL/kg of 25% solution; may be repeated q30-60min to max of 50 mL (IV)	Na thiosulphate helps to convert cyanide to thiocyanate which is excreted by the kidneys.
2.	Methanol and ethylene glycol (EG) poisoning	Fomepizole	15 mg/kg load; 10 mg/kg q12h × 4 doses; 15 mg/kg q12h until EG level is < 20 mg/dL (IV)	If Fomepizole is not available, treat with an ethanol infusion. If both are not available hemodialysis or oral alcohol has been used
3.	Organophosphates and carbamates Cholinesterase-inhibiting insecticides	Atropine	0.05-0.1 mg/kg repeated q5-10min as needed (IV)	Pralidoxime is not necessary for carbamate poisonings
		Pralidoxime (2-PAM)	25-50 mg/kg over 5-10 min (max, 200 mg/min); can be repeated after 1-2 hr, then q10-12hr as needed	
4.	Tricyclic antidepressants, Type 1 antiarrhythmics Sodium channel blockers	Sodium bicarbonate	Initial bolus of 1-2 mEq/kg sodium bicarbonate is given followed by continuous infusion.	Indications for sodium bicarbonate - QRS duration >100 ms, ventricular dysrhythmias and hypotension.
5.	Sulfonylureas Oral hypoglycaemic agents	Octreotide		Symptomatic hypoglycemia-dextrose infusion

	Toxin	Antidote	Dose	Remarks
6.	Iron preparations	Deferoxamine	Infusion of 5-15 mg/kg/hr (max 6 g/24 hrs IV)	Activated charcoal does not adsorb iron and whole bowel irrigation remains the decontamination strategy of choice
7.	Acute digoxin toxicity	Digoxin-specific Fab antibody fragments (Digibind or DigiFab)	1 vial binds 0.6 mg of digitalis glycoside; ingested dose may be estimated from the serum level (IV)	Allergic reactions
8.	Calcium channel blockers	High-dose insulin therapy and glucose	If initial blood glucose is < 200 mg/dL, give 0.25 g dextrose IV before giving a bolus with regular insulin 1 unit/kg IV, followed by an infusion of regular insulin 0.5 to 1unit/kg/hr IV drip (max 35 to 100 units/hour), using an infusion pump and dedicated IV line. Simultaneously start glucose infusion at 0.5 mg/kg/hr (D10) and maintain blood glucose (BG) between 100-200 mg/dL. Assess the response clinically and by ECHO. If there is no significant response, increase the insulin drip to 0.5 units/kg/hr every 15 minutes to a max dose of 4 units/kg/hr. These kids should be monitored for hypoglycemia, hyponatremia and hypokalemia and managed accordingly. Dextrose infusion is continued for an average of 18 hours after the insulin infusion is stopped, as dextrose requirements increase when organ perfusion improves	
		Calcium salts	Dose depends on specific calcium salts (IV)	
9.	β-Adrenergic receptor blockers	Glucagon	0.15 mg/kg bolus followed by infusion of 0.05-0.15 mg/kg/hr (IV)	Seizures are managed with benzodiazepines, and QRS widening should be treated with sodium bicarbonate.
10.	Suboxone and methadone Oral opioids Fentanyl patch Codeine / Dextromethorphan in cough syrup	Naloxone	0.1 mg/kg (max, 2 mg/ dose) (IV)	Acute withdrawal symptoms if given to addicted patients May also be useful for clonidine ingestion

	Toxin	Antidote	Dose	Remarks
11.	Paracetamol	N acetylcysteine	140 mg/kg loading, followed by 70 mg/ kg q4h for 17 doses PO	
		IV N -Acetylcysteine	Another choice: 150 mg/kg over 1hr, followed by 50 mg/ kg over 4 hr, followed by 100 mg/kg over 16 hr	Anaphylactoid reactions (most commonly seen with loading dose)
12.	Dystonic reactions caused by drugs. Common: Antipsychotic and antiemetic agents Rarely: Anti-malarial, antidepressants, antihistamines and anticonvulsants (carbamazepine)	Diphenhydramine and/ or benztropine; second-line therapy with IV benzodiazepines may be considered	IV or IM lorazepam at 0.05 to 0.10 mg/kg or IV diazepam at 0.1 mg/kg may be considered	
13.	Benzodiazepines	Flumazenil	0.2 mg over 30 sec; if response is inadequate, repeat q1min to 1 mg max (IV) - The initial dose of 0.01 mg/kg given over 15 seconds (up to a maximum dose of 0.2 mg) - If the desired level of consciousness is not obtained after 45 seconds, repeat 0.01 mg/kg (up to 0.2 mg) at 1-minute intervals as needed, up to four additional doses. - The maximum total cumulative dose of 1 mg or 0.05 mg/kg, whichever is lower - Flumazenil should not be used routinely	Caution: Many experts believe that its risks may outweigh its benefits. Its effects are not consistent or predictable. This may precipitate seizures and withdrawal in patients who have been using benzodiazepines for a medical disorder. Should not be be used in patients with a history of seizures, head injury, or those who have ingested in addition tricyclic antidepressant. Contraindicated in patients with unknown or mixed overdose, seizure disorders or a prolonged QRS interval
14.	Carbon monoxide	Oxygen	100% FiO_2 via non-rebreather mask (or ET if intubated)	
15.	Isoniazid (INH)	Pyridoxine	Empirical dosing: 70 mg/kg (max dose = 5 g) If ingested dose is known: 1 g per gram of INH Preferable route IV; If IV injection not available, same dose can be given orally by crushing pyridoxine tablets and given through NG tube.	May also be used for Gyromitra mushroom ingestion

	Toxin	Antidote	Dose	Remarks
16.	Lead and other heavy metals (e.g., arsenic, inorganic mercury)	BAL (dimercaprol)	3-5 mg/kg/dose q4hr, for the 1st day; subsequent dosing depends on the toxin Route : - deep IM	Caution: Prepared in peanut oil; contraindicated in patients with peanut allergy
		Calcium disodium EDTA	35-50 mg/kg/day × 5 days; may be given as a continuous infusion or 2 divided doses/ day IV/ IM	
19.	Methemoglobinemia	Dimercaptosuccinic acid (succimer, DMSA, Chemet)	10 mg/kg/dose q8h × 5 days, then 10 mg/kg q12h × 14 days (PO)	
		Methylene blue, 1% solution	0.2 mL/kg (2 mg/kg) over 5-10 min; may be repeated q30-60 min (IV). Maximum dose 7 mg/kg. Prior to giving antidote,check for G6PD deficiency, as methylene blue is contraindicated in the presence of G6PD deficiency.	
20.	Salicylates	Sodium bicarbonate	Fluid resuscitation should utilize D5 with sodium bicarbonate. The dextrose will correct hypoglycemia and sodium bicarbonate will help correct the metabolic acidosis. Potassium may be supplemented if hypokalemia is present. Goal urine output is 2 to 3 mL/kg per hour. In severe cases mechanical ventilation and emergent hemodialysis may be needed. Bolus of 1 to 2 mEq/kg of sodium bicarbonate may be needed at the time of intubation.	Follow potassium closely and replete as necessary

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GENERAL ARTICLE

GROWTH MONITORING IN INDIAN CHILDREN - RECENT CONCEPTS

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Abstract: *Proper choice of growth charts and meticulous growth monitoring is an integral part of preventive pediatrics. The Infancy Childhood Puberty model of growth remains a valuable tool to interpret growth of children and narrow down the causes for deviant growth. The Indian Academy of Pediatrics (IAP) recommends that pediatricians use the IAP modified WHO 2006 chart for children below five years and new pediatrician friendly IAP growth charts in children above 5 years. The new Body Mass Index (BMI) look up tool is useful in children above 8 years and complements BMI interpretation using the growth charts. The mid parental height calculator obviates need for calculation of target height and helps interpret the child's height in the perspective of parental height. The cut-offs for recognition of abnormal growth are predominantly prescriptive and linked to diseased states. New growth charts have been developed for interpretation of waist circumference, growth velocity, body proportions and mid upper arm circumference in Indian children. The cut-offs in these charts include 70th percentile, 25th percentile, 2SD and 25th percentile, to identify cardio-metabolic risk, growth faltering, disproportionate short stature and thinness, respectively. The extended growth charts are useful diagnostic tools in growth clinics and NICU follow up clinics. Growth charts for Indian girls with Turner syndrome are available for use. Synthetic growth charts are exciting potential areas for future research in childhood growth.*

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Keywords: *Growth monitoring, Pediatrician friendly growth chart, BMI looks up tool, MPH calculator.*

Growth monitoring is a valuable pillar of preventive pediatrics, along with vaccination.[1] Monitoring of growth helps in early identification of many disease states. Growth monitoring helps reassure normalcy, early identification of many chronic disease states, response to therapy and assessment of nutritional status of a child.[1] Growth indicators speak of the socio-economic status of any country. There is a plethora of charts available for growth monitoring.[2-6] For optimal growth monitoring, a proper choice of updated charts representative of the country's population and a proper cut-off that identifies disease states are essential. The principles of growth monitoring for Indian children have been described by the authors in their previous article in 2017.[7] Subsequent to the publication, there have been many updates on growth monitoring for Indian children. This manuscript is an update on recent concepts of evidence-based rational growth monitoring for Indian pediatricians.

Current choice of growth charts

A mathematical model for human growth that is biologically oriented was proposed by Karlberg in 1989 and stands much valid even today.[8] Growth is divided into three phases: infancy, childhood and puberty. These phases are driven by maternal and infant nutrition, growth hormone and genetic factors and sex hormones, respectively. However, the three phases are not mutually exclusive, there does exist an element of overlap. The Indian Academy of Pediatrics (IAP) recommends that pediatricians use the IAP modified WHO charts in children below 5 years (Fig. 1a-d) and new Pediatrician friendly growth charts in children above 5 years (Fig. 1e-h).[9,10] These charts are a reflection of the ICP model.

The World Health Organization (WHO) conducted the Multicentre Growth Reference Study (MGRS study) and devised the WHO 2006 charts based on a population of infants with optimal nutrition (breast feed and proper complementary feed), optimal healthcare (proper immunization and routine care) and optimal environment (no smoking and microbiological contamination). The intergrowth consortium constructed the

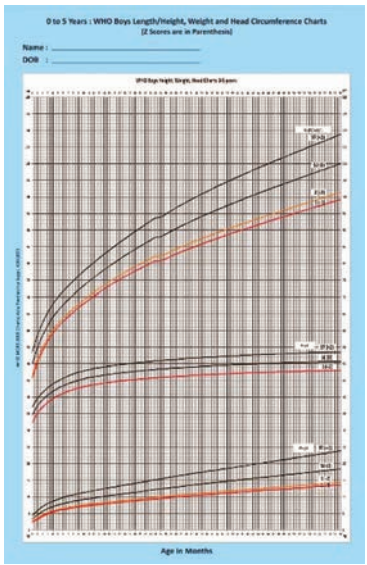

Figure 1(a) IAP modified WHO charts for boys

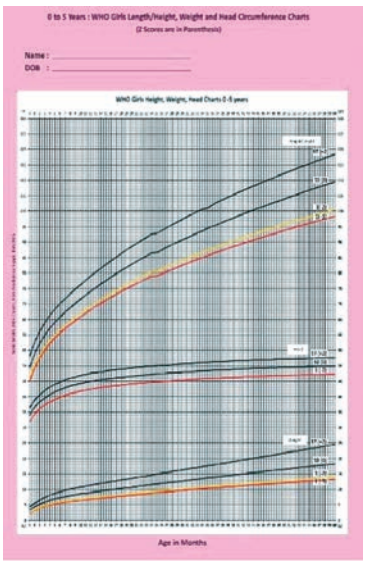

Figure 1(b) IAP modified WHO charts for girls

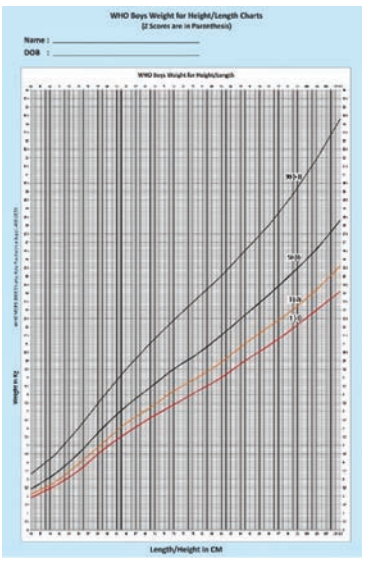

Figure 1(c) Weight for height IAP modified WHO charts for boys

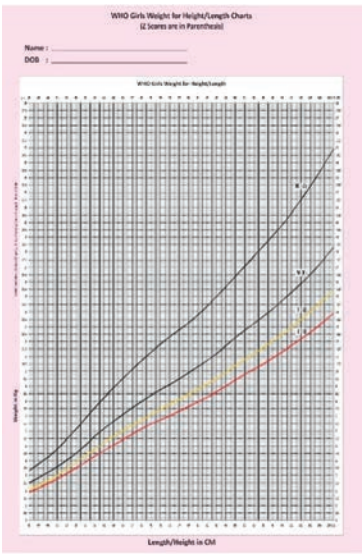

Figure 1(d) Weight for Height IAP modified WHO charts for girls

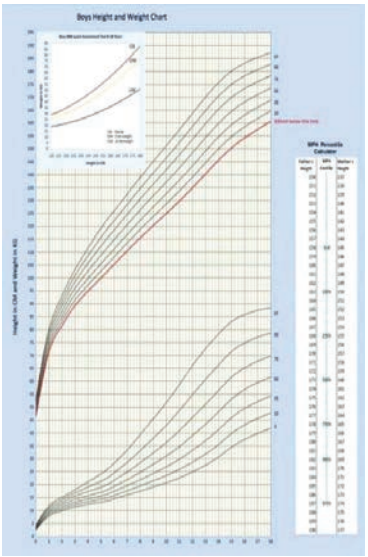

Figure 1(e) New Pediatrician friendly growth charts for boys

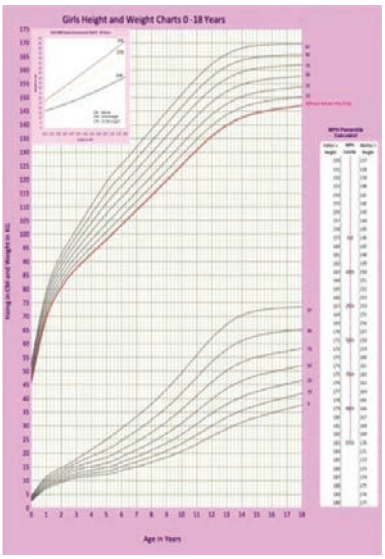

Figure 1(f) New Pediatrician friendly growth charts for girls

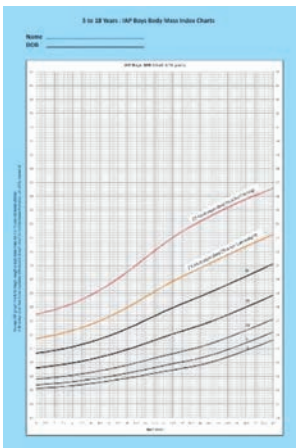

Figure 1(g) IAP 2015 BMI charts for boys

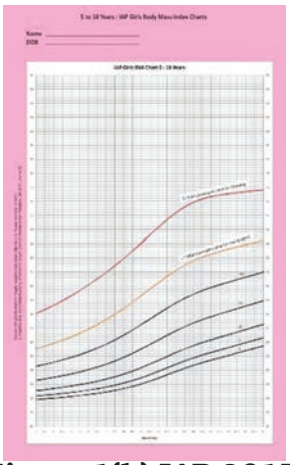

Figure 1(h) IAP 2015 BMI charts for girls

Fig.1a-1h. Growth charts for growth monitoring of Indian children and neonates

Figures originally published in Indian Pediatrics,[10,12,14] reproduced here with permission

intergrowth 21 standards on mothers with proper nutrition and healthcare and produced the intergrowth 21 at birth charts.[11] The percentile lines of the intergrowth 21 at birth charts and the WHO MGRS study merge very well indicating that maternal nutrition and infant nutrition is a continuum. Subsequently, the IAP collected growth data of affluent Indian population with no constraints to optimal growth from various parts of our country and constructed the IAP 2015 charts for children above 5 years. These charts are updated, based on same statistical tools as WHO standards and have excluded obese children from the datasets (to avoid normalization of obesity). The IAP has modified the WHO MGRS curves to produce the IAP modified WHO charts wherein a single sheet of paper allows assessment of weight, height, head circumference and weight for height in children below 5years. The number of percentile lines have been reduced to four, to, facilitate easy plotting and interpretation. The pediatrician friendly charts represent the WHO MGRS data in children below 5 years (which dwells well with the Intergrowth 21 charts at birth) and IAP 2015 data in children above 5 years.[12] Both the WHO MGRS study and Intergrowth 21 study had adequate representation from New Delhi and Nagpur, respectively. Thus, the new pediatrician friendly growth charts are a true representation of the infancy-childhood-puberty (ICP) model proposed by Karlberg for Indian children. All pediatricians should use IAP modified WHO charts for children below 5years (Fig.1a-d) and pediatrician friendly growth charts for children above 5 years (Fig.1e-h).

Methodology of plotting

The first step of plotting a growth chart involves a proper selection of the chart for the age and sex (pink charts for girls and blue chart for boys). The name and date of birth are entered into the chart at appropriate places. The IAP published the growth monitoring guidelines in 2007.[13] Subsequently, the charts to be used have been updated by IAP, but the frequency of growth measurements during visits to pediatrician have remained the same. Hence, all pediatricians should monitor growth as per these guidelines, summarized in Table I. One should remember to measure length even if a child below 2 years can stand. Also, one should avoid frequent weighing within 15 and 30 days interval during infancy and beyond infancy, respectively, to avoid unnecessary anxiety. The measured anthropometric parameters should be plotted at the point of intersection of the anthropometric measure on the Y-axis and chronological age on the X-axis. The plot should be done with a dot; not with a cross or a circle. The measure on the Y-axis represents 1 cm of height or 1 kg of weight or 1 cm of head circumference. The measure on the X-axis represents one day on the intergrowth 21 charts, 15 days (light line) and 30 days (dark line) on IAP modified WHO charts; and 3 months (light line) and 1 year (dark line) in pediatrician friendly charts. Weight for height is marked at the point of intersection of measured weight on X-axis and measured height on the Y-axis, on similar principles. The Body Mass Index (BMI) is plotted at the point of intersection of the BMI on Y-axis and age on the X-axis. These intervals of markings have been designed by the IAP to facilitate the IAP growth monitoring guidelines with the currently available growth charts and proper identification of growth abnormality. Once the growth chart is plotted, the interpretation of the chart is explained to the parents and they should be explained about the next point of growth assessment. Children with normal growth are reassured and abnormal growth is identified as described, subsequently.

Identification of abnormal growth and diagnosis

A diagnosis of normal growth and reassurance or abnormal growth and evaluation is made based on the position of the child on the growth chart, in the perspective of the chronological age. A child with growth measure below the 3rd percentile or above the 97th percentile for the population is generally considered deviant. The diagnosis of short stature, tall stature, underweight, wasting, thinness, overweight and obesity is made as described in Table II. One should remember that weight is preferably interpreted

Table I. IAP growth monitoring guidelines

Age	Measurement	Frequency
<2 years	Length, weight and head circumference	0, 6, 10 and 14 weeks, 6, 9, 15, 18 months (every vaccination visit)
2-5 years	Height, weight and head circumference	Every 6 months
>5 years	Height, weight, BMI SMR (Tanner's stage)	Every 6 months till 9 years and annually there after Every year

Table II. Definition of various growth abnormalities for routine office practice

	Neonates	Below 5 years	Above 5 years
Charts to be used	Intergrowth 21 charts (At birth)	IAP modified WHO charts	Pediatrician friendly growth charts
AGA	Birth weight/ length or head circumference between 3rd and 97th percentile		
SGA	Birth weight/ length or head circumference below 3rdpercentile		
LGA	Birth weight/ length or head circumference above 97th percentile		
Short stature / Stunting		Height below 3rd percentile	Height below 3rd percentile
Severe stunting		Height below 1st percentile	Nil
Underweight		Weight below 3rd percentile	Nil
Severe underweight		Weight below 1st percentile	Nil
Moderate acute malnutrition		Weight for height/ BMI below 3rd percentile	
Severe acute malnutrition		Weight for height/ BMI below 1st percentile	
Thinness			BMI below the 3rd percentile
Overweight		BMI or weight for height above 97th percentile	BMI above the 23rd adult equivalent
Obesity		BMI or weight for height above 99th percentile	BMI above the 27th adult equivalent
Catch down growth		Shifting down of growth by 2 major percentile lines in 6 months	Shifting down of growth by 2 major percentiles in 1 year
Rapid catch up growth		Shifting up of growth by 2 major percentile lines in 6 months	Shifting up of growth by 2 major percentiles in 1 year

in the perspective of height. Hence, underweight is reserved for children below 5 years and not made in older children. Also, to facilitate early recognition of microcephaly and early intervention, head circumference has only 3rd percentile at lower limit (unlike height and weight which has an additional 1st percentile). The diagnosis of SAM and MAM may be made after 6 months of life. Also, weight for height should be carefully interpreted in babies born SGA to avoid over diagnosis of SAM. Short stature is a terminology preferred to be used in individual cases with short stature; stunting is preferred to be used from a community perspective in nutritional surveys. However, practically both the terminologies denote a position of height below the 3rd percentile.

Growth references denote the comparison of an individual child's growth with the local population. Growth standards are the position of the child in a reference population and are sole criteria on which growth abnormalities can be diagnosed.[1] The cut-offs for stature and weight for height provided by WHO for children below 5 years are prescriptive in nature. The BMI cut-offs provided by the IAP are prescriptive as they have been linked to the adult cardiovascular risk factors as

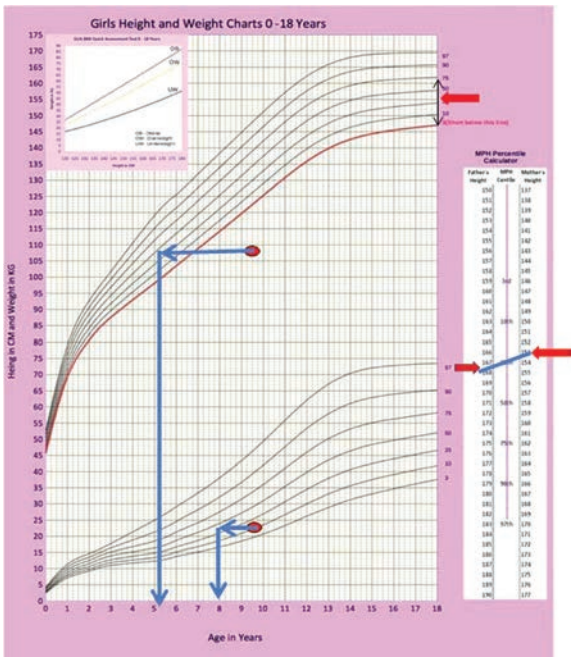

Fig.2.Calculation of height age and weight age

recommended by the International Obesity Task Force. However, stature related cut-offs of IAP are descriptive as it is practically difficult to recruit an ideal population not confounded by pubertal timing. Thus, the current growth charts are predominantly prescriptive and help clinicians use anthropometry as sole independent criteria to identify disease states.

Identification of probable cause of deviant growth

Whenever a clinician encounters a growth abnormality, one should recheck the measurement. Also, one should remember that serial measurement of trend of growth is much superior to abnormality on one cross sectional assessment. Once there is a strong clinical consideration of abnormal growth, the next step is to measure height age and weight age. A line is drawn from the plotted measure to the 50th percentile and a vertical line connects it to the X-axis (Fig.2). This arrives at the corresponding height age and weight age. This height age denotes the age of the child with same average height (50th percentile); weight age denoted the age of the child with the same average weight (50th percentile). A child without any growth abnormality has chronological age (CA), weight age (WA) and height age (HA) within one year difference. A difference beyond one year suggests deviant growth. The pattern of deviant growth gives clues to a possible etiology and guides the pediatrician on the investigation plan (described in Table III). The presence of height and weight on two different sides of the 50th percentile suggests a possible pathological cause. Also, the direction of the lines towards the 50th percentile in different directions point to a pathological cause.

BMI look up tool

The IAP devised the BMI look up tool in 2020.[14] Pediatricians should measure height and weight and plot it at the point of intersection of height in cm (X-axis) and weight in kg (Y-axis). The presence of the plotted point above red line indicates obesity, between red line and orange line indicates overweight and below the black line indicates underweight (Fig.3a,3b). This tool is useful in children above 8 years of age. Use of this tool obviates the need for complicated BMI calculation and facilitates many pediatricians to diagnose obesity early.[15] This tool complements the use of the new IAP charts to recognize both ends of overnutrition and undernutrition, early.

MPH calculator

The target height is calculated as below and marked with a horizontal arrow at 18 years.[16] Target range is marked as 6 cm above and below the target height.

Table III. Identification of growth abnormality

Growth pattern	Growth formula	Likely physiology	Likely diagnosis
Normal	CA= HA = WA	Normal nutrition and hormones	Normal child
Undergrowth	CA > HA > WA	Nutritional deprivation or a systemic disorder preventing normal growth	Malnutrition/ systemic disease
	CA > WA > HA	Endocrine abnormality	Endocrine disease
Overgrowth	WA > HA > CA	Insulin excess state	Nutritional obesity
	WA > CA > HA	Endocrine abnormality	Endocrine obesity
	HA > WA > CA	Overgrowth triggered by sex hormones	Precocious puberty

Legends: CA-Chronological age, WA – Weight Age, HA – Height Age

$$\text{Target height in boys} = \frac{\text{Father's height} + \text{Mother's height} + 13}{2}$$

$$\text{Target height in girls} = \frac{\text{Father's height} + \text{Mother's height} - 13}{2}$$

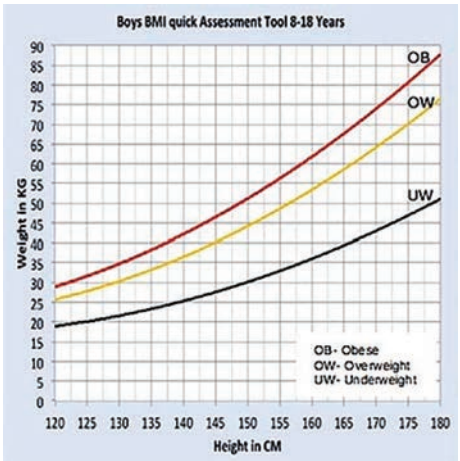

Fig.3a BMI look up tool for boys

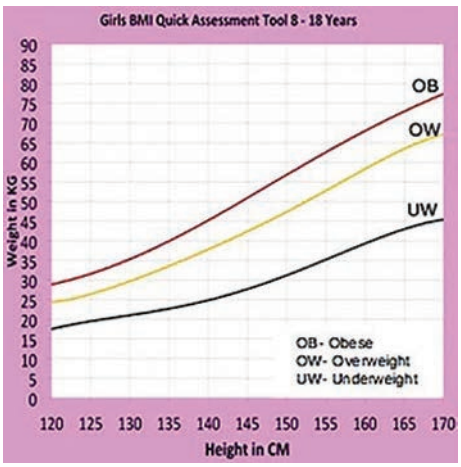

Fig.3b BMI look up tool for girls

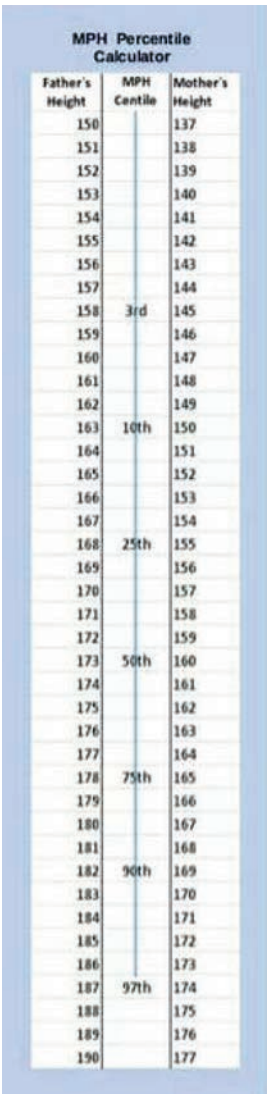

Fig.3c MPH calculator for boys

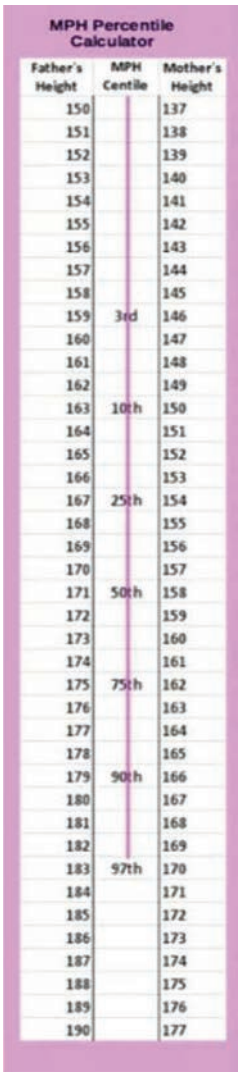

Fig.3d MPH calculators for girls

To obviate the complex calculation, the IAP has devised the MPH calculator should be measured.[12] The father's height and mother's height are measures and joined on the MPH calculator. The percentile at which the line intersects is considered as the MPH percentile (Fig.3c,3d). A discrepancy of 2 major percentiles between the MPH percentile and the child's height percentile is considered as short stature.[17] Thus, a child can be diagnosed as short stature despite having height above the 3rd percentile if the child's height is 2 major percentiles height discrepant from the target height percentile.

Growth velocity

Growth velocity data on Indian children is available from Southern, Western and Northern parts of our country.[18-20] Recently a seven year longitudinal follow up study was conducted on a cohort of 2949 children for a minimum period of 3 years with annual measurements at similar time of the year by the same set of observers.[21] These growth velocity percentile curves are depicted in Fig.4a and 4b. Annual growth velocity is computed based on the difference in between the height measurements divided by the time period (minimum period of 6 months). The calculated growth velocity should be plotted at the point of intersection of chronological age (midpoint between the time of two height measurements) on X-axis and growth velocity on the Y-axis. Growth velocity below the 25th percentile is considered as significant growth faltering and warrants evaluation.

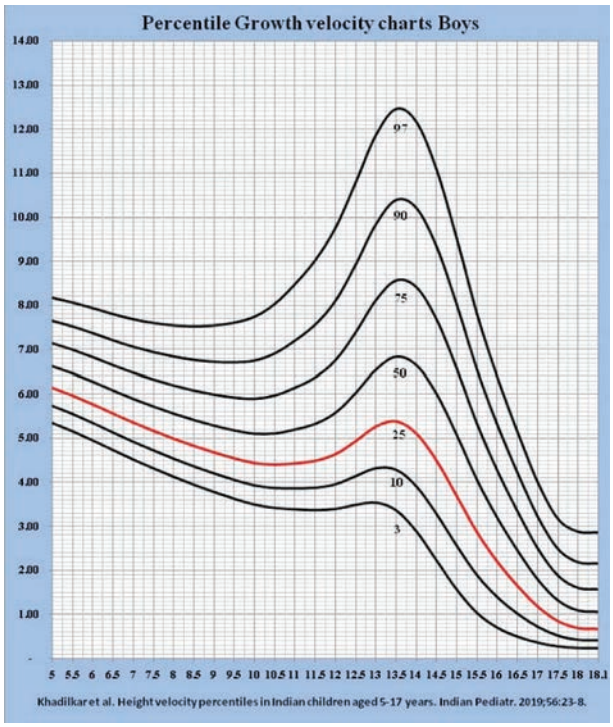

Fig.4a Growth velocity charts for Indian boys

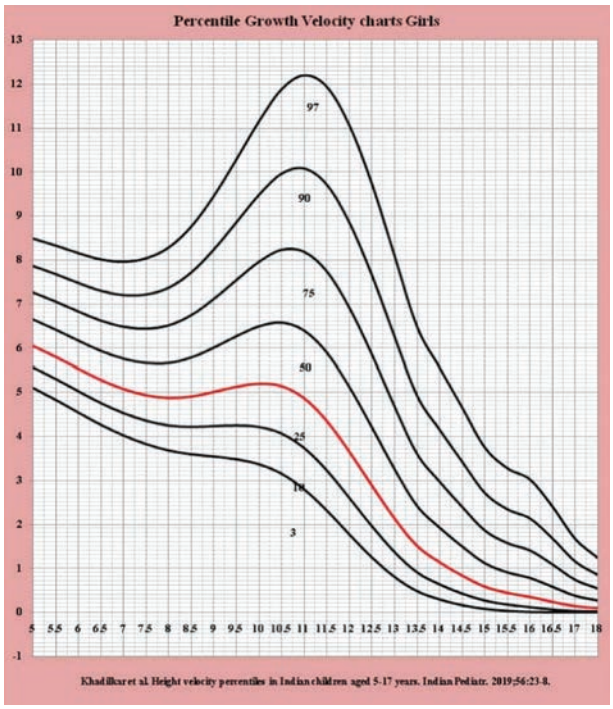

Fig.4b Growth velocity charts for Indian girls

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Waist circumference charts

Recently, Indian charts have been developed for waist circumference.[22] These charts were developed from 10842 Indian children from five major Indian cities. 70th percentile is reported to be an optimal cut-off to identify children with cardio-metabolic risk. Waist circumference is measured with an inelastic tape midway between lowest rib and iliac crest at the end of gentle expiration to the nearest 0.1 cm. Waist circumference complements the BMI assessment in children. Pediatricians should measure waist circumference to identify children and adolescents with metabolic syndrome.

Growth charts for Indian newborns

A plethora of charts are available for growth monitoring in preterms and neonates. The Babson and Benda, Gardner and Pearson, Fenton charts and Lubchenco charts are available for growth assessment in the neonatal period. The Fenton 2013 charts which is composed of a meta analysis of 6 studies from Germany, USA, Italy, Australia, Canada and Scotland on 396856 neonates including those below 30 weeks whose data amalgamates well with the WHO MGRS charts followed in many centres.[23,24] Recently, Intergrowth 21 consortium recruited a prescriptive sub-population with low risk of impaired fetal growth, accurate dating and included 20148 neonates above 33 weeks and 408 babies below 33 weeks and constructed the Intergrowth 21 at birth charts.[11,25] These charts may be used in neonates at birth to classify the baby as AGA, SGA and LGA. Many recent studies have established that Intergrowth 21 charts identify more at-risk babies versus the Fenton's charts.[26,27]

Specialized situations

Children with special growth pattern because of a specific disease may be monitored on specialized growth charts. Such specialized growth charts are available for achondroplasia, hypochondroplasia, Russell silver syndrome, Turner syndrome, Downs syndrome and Noonan's syndrome. Recently, Indian Turner syndrome charts have been published for growth assessment in Indian girls with Turner syndrome.[28] Use of these charts in specialized situations helps assess response to growth promoting therapy, identification of co-morbid states like hypothyroidism and celiac disease, early. There is a need to establish registries of rare disorders to collate auxological data and generate ethnic specific growth charts for these specialized conditions.

Extended growth charts

Recently, extended growth charts have been published for Indian children.[29] These charts are an extension of the

pediatrician friendly growth charts with three additional percentile lines: -2.25 SDs (for identification of children with idiopathic short stature requiring growth hormone), -2.5 SDs (for identification of children born SGA who are eligible to receive growth promoting therapy) and -3 SDs (for identification of those with pathological stunting), early. These charts are useful in growth clinics and NICU follow up clinics, where high risk babies are followed up.

Miscellaneous charts

Children with short stature should have their body proportions assessed either by upper segment: lower segment ratio or sitting height. Lower segment is measured with the child standing, measured from pubic symphysis till ground. Upper segment can be calculated by subtracting lower segment from height / length. By convention, at birth: 1.7:1, at 3 years 1.4:1, at 6 years 1.2:1; at 8 years 1:1 and at 10 years: 0.98:1 are considered as normal. If feasible, the ratio should be measured and plotted on the US:LS ratio charts.[30] Children with ratio below -2 SDs are considered as short trunk dwarfism, above +2 SDs are considered as short limb dwarfism, and those between -2 and +2 SDs are considered as proportionate short stature.

Recently, a multicentric study on 6680 healthy 5-17 year old children was conducted and sex specific mid upper arm circumference percentiles were devised.[31] Cut-offs for MUAC Z scores for thinness and overnutrition have been defined at -0.7 Z-score (25th percentile) and +1.5 Z-score (95th percentile). This anthropometric measures may be useful in children with cancer and other chronic disorders with growth failure.

Table IV. Equivalent percentiles and Z-scores for interpretation of anthropometric measures

Z-scores	Percentiles
0	50
-1	15
-2	3
-3	1
+1	85
+2	97
+3	99

Z scores versus percentiles

Interpretation of anthropometric data can be done using percentiles and Z-scores.[32] The percentile depicts the position of the anthropometry of a child on a ranking system. A growth parameter below the 3rd percentile indicates that the particular parameter, in 97% of children matched for age and sex, is more than that of the given child. Z-score indicates the degree of discrepancy and direction of discrepancy from the median. A Z-score of minus three indicates that the child is three standard deviations away from the median in the negative direction. By convention, anthropometric parameters between 3rd and 97th percentile, Z-scores between minus 2 and plus 2 are considered acceptable for the population. Anthropometric parameters can be converted from percentile to Z-score and vice-versa as shown in Table-IV. The currently recommended growth charts (Intergrowth 21, WHO 2006 and IAP 2015 charts) allow pediatricians to depict growth as both percentiles and Z-scores. Percentiles are used in routine clinical practice and Z-scores are used for research purposes or in diseased children.

Potential areas for future research

Collection of data for construction of growth charts is laborious and expensive. Recent researchers have attempted to produce synthetic references for Indian children based on mean heights and weights at key ages (birth, 2, 6, 12 and 15 years in girls; birth, 2, 6,14 and 18 years in boys). A deviation in anthropometric means was observed in extremes of weight and BMI measurements. Synthetic curves may be more representative and useful for growth monitoring in the future, especially in children below 5 years.[33-35] Large prospective studies are needed to validate the utility of these charts.

Points to Remember

- ***Pediatricians should use the Intergrowth 21 at birth charts, IAP modified WHO charts and pediatrician friendly growth charts for growth monitoring at birth, below 5 years and above 5 years, respectively.***
- ***Pediatricians should follow the IAP growth monitoring guidelines to measure growth in children.***
- ***The new BMI look up tool should be used to identify underweight, overweight and obese children above 8 years of age.***
- ***The new mid parental height percentile calculator may be used to assess the child's height in the perspective of the parental height.***

- ***Abnormal growth should be identified based on standard definitions as per WHO and IAP recommendations.***
- ***The Indian waist circumference charts, proportion charts and growth velocity charts should be used as necessary.***
- ***Extended growth charts for Indian children are useful in growth clinics and NICU follow up clinics.***

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CLIPPINGS

A study of fatal poisoning by autopsy based retrospective study

An autopsy based retrospective study was conducted from January 2000 to December 2006 at Manipal in Southern India, and a profile of the victims of poisoning was prepared. The study was done to understand the magnitude and pattern of all poisoning fatalities in relation to the manner of death in Manipal region of Southern India.

The study included a total of 198 cases of fatal poisoning. Self-poisoning was reported in 92.9% cases. Fatal accidental poisoning was seen in 6.1% cases. Homicide by poisoning was not reported during the study period. Uncertainty regarding the manner of death due to poisoning was observed only in two cases. Males were predominantly affected (71.2%). The majority of the victims were in the 3rd decade (28.3%) of life. The age of the victims ranged from 2 to 82 years with a mean age of 38.4 years.

While majority of the victims consumed poison during daytime, most of the poisoning fatalities were reported during summer months. Organophosphate compounds were implicated in 68.7% of the total poisoning related fatalities. Males in the 3rd to 5th decades were prone to self-poisoning with organophosphate compounds. Accidental poisoning deaths were uncommon and poisoning was not a preferred method of homicide in this region. Our approach to the study reveals that quantitative chemical (toxicological) analysis is required to further strengthen and improve the databases of epidemiology of poisoning in our region.

Kanchan T, Menezes RG, Mohan Kumar T, Bakkannavar S, Bukelo MJ , Sharma PS.(2010). Toxicoepidemiology of fatal poisonings in Southern India. J Forensic Leg Med; 17(6):344-347. https://doi.org/10.1016/j.jflm.2010.05.006.

DRUG PROFILE

DOSAGE ADJUSTMENTS IN PATIENTS WITH RENAL IMPAIRMENT - ANTIVIRALS

Jeeson C Unni

Abstract: *Dosage calculation of medications for children with renal impairment is a challenge for pediatricians. The balance between risk of toxicity and the ability to achieve adequate levels in target organs is the key. This article, the first of three, will deal with doses of some antiviral drugs in renal failure.*

Keywords: *Renal impairment, Dosage adjustment, Antivirals.*

Renal failure in children poses many issues regarding dosing of drugs, mainly toxicity due to accumulation of the drug or its metabolites, poor tolerance, increased sensitivity and ineffectiveness of certain molecules. Many of these problems could be overcome by either reducing the dose, increasing interval between doses or by administering alternative drugs.

Principles of dose adjustment in renal impairment

The percentage renal elimination of a drug, its toxicity and the degree of renal impairment would determine the dose reduction recommended for that given drug.[1]

- If side effects of the medication is minimal, dosage alterations may be nil or minimal.
- The glomerular filtration rate (GFR) is used to decide doses of drugs with narrow margin of safety (Box 1).
- Drugs for which plasma drug concentration determines efficacy and toxicity, only initial dosages are suggested; plasma concentration and response to treatment guides further dosing.
- A reduced maintenance dose is recommended for many drugs, because the plasma half-life of drugs excreted by the kidney is prolonged in renal impairment and therefore many doses at the reduced dosage may be required to achieve a therapeutic plasma concentration.
- Drugs known to be nephrotoxic may be avoided in children with renal disease as the renal toxicity is more severe when renal function is poor.

This is the first in the series of articles on dose adjustments of antimicrobials prescribed for children with renal impairment, which focuses on antivirals.

Acyclovir

Usual route of clearance: Acyclovir is predominantly cleared by kidneys (75-80% excreted unchanged in the urine)[1] through glomerular filtration and tubular secretion. There is only one significant metabolite, which accounts for 10-15% of the dose excreted in the urine.

Dose adjustment in renal impairment:

GFR 25-50 mL/min - normal dose IV every 12 hours;

GFR 10-25 mL/min - normal dose IV every 24 hours;

GFR <10 mL/min - half the normal dose IV every 24 hours.

Dose adjustment in hemodialysis (HD): HD removes approximately 60% of a dose. Give half the normal dose IV every 24 hours after dialysis session.

Dose adjustment in peritoneal dialysis (PD). Give half the normal dose IV every 24 hours.

Box 1. Calculation of estimated glomerular filtration rate (GFR)

Dose recommendations are based on the severity of renal impairment. This is expressed in terms of glomerular filtration rate (GFR - mL/minute/1.73 m^2).

The following equations provide a guide to glomerular filtration rate.

Neonate:

Estimated glomerular filtration rate (mL/minute/1.73 m^2) = 30 x height (cm)/serum creatinine (mmol/L) Child over 1 year:

Estimated glomerular filtration rate (mL/minute/1.73 m^2) = 40 x height (cm)/serum creatinine (mmol/L)

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Dose adjustment in Continuous Veno-Venous Hemofiltration (CVVH): Give normal dose IV every 24 hours. Increase to every 12 hours if severe infection e.g. herpes encephalitis.

Cidofovir

The major route of elimination of cidofovir is by renal excretion of unchanged drug via glomerular filtration and tubular secretion [2] and 80-100% of a dose is excreted unchanged in the urine within 24 hours. No metabolites have been detected in the serum or urine of patients receiving cidofovir.

Dose adjustment in renal impairment

GFR >55 mL/min - normal dose

GFR 10-55 mL/min 1mg/kg IV three times per week for two weeks (induction), then 1mg/kg IV every two weeks (maintenance) [3]

GFR <10 mL/min - 0.5 mg/kg IV once per week for two weeks (induction), then 0.5mg/kg IV once every two weeks (maintenance).

Dose adjustment in HD: Give 2 mg/kg IV once per week for two weeks (induction), then

2 mg/kg IV once every two weeks (maintenance). Administer dose 2 hours before dialysis session to benefit from peak concentration without having delayed clearance.[2]

Dose adjustment in PD and CVVH: Give 0.5 mg/kg IV once per week for two weeks (induction), then 0.5 mg/kg IV every two weeks (maintenance) [2].

Gancyclovir

The major route of elimination is renal excretion of unchanged drug by glomerular filtration and active tubular secretion (approximately 80-100% of the dose is excreted unchanged).[1]

Dose adjustment in renal impairment

GFR >55 mL/min - normal dose

GFR 10-55 mL/min - 1 mg/kg IV three times per week for two weeks (induction), then 1mg/kg IV every two weeks (maintenance)[3]

GFR <10 mL/min - 0.5 mg/kg IV once per week for two weeks (induction), then 0.5 mg/kg IV once every two weeks (maintenance).

Valacyclovir[4]

For herpes zoster,

1 g every 12 hours if estimated GFR - 30-50 mL/minute/1.73 m^2

1 g every 24 hours if estimated GFR - 10-30 mL/minute/1.73 m^2

500 mg every 24 hours if estimated GFR - < 10 mL/minute/1.73 m^2.

For treatment of herpes simplex

500 mg (1 g in immunocompromised or HIV-positive children) every 24 hours if estimated GFR - less than 30 mL/minute/1.73 m.[2]

For treatment of herpes labialis, if estimated GFR - 30-50 mL/minute/1.73 m^2, initially 1 g, then 1 g 12 hours after initial dose (if estimated GFR - 10-30 mL/minute/1.73 m^2, initially 500 mg, then 500 mg 12 hours after initial dose; if estimated GFR - less than 10 mL/minute/1.73 m^2, 500 mg as a single dose).

For suppression of herpes simplex, 250 mg (500 mg in immunocompromised or HIV-positive children) every 24 hours if estimated GFR-less than 30 mL/minute/1.73m^2. Reduce dose according to estimated GFR - for cytomegalovirus prophylaxis following solid organ transplantation.

Oseltamivir

Oseltamivir is predominantly eliminated via kidney after conversion by liver esterases to an active metabolite oseltamivir carboxylate. Less than 20% of an oral dose is excreted in the faeces.

Dose adjustment in renal impairment[5]

GFR 30-60 mL/min - for treatment 40% of normal dose twice daily and for prophylaxis 40% of normal dose once daily.

GFR - 10-30 mL/min - for treatment give 40% of normal dose once daily and for prophylaxis 40% of normal dose every 48 hours.

GFR <10 mL/min - avoid for treatment and prophylaxis.

Dose adjustment in HD: For treatment and prophylaxis, give 50% of the normal dose after each dialysis session.

Dose adjustment in PD: For treatment give 50% of the normal dose as a single dose once a week after dialysate

exchange and for prophylaxis give 50% of the normal dose as a single stat dose. A second dose may be given after one week.[6]

Zanamivir

Intranasal administration at normal dose in renal failure and in children undergoing renal replacement therapy.

Foscarnet (Table I)

Dose-related nephrotoxicity occurs in a substantial proportion of foscarnet recipients. Renal dysfunction usually (though not always) resolves 1-5 weeks after discontinuing foscarnet.[7] During initial therapy and during hospitalization, serum creatinine should be monitored daily. Sustained (e.g. on 2 separate occasions) changes in serum creatinine of 0.4 mg/dL or more should warrant consideration for dose adjustment. For patients receiving foscarnet in an outpatient setting, serum creatinine should be monitored at least twice weekly. If creatinine increases substantially (e.g. >0.4 mg/dL), consideration should be given to re-checking serum creatinine before infusion of the next dose to determine if dose adjustment is necessary.

Safety and efficacy data are limited for patients with baseline serum creatinine levels greater than 2.8 mg/dL or measured 24-hour CrCl (creatinine clearance) less than 50 mL/min.

Foscarnet is not recommended in patients undergoing hemodialysis because dosage guidelines have not been established.

Nevirapine

No dose adjustment is required for patients with CrCl > 20 mL per min. The pharmacokinetics of nevirapine have not been evaluated in patients with CrCl less than 20 mL per min. Patients on dialysis receive an additional dose of 200 mg following each dialysis treatment.[8]

Abacavir

No dosage adjustment needed as renal excretion is a minor route of elimination, however avoid in end stage renal disease.

Didanosine

Reduce dose if estimated GFR - less than 60 mL/minute/ 1.73 m^2.

GFR 30-59 mL/min - 150 mg/day in 1-2 divided doses

GFR 10-29 mL/min - 100 mg/day

GFR < 10 mL/min - 75 mg/day.

Child on CAPD (not dialysed) or HD (dialysed): as in GFR <10 mL/min;

CAV/VVHD (dialysed): as in GFR 10-29 mL/min.

Table I. Dosage of foscarnet in renal impairment

CrCl (mL/min/kg)	CMV retinitis induction	CMV retinitis maintenance	HSV induction
>1.4	60mg/kg IV 8th hrly or 90 mg/kg IV 12th hrly	90 or 120 mg/kg IV every 24 hours	40 mg/kg IV 8th or 12th hrly
>1-1.4	45mg/kg IV 8th hrly or 70 mg/kg IV 12th hrly	70 or 90 mg/kg IV every 24 hours	30 mg/kg IV 8th or 12th hrly
>0.8-1	50 mg/kg IV 12th hrly	50 or 65 mg/kg IV every 24 hours	20 or 35 mg/kg IV 12th hrly
>0.6-0.8	40mg/kg IV 12th hrly or 80 mg/kg IV every 24 hours	80 or 105 mg/kg IV every 48 hours	35 mg/kg IV every 24 hours or 25 mg/kg IV 12 hrly
>0.5 to 0.6	60 mg/kg IV every 24 hours	60 or 80 mg/kg IV every 48 hours	25 or 40 mg/kg IV every 24 hours
>0.4 to 0.5	50 mg/kg IV every 24 hours		20 or 35 mg/kg IV every 24 hours
0.4 to 0.5		50 or 65 mg/kg IV every 48 hours	
<0.4		Not recommended	

Table II. Renal effects of ARV drugs

ARV drug	Renal effect
Raltegravir	Inhibition of tubular secretion of serum creatinine by organic cation transporters Rhabdomyolysis Possible reduction in true GFR
Elvitegravir	None reported
Dolutegravir	Inhibition of tubular secretion of serum creatinine by organic cation transporters
Cobicistat	Inhibition of tubular secretion of serum creatinine by multidrug and toxin extrusion 1 (MATE 1) It increases the serum concentration of , tenofovir disopoxil fumarate (TDF) with potential risk for enhancement of TDF tubular toxicity if co-administered
Ritonavir	It is often included in combination therapy as a booster, which partially inhibits MATE1 and may therefore increase serum TDF
Tenofovir alafenamide fumarate	No renal toxicity reported
Atazanavir	Renal stones Acute tubular injury (interstitial nephritis)

Lamivudine (3TC)

3TC is a well-tolerated drug with a wide therapeutic window, dose adjustment may be unnecessary with eGFR between at least 30 and 49 ml/min per 1.73 m2 or less.[9] Clinical judgement is key when weighing the risks and benefits of 3TC dose adjustment.

GFR 30-50 mL/min: HIV-150 mg/day, Hepatitis B-100 mg stat followed by 50 mg/day

GFR 15-29 mL/min: HIV-150 mg stat followed by 100 mg/day, Hepatitis B - 100 mg stat followed by 25 mg/day.

GFR 5-15 mL/min: HIV-150mg stat followed by 50 mg/day, Hepatitis B - 35mg stat followed by 15mg/day

GFR <5 mL/min: HIV - 150 mg stat followed by 25-50 mg/day, Hepatitis B - 35 mg stat followed by 10 mg/day.

Child on CAPD (not dialysed) or HD (dialysed): as in GFR <5 mL/min

CAV/VVHD (unknown dialysability):as in GFR 5-15ml/min.

Zidovudine (AZT)

GFR <10ml/min: half the normal dose 8th hrly.

Child on CAPD (not dialysed) or HD (dialysed): as in GFR <10ml/min

CAV/VVHD (unknown dialysability): Full normal dose 8th hourly.

Possible renal effects of novel ARV drugs is given in Table II.[10]

Ribavirin

Ribavirin is metabolised principally to deribosylated ribavirin (1, 2, 4-triazole-3- carboxamide), probably in the liver. It is excreted primarily in the urine and a small amount is excreted in the faeces.

Dose adjustment in renal impairment-GFR <50ml/min - Avoid oral ribavirin, monitor haemoglobin concentration closely. Manufacturer advises use intravenous preparation with caution if estimated glomerular filtration rate less than 30 mL/minute/1.73 m^2.

Conclusion

Well established, evidence-based dosing for renal impaired children are not readily available in standard pediatric formularies like the British National Formulary for Children (BFNC) or the Indian Academy of Pediatrics (IAP) Drug Formulary and we need to rely on the manufacturer's label as the primary source of pediatric renal dosing information. This is especially so when dealing with use of antivirals in children with renal impairment.

Points to Remember

- ***Determining the dosage in children with renal failure is a challenging task in children because of drug toxicity and ineffectiveness of certain molecules. These problems could be overcome by either reducing the dose, increasing interval between doses or by administering alternative drugs.***
- ***A reduced maintenance dose is recommended, because the plasma half-life of drugs excreted by the kidney is prolonged in renal impairment and therefore many doses at the reduced dosage may be required to achieve a therapeutic plasma concentration.***
- ***Dose recommendations are based on the severity of renal impairment, which is expressed in terms of glomerular filtration rate.***
- ***Dosage adjustments of common drugs like acyclovir, cidofovir, gancyclovir, valacyclovir, oseltamivir, zanamivir and foscarnet is described here.***

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CLIPPINGS

Pattern and outcome of Cleistanthuscollinus (Oduvanthalai) poisoning in a tertiary care teaching hospital in South India.

There is paucity of information on human studies about Cleistanthuscollinus (Oduvanthalai) poisoning at global level. The present study was done to find out the pattern and outcomes with acute poisoning of this plant poison. Retrospective record based study was conducted among acute *C. collinus* (Oduvanthalai) poisoning cases admitted between January 2010 and December 2010 in a tertiary care teaching hospital in South India. A total of 51 cases were analyzed with 52.9% of them being females and 51% belonged to 21–40 years age group. Interpersonal conflict was the stressor for poisoning in 76% cases. Mortality rate was 17.6% with a median duration of 3.5 days from time of ingestion. Majority of the patients who died during hospitalization had ingested decoction (77.8%), and had neurological manifestations (77.8%), hypokalemia (77.8%), neutrophilia (66.7%), leucocyotosis (55.6%) and elevated blood urea (77.8%). It was found that lower potassium level, white blood cell and neutrophil count were significantly associated with mortality due to poisoning.

Bammigatti C, Surynarayana BS, Harichandra Kumar KT, Ganesh Kumar S. Pattern and outcome of Cleistanthuscollinus (Oduvanthalai) poisoning in a tertiary care teaching hospital in South India. J Forensic Leg Med. 2013 Nov;20(8):959-61. doi: 10.1016/j.jflm.2013.08.011. Epub 2013 Aug 28. PMID: 24237798.

RADIOLOGY

EVALUATION OF PULMONARY TUBERCULOSIS IN CHILDREN

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***** Kasi Visalakhshi KP***

Tuberculosis remains a formidable disease with newer forms like the drug resistant variety and HIV complicated disease. The X-ray of the chest is an important part of the detection and evaluation of the disease.

Tubercle bacilli are commonly inhaled and lodge in the lungs, usually in the upper parts of the lower lobes or the lower parts of the upper lobes. An inflammatory response is set up. Initially macrophages try to destroy the bacilli but the mycobacteria resist lysis and continue to grow and proliferate spreading in a radial fashion. After about three weeks, more T, B cells and neutrophils - surround the infective site forming a granuloma. The tissue in the centre undergoes caseous necrosis. This is called the 'Ghon focus'.

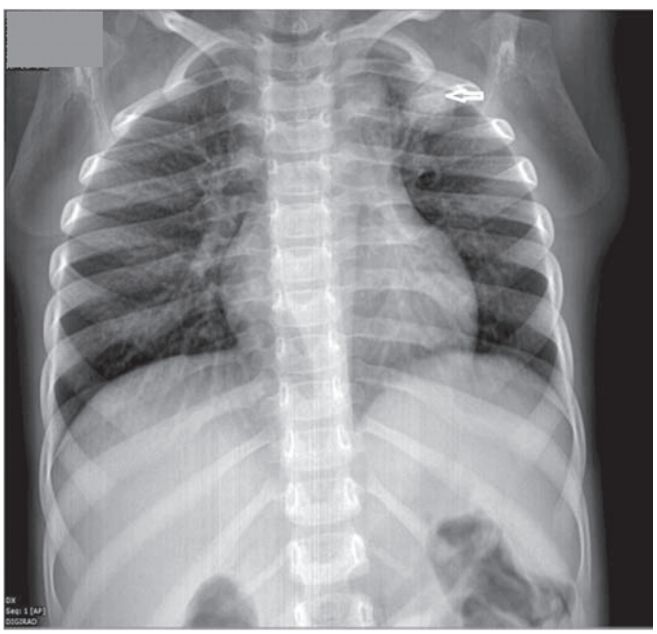

Fig.1. Ghon complex

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Radiological features

The Ghon focus is seen as a round opacity from which linear white strands course towards the hilum. These lines represent the spread of the infection along the swollen lymphatics to the hilar and then to the mediastinal nodes. The inflamed enlarged mediastinal lymph node appears as a paratracheal bulge. These three components which are the pulmonary focus, the draining lymphatics and the node, constitute the 'primary complex' or the 'Ghon complex'(Fig.1). The Ghon focus is not seen in the x-ray unless it has attained a large size or it has calcified. It is rarely seen as with good and efficient immune surveillance it disappears quickly the only evidence of previous infection being a calcified lung focus or a calcified mediastinal node. However, the node remains for a longer time. Therefore the commonest chest x-ray finding in primary TB is the presence of nodes-paratracheal, subcarinal or hilar nodes, that may be seen with or without a parenchymal lesion. Infective foci in the upper zones extend to the para-tracheal nodes. These are seen as smooth bulges lateral to the trachea on the ipsilateral side (Fig.2). Lower zone infections spread to the subcarinal nodes. Hilar nodes are seen at the lung hilum. With the appropriate immune response nodal disease also resolves.

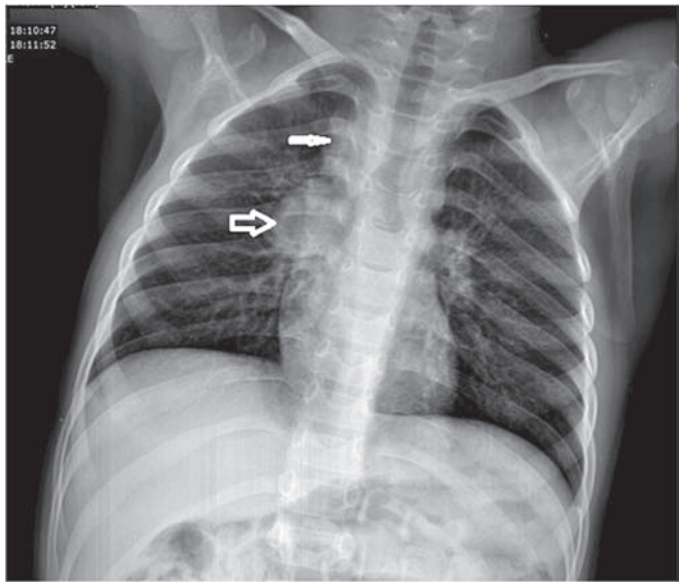

Fig.2. Hilar node and mediastinal nodes

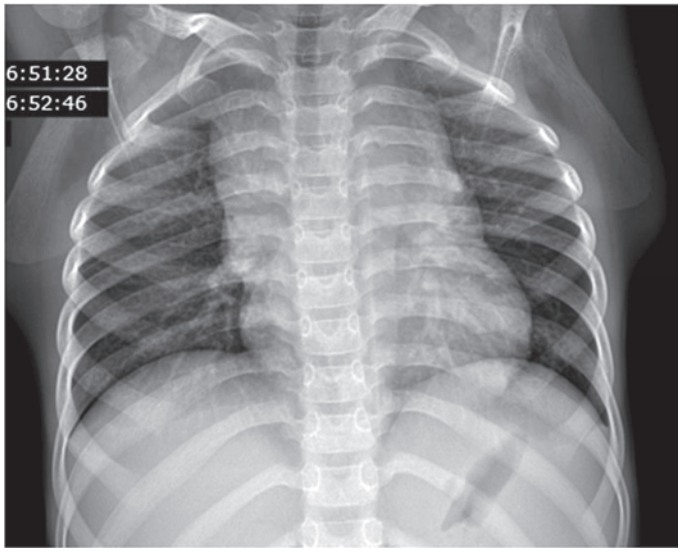

Fig.3. Mediastinal widening due to glands

Mediastinal widening due to enlarged lymph nodes (Fig.3). This is seen in lymphoma. In lymphoma, the nodes are many and large which is not the case with tuberculosis. Rarely a single node has turned out to be lymphoma but commonly it is due to TB. Another pitfall is that of the right aortic arch which is seen as a right paratracheal bulge. It may sometimes be difficult to distinguish vascular structures and thymus from nodes in children. This is why computer aided detection software recommended as an alternative to human reading for chest x-ray screening for TB is at present limited to children older than 15 years and adults.

When infection advances to frank disease it is called progressive primary TB. In the susceptible or in those with a large bacillary burden, this takes place in about 6 months to a year from exposure. Post primary TB occurs in older children due to the reactivation of dormant bacilli in the primary infective site or in the draining nodes. Pathological process and radiological features are essentially the same in both types except for a few differences such as the prevalence of adenopathy which decreases with age.

The commonest finding in progressive primary TB is air space opacification. Since such a finding is frequently seen in non-tuberculosis situations it can only be considered along with clinical features that may suggest TB. The air space opacification is seen as patches of pneumonia to frank lobar consolidation (Fig.4). Parenchymal involvement starts in the peripheral subpleural regions, commonly in the middle and lower zones in the chest X-ray. They may be difficult to see in X-rays, so that quite often the X-rays

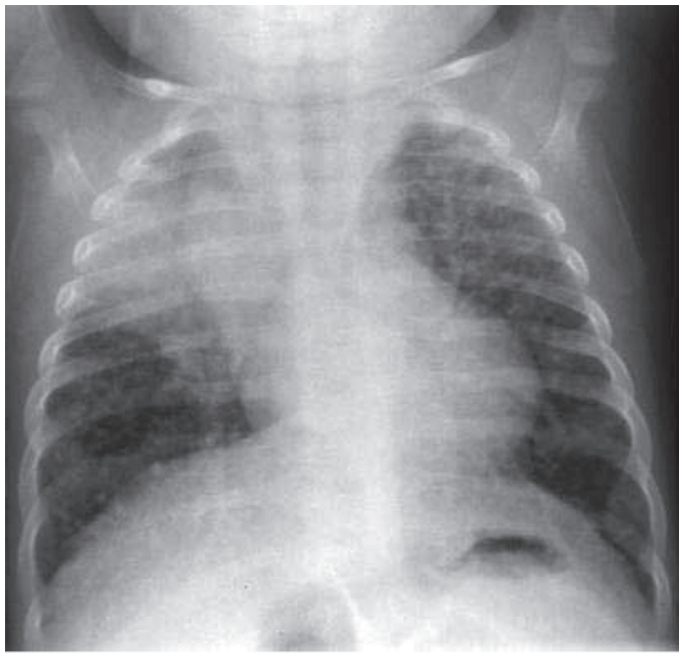

Fig.4. Consolidation in right upper lobe with para-tracheal node

appear normal. In fact, in immune-competent children who remain asymptomatic, the only clue of an earlier infection is a calcified pulmonary focus or a calcified node. Radiographically detectable lung involvement is higher in older children and adults, while the prevalence of adenopathy decreases with age. But, the hallmark of the disease in children remains the presence of enlarged nodes.

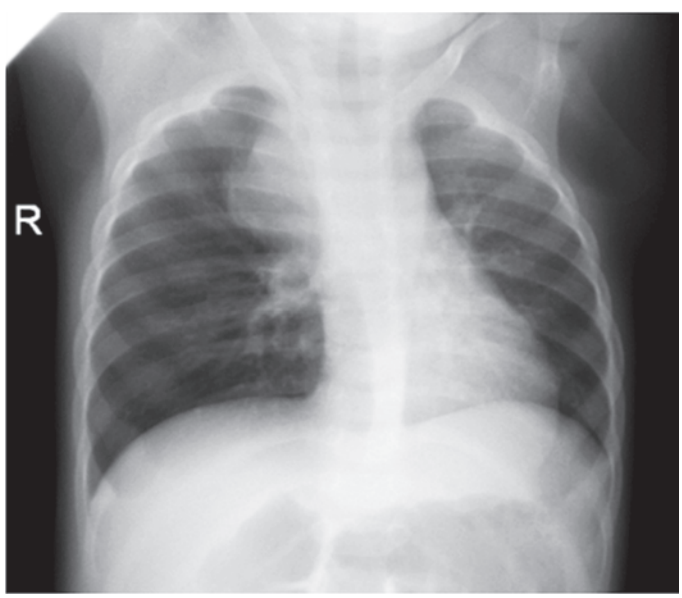

Fig.5. Mediastinal node and hilar node causing obstructive emphysema due to compression

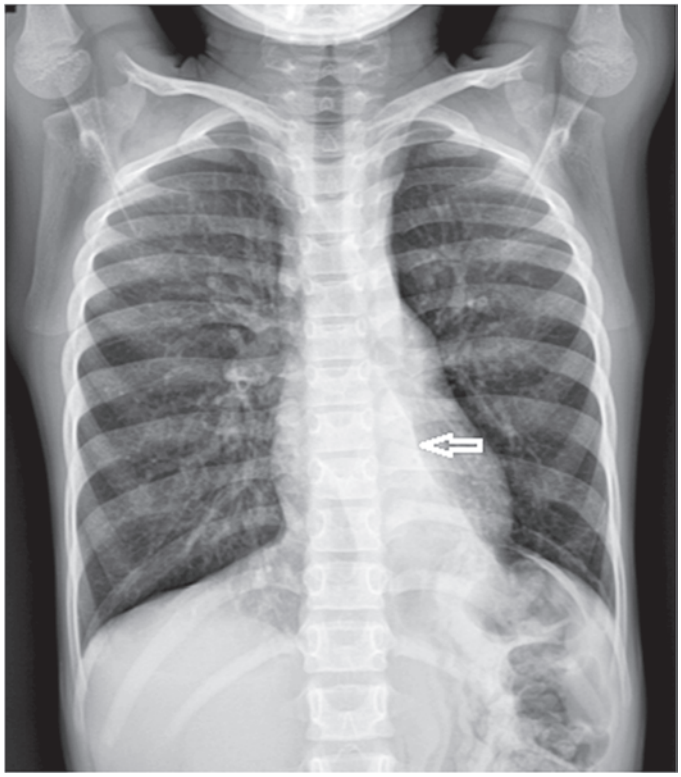

Fig.6. Collapse of the left lower lobe

Nodes continue to enlarge and may complicate the disease if not treated. An enlarged node may compress a bronchus, usually the right main bronchus or bronchus intermedius. Fig.5 shows hilar node and a mediastinal node compressing the bronchus causing obstructive emphysema of the right lung. A node can also ulcerate and erode into the adjacent bronchus. Luminal narrowing may also be due to endobronchial TB due to hematogenous dissemination or to ascending infection. The ensuing bronchial stenosis can lead to collapse of the lobe (Fig.6). Long standing collapse, pent up secretions, infection and destruction of surrounding lung parenchyma can cause cicatricial bronchiectasis. Bronchiectasis is an irreversible dilatation with thickening of the bronchial wall. It is seen as multiple small ring like shadows which represent a cross section of the dilated airways. They may have air-fluid levels and predispose to recurrent pneumonia with secondary bacterial infection. Bronchiectasis with surrounding pneumonic changes are seen in Fig.7.

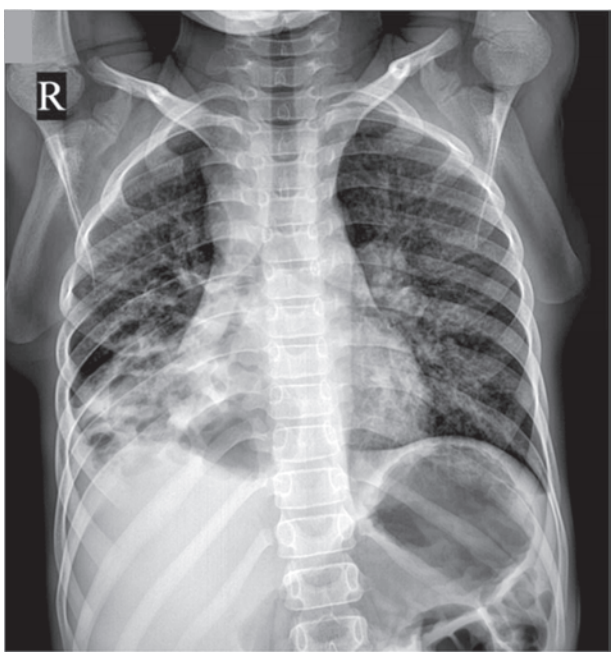

Fig.7. Bronchiectasis in right lower lobe with pneumonia

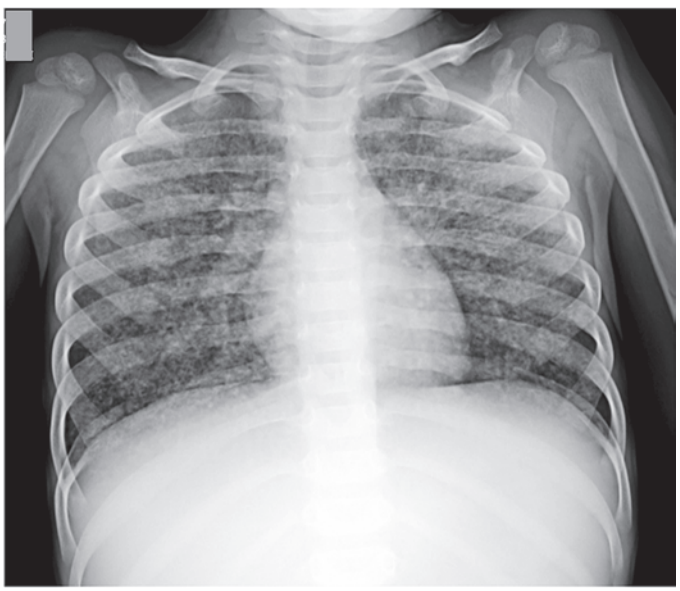

Fig.8. Miliary TB

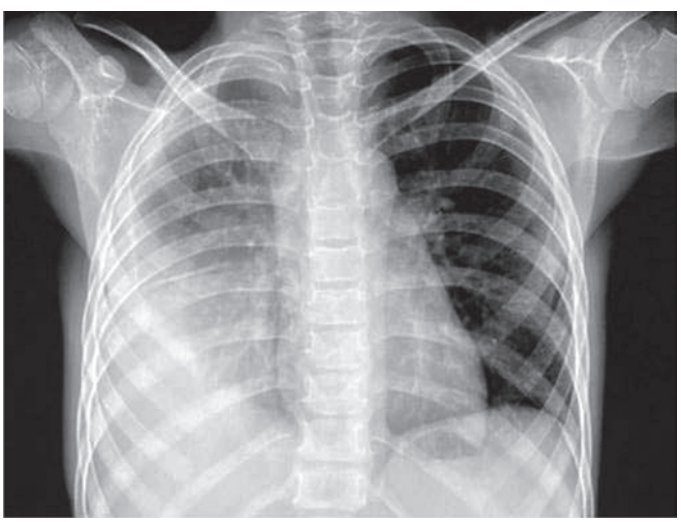

Fig.9. Pleural fluid on right

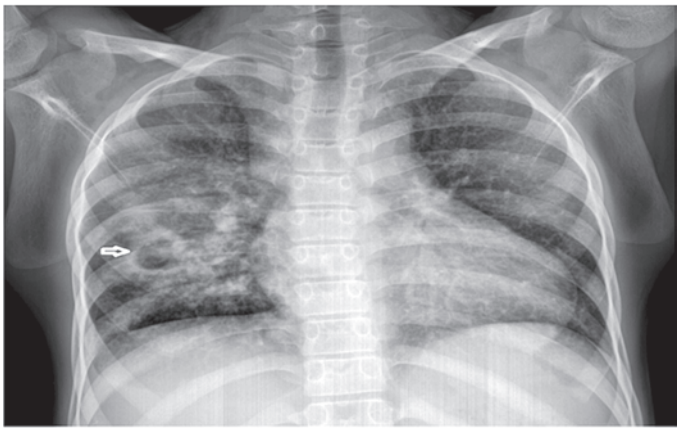

Fig.10. Cavity in the right lower lobe

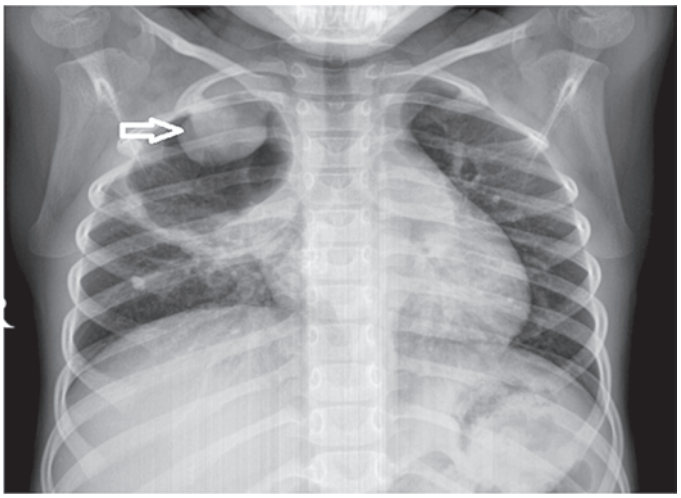

Fig.11. Fungal ball within cavity

Miliary TB is a haematologically disseminated form of the disease associated with prolonged exposure, heavy bacteremia and a compromised cellular immunity. Since there is a shower of bacilli the lesions are diffusely spread in a random distribution. Both lungs are filled with multiple small nodular shadows likened to millet seeds (Fig.8). They are of uniform size as they have all formed at the same point of time. Miliary TB may not be seen in the X-ray early in the course of the disease, as in the case of interstitial shadows. HRCT is then useful and can be used if there is a strong clinical suspicion.

Pleural effusion as a part of primary tuberculosis results from obstruction of lymphatic drainage or a hypersensitivity reaction to mycobacterial protein. It is seen as a free effusion without loculations, can be asymptomatic and will resolve (Fig. 9). In post primary TB, pleural fluid is the result of contiguous spread from a sub pleural focus. Ultrasound will show debris and septations in the fluid. The empyema can break through the parietal pleura and form a subcutaneous abscess that can rupture through the skin.

The adult type or post primary TB is also called reactivation TB because it arises out of reactivation of dormant foci. In the pediatric age group it is seen in adolescents and is considered a late progression of the primary infection. The most commonly affected locations are the apical and posterior segments of the upper lobes and the apical segment of the lower lobe because of better oxygen tension. The lesion starts as patchy opacities that coalesce to form an area of consolidation. This undergoes caseous necrosis. The liquefied and fragmented tissue is coughed out through the communicating airway and a cavity is formed (Fig.10). The cavity maybe thick or thin walled. Thin walled cavities are difficult to differentiate from pneumatoceles and clinical features and molecular diagnostic tests should be used. Quite often there are multiple fluffy or nodular shadows in other parts of the lung due to coughed up infective tissue spreading through the airways. These are signs of active disease. Sometimes tuberculous cavities are colonised by fungus. The aspergilloma is seen as a rounded lesion within the cavity and can be shown to be mobile with changing position (Fig.11).

With progressive disease the alveoli and septae are destroyed and normal lung architecture is lost. The lung is replaced by large air or fluid filled cavities (Fig.12). It can

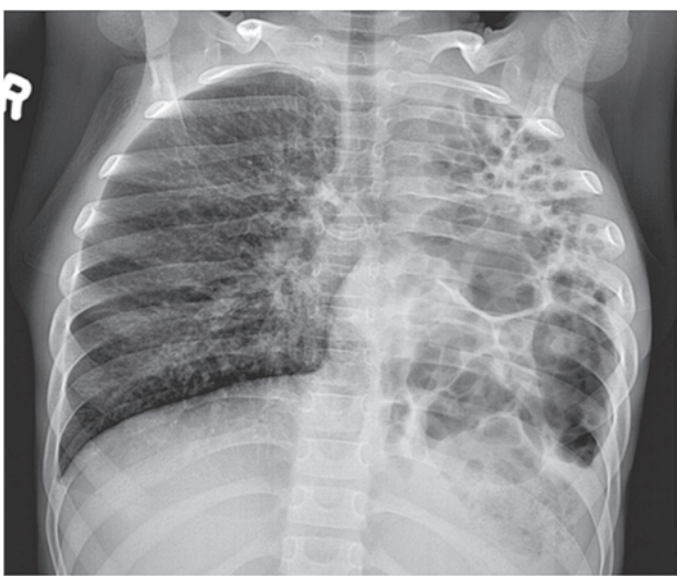

Fig.12. Destroyed left lung

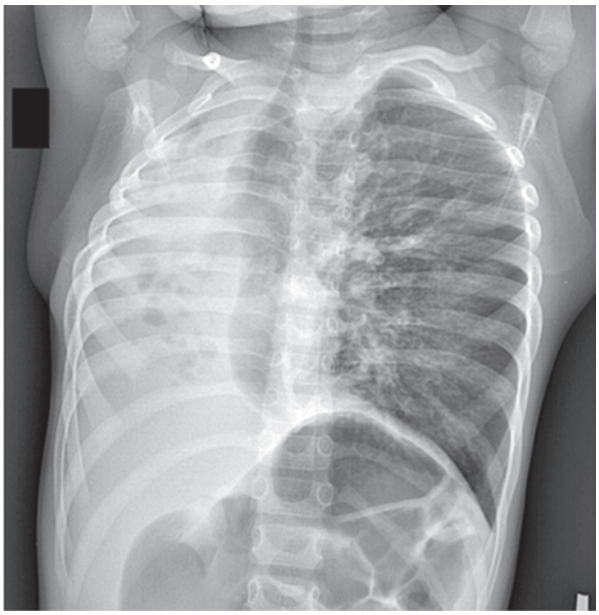

Fig.13. Collapsed right lung with destruction of parenchyma

be totally collapsed (Fig.13). There is a loss of volume. The mediastinum is pulled to the side of disease and the ribs are crowded with narrow intercostal space.

The chest x-ray is a valuable modality for assessing tuberculosis activity. One PA or AP film is adequate. Lateral projections have not been found to add information. Indicators of active TB disease include fluffy, nodular air space opacities, lymph node enlargement with or without consolidation, miliary nodules, thick walled cavity or a cavity surrounded by pneumonia and pleural fluid. Calcified pulmonary foci, calcified pleura or calcified nodes are signs of healed disease, although activity at present should be evaluated clinically. The chest x-ray has a definite place in the algorithm for TB screening for symptomatic or asymptomatic exposed children and can direct them for preventive or definitive treatment. It can also be used to rule out other possible diagnoses. Preliminary chest X-ray also helps in triaging for expensive molecular testing.

CLIPPINGS

Acute pesticide poisoning: 15 years experience of a large North-West Indian hospital

Acute pesticide poisoning is an important cause of morbidity and mortality in developing countries. Better preventive and management strategies can be developed if the incidence and pattern of acute poisoning are known.

Methods: This retrospective study covered 15 years (1990 to 2004). The case records of all cases admitted with acute poisoning during these years were reviewed and the results compared to earlier studies.

Results: A total of 2884 patients with acute poisoning were admitted during the study period (1918 men). The mean age was 27.8 years (range 13 to 82 years). The commonest agents were anticholinesterases (35.1%) and aluminum phosphide (26.1%). A seasonal variation in anticholinesterase poisoning was observed (most cases occurring July to September) but not for aluminum phosphide. No difference in mortality was observed over different months for different agents. Maximum case fatality ratio was due to aluminum phosphide exposures followed by anticholinesterase agents. The case fatality ratios for aluminum phosphide and organophosphate poisonings declined since 2000 despite an increase in aluminum phosphide exposures. The decline in aluminum phosphide mortality may be due to limited availability of 3 gm tablets and improved intensive care. Conclusions. Though incidence of acute pesticide poisoning increased over decades, there has been a decline in mortality for both aluminum phosphide and anticholinesterases. There is still need for measures like integrated pesticide management, development of safer aluminum phosphide formulations, and training of farmers in spraying techniques.

Murali R, Bhalla A , Singh D, Singh S. Acute pesticide poisoning: 15 years experience of a large North-West Indian hospital. Clin Toxicol (Phila). 2009 Jan; 47(1):35-8. doi: 10.1080/15563650701885807. PMID: 18608278.

CASE REPORT

BASSEN - KORNZWEIG SYNDROME

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Abstract: *Abetalipoproteinemia is a rare, autosomal recessive disease characterized by steatorrhea, acanthocytosis and hypolipidemia in infancy with a frequency <1 in 100,000. Deficiency of fat-soluble vitamins, atypical retinitis pigmentosa, coagulopathy, posterior column neuropathy and myopathy may develop by late childhood. Low fat diet and fat-soluble vitamins especially mega doses of Vitamin E are the main stays of therapy.*

Keywords: *Abetalipoproteinemia, Acanthocytes, Steatorrhea, Retinitis pigmentosa, MTTP gene*

Abetalipoproteinemia (ABL, OMIM 200100) an inherited disorder presents with impaired absorption of fats and vitamins from the diet. Most clinical features of abetalipoproteinemia result from a severe deficiency of fat-soluble vitamins (vitamins A, E, and K). Incidence is reported to be 1 in 100,000. A typical case of ABL is presented here.

Case Report

A 13-year-old boy was brought with complaints of recurrent diarrhea and fatty stools since infancy, growth faltering and defective vision, followed by gradually progressive weakness of lower limbs. He is the first child of non-consanguineous parents and was born by an emergency caesarean section with a birth weight of 3.5 kg. Postnatal period was uneventful and baby was gaining weight adequately initially. At 4 months of age, he developed spontaneous bruising which responded to vitamin K injections. Later, he developed similar lesions at 2 years and 3 years also. A complete hematological work up was done which was found to be normal. By 3 years, he had a firm hepatomegaly without splenomegaly. A liver biopsy was done as part of the work up which revealed micro and macrovascular steatosis.

No further interventions were done.His developmental milestones were normal initially. At 5 years of age, his parents were worried as he was not gaining weight. His teacher noticed visual difficulties and he was prescribed glasses for myopia. He gradually developed weakness of lower limbs and difficulty in getting up from sitting position. He also had history of swaying while walking in a straight line and had difficulty in performing skilled activities. He also developed difficulty in night vision and squint by 8 years. He was advised surgery for squint at 13 years of age and then he was brought to us for a second opinion regarding surgery. He is now studying in class 7 and has poor scholastic performance.

On examination, he was conscious, alert and vitals were stable. He had bilateral ptosis with divergent squint, high arched palate, dry scaly skin and phrynoderma of lower limbs, his weight was 24 kg, height 130.5cm and head circumference 49.5 cm (all <3rd centile). Adduction of right eye was restricted and there was fasciculation of tongue. Fundus showed early features of retinitis pigmentosa. He had hypotonia with normal power in upper limbs and trunk with minimal weakness of lower limb muscles (grade 4 power). Superficial reflexes were normal, plantar was flexor bilaterally and all deep tendon reflexes were sluggish. He had intention tremor, dysdiadochokinesia, wide based gait, impaired tandem walking, positive rebound phenomenon and Gowers sign and impaired vibration sense.

His liver was palpable 3 cm below the right costal margin in the mid-clavicular line, non-tender and firm. Spleen was not palpable and there was no ascites. Cardiovascular and respiratory systems were normal.

Hb was 9.8 g%, total count 10,200 cells/cumm with lymphocytes 55%, polymorphs 40% and eosinophils 5%. ESR was low (3 mm/hour). Stool contained plenty of fat

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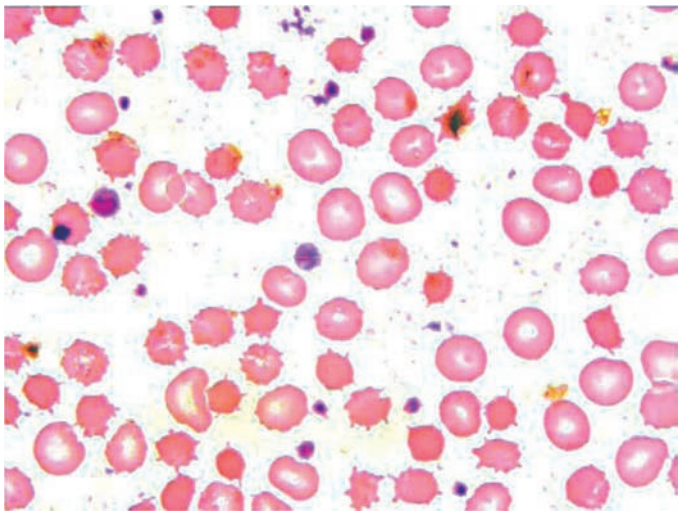

Fig. 1. Peripheral smear showing acanthocytes

globules and occult blood was negative. Serum bilirubin was 0.5 mg /dL, AST 175 U/L, ALT 155 U/L, SAP 650 IU/L, GGT 25 U/L, total proteins 6.5 g/dL and albumin 4 g/dL. CPK was 480 mcg/L and LDH 550 IU/L. PT was 20 seconds and INR 1.8. Serum ferritin was 38 mg/dL and serum ceruloplasmin 30 mg/dL (normal 20-40 mg/dL).

Peripheral smear showed anisopoikilocytosis with acanthocytes and microspherocytes (Fig.1). Lipid profile showed LDL 8 mg/dL, HDL 20 mg/dL and VLDL 15 mg/dL. Serum folate and vitamin B 12 levels were normal. Serum calcium was 8.5 mg/mL and vitamin D was 20 ng/mL (sufficiency> 30ng/mL). Serum vitamin E was very low- <2 mcg/mL(normal 3-18.4 mcg/mL). HBsAg and anti-HCV were negative. T4 and TSH were normal. The lipid profile of both parents was normal.

Echocardiogram with doppler revealed a normal study. Nerve conduction studies showed decreased conduction velocities in tibial and peroneal nerves. MRI showed thinning of extraocular muscles. Clinical exome study revealed a homozygous single base pair deletion in Exon 9 of MTTP gene suggestive of ABL

Child was given 7.5 mg of vitamin K injection for 3 days following which his PT/INR became normal. He was started on 1200 mg of vitamin E daily, other supportive measures and on follow up. He was symptomatically better at 10 months follow up.

Discussion

Abetalipoproteinemia was first reported in 1950 by Bassen and Kornzweig.[1] It is classified as a neuroacanthocytosis syndrome, which refers to a group of disorders characterized by spiky or burr-shaped red blood cells (acanthocytosis) and neurological manifestations, especially movement disorders. This rare autosomal recessive multisystem disorder is caused by mutations in the microsomal triglyceride transfer protein (MTTP) gene. MTTP is responsible for the intracellular assembly of apolipoprotein B (apo B), the lipid that coats and transports chylomicrons and lipids in the liver and intestine.[2]

In 1993, the region on chromosome 4q22-24 that encodes the large subunit of MTTP was cloned, sequenced and human MTTP mutations in ABL patients were reported.[3] As apo B-containing lipoproteins are found in the plasma, LDL-C levels may be almost zero. This leads to impaired transport of all fat-soluble vitamins such as A, D, E and K. There is a disproportionate decrease in lecithin in exchange for sphingomyelin in RBCs which become more rigid. This results in an imbalance in membrane lipids and causes immature RBCs to stiffen, pucker, wrinkle and form spicules resulting in the formation of acanthocytes. The associated fat malabsorption leads to deficiencies in iron, folic acid and other nutrients resulting in anemia. Recurrent diarrhea is common in young children but is rare in older children and adolescents as they learn to avoid fatty foods. Parents of children with ABL have normal blood lipid and apo B levels.

Peripheral blood smear shows a mild, normocytic anemia with acanthocytes constituting up to 50 to 90 percent of the circulating RBC population.[4] Serum triglyceride levels and total cholesterol levels are very low (less than 1.5 mmol/L). Because of their inability to form rouleaux, erythrocyte sedimentation rates could be very low. Some patients with ABL develop peripheral neuropathy which is mild and often subclinical, manifesting with distal muscle wasting, depressed distal deep tendon reflexes and mild sensory abnormalities, particularly impaired vibration sense.[5]

Vitamin E is a powerful antioxidant that protects cells from free radicular damage. Vitamin E malabsorption which is very common in ABL causes lipid peroxidation of cells and hemolysis which may aggravate anemia. In some children the presenting feature may be easy bruisability, as in index case due to the malabsorption of vitamin K which is essential for gamma carboxylation of clotting factors II, VII, IX and X, a vital step in coagulation in the coagulation cascade.

Severe vitamin E deficiency may also lead to spinocerebellar degeneration. This manifests as ataxia, loss of deep tendon reflexes, and later spasticity of lower extremities by adulthood. Many children develop intellectual disability and muscle weakness also.

Vitamin E may be undetectable in the serum of patients with neurologic abnormalities. Many children may develop a progressive retinitis pigmentosa associated with decreased night and colour vision and even eventual blindness. These children require long-term treatment with calcium, vitamin D and high-doses of vitamin A (10-15,000 IU/day) and vitamin E (100 mg/kg/day, equivalent to 150 IU/kg).[6] However, there is a dual defect in vitamin E metabolism in ABL viz a block in intestinal absorption of vitamin E and also a defect in hepatic alpha tocopherol transfer to circulating lipoproteins. Hence, in spite of mega dose vitamin E therapy, plasma levels of vitamin E may not return to the normal range. Some patients develop elevated transaminases due to hepatic steatosis.[7] The growth failure and gastrointestinal symptoms like fatty stools can be prevented with a diet modified to contain medium-chain triglycerides.

Abetalipoproteinemia may be mistaken for Friedreich ataxia due to the associated retinitis pigmentosa (RP) and neurologic manifestations. However, the presence of steatorrhea, severe hypolipidemia and acanthocytosis in ABL help in the differentiation.

We had the opportunity to completely work up the health issue of this boy including genetic study and wanted to share the details as case report. Even though ABL is a very are disease, it responds well to treatment. Early diagnosis and prompt treatment are vital to prevent the development of serious sequelae. Low levels of serum lipids are a useful clue and the diagnosis can be confirmed by clinical exome.

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CLIPPINGS

Once versus twice daily budesonide metered-dose inhaler in children with mild to moderate asthma: Effect on symptoms and bronchial responsiveness

Simplifying dosing regimens could improve both adherence and asthma-related morbidity, now there is little information on the effectiveness of once-daily budesonide, administered through a metered dose inhaler (MDI) plus spacer, on asthma symptoms and pulmonary function in asthmatic children.

The aim of this study was to compare the effect of once-daily versus twice-daily doses of inhaled budesonide on symptoms, lung function and bronchial hyper responsiveness (BHR) in asthmatic children. This study was a randomized, single-blind, parallel clinical trial. Patients received budesonide from an MDI either 800 ìg as a daily dose or fractionated in 400 ìg twice a day for 12 weeks. Statistical analysis was performed using tests for independent and paired samples.

In both groups, asthma symptoms significantly decreased. However, the improvement in asthma symptoms decreases in BHR and treatment adherence were significantly greater in the once-daily group than in the twice-daily group ($p < 0.05$). No significant differences were found between the two groups in spirometric parameters, morning peak expiratory flow or plasma cortisol value.

M***allol J, Aguirre V. Once versus twice daily budesonide metered-dose inhaler in children with mild to moderate asthma: effect on symptoms and bronchial responsiveness. Allergol Immunopathol 2007 Jan 1; 35(1):25-31.***

CASE REPORT

SYSTEMIC PSEUDO HYPOALDOSTERONISM TYPE I – A RARE SALT WASTING SYNDROME

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*****Ashvij Shrian**
******Santosh T Soans**
*******Asif Ahmad Jakati**

Abstract: *Pseudo hypoaldosteronism is a genetic disorder, presenting with significant salt wasting and hyperkalemia and not very common. This condition has to be considered in neonates presenting with refractory hyperkalemia. A neonate who presented with a novel mutation causing this condition is being reported.*

Keywords: *Hypoaldosteronism, Hyperkalemia*

Pseudo hypoaldosteronism (PHA) a salt wasting condition due peripheral resistance to aldosterone with a prevalence of less than 1/1,000,000 globally and manifests with hyponatremia, hyperkalemia and metabolic acidosis in the newborn period itself.

A five-day old female neonate, 2nd of the twins born to a non-consanguineous couple at 32 weeks gestation by caesarian section with birth weight of 2270 grams presented with vomiting, lethargy and poor feeding. On examination the baby looked ill with respiratory distress, severe dehydration and shock. External genitalia appeared normal. On auscultation, there was bradycardia and irregular rhythm. Oxygen saturation at room air was 80 to 85%. Blood pressure was normal. ECG showed ventricular tachycardia. Baby weighed 1800 grams (20% weight loss) on 5th day of life.

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Table I. Laboratory investigations

Parameter	Observed value	Normal range
Serum sodium	123mEq/L	135-145 mEq/L
Serum potassium	9.2mEq/L	3.5-5 mEq/L
pH	6.9	7.35-7.45
HCO3	3.3mEq/L	22-26 mEq/L
Plasma osmolarity	278mosm/L	275-295mosm/L
Urine osmolarity	223mosm/L	30-1200 mosm/kg
TTKG	0.3	6-12
Serum aldosterone	3230 ng/dL	5-132 ng/dL
Plasma renin activity	2727 micro IU/ml	4-89 micro IU/ml
Cortisol	59.8 mcg/dL	5-21 mcg/dL
Lactate	48.9mmol/L	10-39 mmol/L
Ammonia	69micromol/L	5-32 mmol/L
17-Hydroxy progesterone	1.28 ng/dL	<2 ng/dL

Laboratory evaluation (Table I) showed normoglycemia, hyponatremia, hyperkalemia (9.2mEq/L) severe metabolic acidosis (pH-6.9, HCO3- 3.3mEq/L). Ammonia was normal and lactate was high. Intravenous fluids and potassium correction steps (calcium gluconate, sodium bicarbonate, nebulized salbutamol, glucose insulin infusion and potassium binders) were initiated. Antibiotics were started for Klebsiella and Enterobacter sepsis. Hyponatremia and hyperkalemia persisted despite all corrective measures. Possibilities of congenital adrenal hyperplasia (CAH), hypoaldosteronism and pseudohypoaldosteronism (PHA) were considered. Urine electrolytes and transtubular potassium gradient (TTKG) was suggestive of defective potassium excretion and sodium retention. 17 hydroxy-progesterone (17 OHP) and cortisol levels were normal. Renal ultrasound was normal. Fludrocortisone was initiated

Table II. Singleton exome sequencing

Gene transcript	Location	Variant	Zygosity	ACMG classification	Disease (MIM#)	Inheritance	Parental origin
SCNN1B NM_000336.3	Exon 3	c.539C>A p.(Ser180Ter)	Hom	Pathogenic	Pseudohypoal-dosteronism type I (264350)	Autosomal recessive	Maternal and paternal

Hom - Homozygous

Test performed: *Singleton exome sequencing was performed using a customized TWIST capture kit. Validation and segregation analysis of the variant is done by Sanger sequencing.*

Results: *Clinically relevant variation in the proband associated with the observed phenotype.*

Interpretation: A novel stop-gain variant c.539C>A, p.(Ser180Ter) is observed in exon 3 of SCNN1B in homozygous state in the proband. Her parents are heterozygous carriers of this variant. This variant is not observed in gnomAD database. In-silico analysis tools (MutationTaster and DANN) are consistent in predicting this variant to be disease causing. These findings confirm the diagnosis of Pseudohypoaldosteronism, type I in (Twin 2).

at 0.1mg/day and increased upto 1mg/day, sodium supplementation was started at 10mEq/kg/day and increased to 15 mEq/kg/day (3% saline mixed with feeds) along with potassium corrective measures. Serum aldosterone level and plasma renin activity were markedly elevated helping to clinch the diagnosis of PHA Type I. Fludrocortisone was stopped. Electrolytes normalized and baby was discharged on 3% saline at 15 mEq/kg/day.

Genetic analysis revealed a novel stop-gain variant c.539C>A, p. (Ser180Ter) on exon 3 of SCNN1B gene in a homozygous state suggestive of PHA Type I (Table II). The parents of the baby are heterozygous carriers of the same mutation. The baby had repeated hospitalizations due to Klebsiella sepsis and electrolyte imbalance and expired at 3 months of age.

Discussion

Pseudo hypoaldosteronism (PHA) is a salt wasting condition due peripheral resistance to aldosterone. The prevalence of this condition is less than 1/1,000,000 in the world.[1] Aldosterone acts on the mineralocorticoid receptor (MR) and helps in sodium absorption and potassium excretion via the epithelial sodium channel (ENaC). Defects in the mineralo corticoid receptor (MR) or ENaC prevent the actions of aldosterone (peripheral resistance) resulting in a false state of its deficiency.[2] Two forms of this disorder have been identified - Autosomal dominant (AD) type or Renal PHA 1 due to mutation in the NR3C2 gene that encodes the MR and autosomal recessive (AR) or systemic PHA resulting from mutation in one of the subunits of ENaC (alpha, beta, gamma).[3] Renal PHA 1 manifest with mild to moderate sodium loss limiting to the kidney, responds well to sodium supplementation and resolves with age.[4] The systemic type causes a severe multi- organ salt wasting condition since ENaC is expressed in distal nephron, colon, sweat, salivary glands and epithelial lung cells, needs large doses of sodium and doesn't remit spontaneously.[3,5]

PHA manifests with hyponatremia, hyperkalemia and metabolic acidosis in the newborn period.[6] It is a mimicker of CAH, which was ruled out due to absence of virilization, hypoglycemia, normal 17 OHP and cortisol levels. Around 80 cases with a molecular basis have been reported to date.[7] Two case series reported novel mutations in SCNN1B gene and severity of clinical presentation varied based on the type of mutation.[3,8] Our patient had a novel mutation not reported till date and presented with life threatening salt wasting crisis and recurrent pneumonia. PHA 1 should be considered as a differential diagnosis in neonates who present with refractory hyperkalemia to facilitate timely intervention.

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CLIPPINGS

Extracorporeal therapy in salicylate poisoning

Salicylate poisoning is a challenging clinical entity associated with substantial morbidity and mortality. The indications for extracorporeal treatments such as hemodialysis are poorly defined. We present a systematic review of the literature along with evidence and consensus-based recommendations on the use of extracorporeal treatment in salicylate poisoning.

The Extracorporeal Treatments in Poisoning (EXTRIP) Workgroup is a multidisciplinary group with international representation whose aim is to provide evidence-based recommendations on the use of extracorporeal treatments in poisoning. We conducted a systematic literature review followed by data extraction and summarized findings, following a predetermined format. The entire work group voted by a 2-round modified Delphi method to reach consensus on voting statements, using a RAND/UCLA Appropriateness Method to quantify disagreement.

Eighty-four articles met inclusion criteria, including 1 controlled clinical trial, 3 animal studies and 80 case reports or case series, yielding an overall very low quality of evidence for all recommendations. Clinical data on 143 patients (130 sets of which could be analyzed for patient-level entry data), including 14 fatalities, were reviewed. Toxicokinetic data on 87 patients were also included. After the second round of voting, the workgroup concluded that salicylates are dialyzable by hemodialysis and hemoperfusion (level of evidence=B) and recommended extracorporeal treatment in patients with severe salicylate poisoning (1D), including any patient with altered mental status (1D), with acute respiratory distress syndrome requiring supplemental oxygen (1D) and for those in whom standard therapy is deemed to be failing (1D) regardless of the salicylate concentration. High salicylate concentrations warrant extracorporeal treatment regardless of signs and symptoms (>7.2 mmol/L [100 mg/dL] [1D] and >6.5 mmol/L [90 mg/dL] [2D]), with lower thresholds applied for patients with impaired kidney function (>6.5 mmol/L [90 mg/dL] [1D] >5.8 mmol/L [80 mg/dL] [2D]). Extracorporeal treatment is also suggested for patients with severe acidemia (pH $\leq$7.20 in the absence of other indications) (2D). Intermittent hemodialysis is the preferred modality (1D), although hemoperfusion (1D) and continuous renal replacement therapies (3D) are acceptable alternatives if hemodialysis is unavailable, as is exchange transfusion in neonates (1D).

Salicylates are readily removed by extracorporeal treatment, with intermittent hemodialysis being the preferred modality. The signs and symptoms of salicylate toxicity listed warrant extracorporeal treatment, as do high concentrations regardless of clinical status.

Juurlink DN , Gosselin S , Kielstein JT, Ghannoum M, Lavergne V, Nolin TD, et al (2015). Extracorporeal Treatment for Salicylate Poisoning: Systematic Review and Recommendations from the EXTRIP Workgroup. Ann Emerg Med 66(2); 165-181. https://doi.org/10.1016/j.annemergmed.2015.03.031.

CASE VIGNETTE

SUCCESSFUL HOME CPAP IN LATE ONSET OBSTRUCTIVE SLEEP APNEA DUE TO KISSING CAROTIDS IN PIERRE ROBIN SEQUENCE

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****Deepika**
*****Shruthi TK**
******Rajakumar PS**
*******Prasanna Kumar S**

A 2-year-old female child with Pierre Robin Sequence who had undergone cleft palate repair at 1 year, presented with history of excess daytime sleepiness, breathing difficulty and edema for 2 weeks. She had history of noisy breathing and disturbed sleep. General examination showed micrognathia, glossoptosis and malnutrition. She had sternal retractions suggestive of upper airway obstruction and dependent edema with hepatomegaly suggestive of right heart failure. Arterial blood gas showed compensated respiratory acidosis. Overnight pulse oximetry showed significant desaturation episodes. Echocardiogram showed structurally normal heart with pulmonary hypertension and good ventricular function. Contrast CT angiogram showed enlarged "Kissing Carotids" (Fig.1). Child was started on diuretics and sildenafil for pulmonary hypertension and right heart failure. Trial of Continuous Positive Airway Pressure (CPAP) via Pixi nasal mask and Resmed home BiPAP machine with Pressures 5-8 cm without oxygen resulted in significant reduction in distress, desaturation and PCO2 levels with a better sleep (Fig.2). Child was discharged after the parents were taught on how to use CPAP at home. On follow-up at 1 year, pulmonary hypertension and right heart failure had resolved and had weight gain of 3 kilograms and was off all medicines.

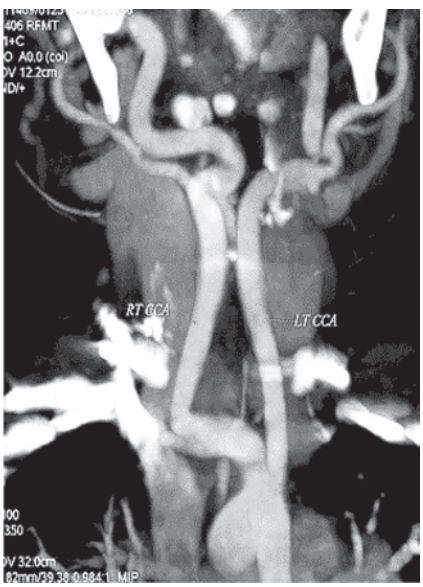

Fig.1. CT angiogram showing kissing carotid arteries

Pierre Robin Sequence (PRS) causes upper airway obstruction due to multiple mechanisms in addition to posterior displacement of the tongue.[1] The term 'Kissing Carotids 'refers to tortuous and elongated carotid arteries which touch in the midline due to congenital or

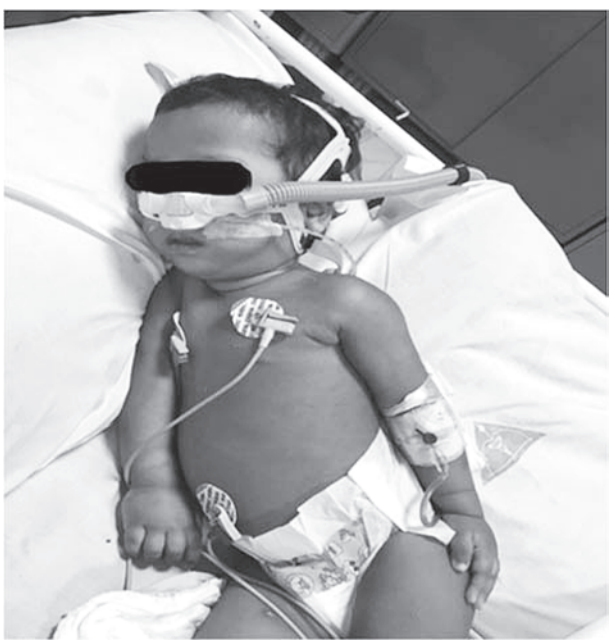

Fig.2.Child comfortably sleeping with nasal CPAP

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acquired cause[2]. Though kissing carotids causes no symptoms in 80% cases, it is known to cause dysphagia, airway obstruction and severe bleeding during adenotonsillectomy surgery.[2] Various treatment modalities adopted for the condition include prone positioning, nasopharyngeal airway, CPAP and surgical options like glossopexy and tracheostomy. [3,4] Use of CPAP in 2 year old child is challenging due to the difficulty in getting proper fitting nasal interfaces and acceptance by the child and family in addition high cost. In our case, gradual introduction of NIV mask after demonstration on child's toy, slow increase in pressure setting, multiple counselling and training sessions with parents, demonstration of improvement in child's symptoms in hospital and troubleshooting backup over phone provided by the treating team ensured that the family used home NIV successfully.

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CLIPPINGS

A study of calcium channel blocker or beta blocker overdose

Calcium channel blockers (CCB) and beta blockers (BB) are primarily used to treat hypertension. Overdose of these medications can occur by accidental ingestion or ingestion for suicide attempt. Morbidity and mortality are higher in these poisonings compared to other poisonings. In this study, BB or CCB drug poisoning cases are discussed and the literature is reviewed.

Between January 2011 and July 2012, 590 cases of drug poisoning were admitted in the Pediatric Intensive Care Unit. In this study, 16 of these 590 subjects who were poisoned with calcium channel blockers or beta blockers were evaluated. 11 (68.8%) patients were female and 5 (31.2%) were male. Mean age of the patients was 11.8±5.94 (2.5-18) years.

Hypotension was the most common clinical sign in CCB poisoning. Two patients were asymptomatic. On ECG, QT prolongation was found in four patients, AV block was found in two patients and ST depression was found in one patient. Nausea, vomiting, hypotension, lethargy and tremor were the most common clinical findings in patients with BB intoxication. Although seven patients had normal ECG, one patient had QT prolongation and one patient had Wolff-Parkinson-White syndrome. Only dopamine was given to two patients with CCB poisoning, dopamine and dobutamine were given to one patient and dopamine, dobutamine, epinephrine, norepinephrine, glucagon and insulin were given to another patient. Inotropic drugs were not given to any patient with BB poisoning. IV Ca-gluconate was given to all patients with CCB poisoning except two patients who were asymptomatic. 15 patients were discharged, while one patient with CCB poisoning was lost.

Because the prognosis of CCB or BB poisoning may be very severe, these patients should be followed up in a fullyequipped pediatric intensive care unit.

Konca C, Yýldýzdaþ RD, Sarý MY, YükselmiþU,Horoz OO, Yýlmaz HL. Evaluation of children poisoned with calcium channel blocker or beta blocker drugs Turk Arch Ped 2013; 48: 138-144.

LEARNING TOGETHER - OSCE

OSCE - Toxicology

***Sabharritha G**
****Annamalai Vijayraghavan**

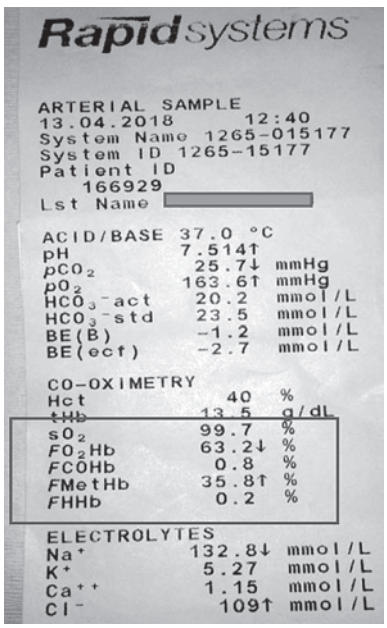
1. A 3 year old female child brought in the evening with altered consciousness, irritability, tachypnea and cyanosis. She was well in the morning. Child had fish in the noon, for the next few hours mother was busy Child was found unconscious outside her home in the evening and was rushed to the ER

O/E Cyanosis, no clubbing ; HR- 128. Pulse well felt ; RR 44. No retractions; BP Normal; SpO2 86%.

CVS - No murmur, RS- normal except tachypnea

Child has cyanosis - mild tachypnea, normal work of breathing, no clubbing, no murmur

Her ABG is as follows



SaO2 is 99.7 % ,SpO2 is 86.0 %

Blood sample of the patient is chocolate brown in colour.

a)What are the causes of cyanosis in general?

b)What is the inference from the ABG?

c) What is the diagnosis?

d) What is the management?

2) A sixteen year old girl was brought with alleged history of rat killer poison ingestion. She consumed paste on 1st day, second dose of paste on the 2nd day morning and cake in the evening.

She was admitted with features of hepatic failure and icterus. No bleeding tendency, shock or altered level of consciousness. Maintained SpO2 in room air

Lab parameters were - SGOT/SGPT IU /L: 1220/617 - 1886/789 - 527/563 ;LDH IU/L: 2288 - 3263 - 1399; INR: 3.55- 5.5 - 6.96; Creatinine, CBC: Normal except low platelet count 1.03L/cumm

a) What are the toxins present in various rat killer poisons?

b) Mechanism of action of various toxins?

c) What is the management?

d) Causes of acute hepatic failure in a child with poisoning?

3.Five years old child has consumed unknown number of thyroxin tablets about 3 hours ago.

- HR: 140/mt RR: 26/mt conscious

a) What are the clinical features of thyroxine poisoning expected ?

b) How to proceed after initial management ?

c)How long it may take for symptoms to develop?

d) What is the antidote?

4) A 15-month old boy, brought to ER with cough, fever and difficulty in breathing. He was said to be alone in the

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room when he ingested an estimated 40 ml of liquid kept in a transparent polyethene container. He was given two cups of salt water to induce vomiting by the parents at home.

On examination: Temperature 38.9°C, mild pallor, dehydrated and breath smelt of kerosene. He was also found to be in respiratory distress with flaring of alae nasi, intercostal recession and tachypnea (RR=52/min). He had asymmetrical chest movement with trachea deviation to the left and the apex beat at left 5th intercostal space, lateral to midclavicular line. There were hyperesonant percussion notes and absent breath sound on the entire right hemithorax. Other findings on examination were essentially normal.

a)What is the diagnosis and cause ?

b) What is the mechanism for the air leak ?

c) What are the complications

d) How to manage ?

e) What are the investigations needed ?

5 a) Identify the above black powder kept near its container which is used in the initial management of poisoning for decontamination and also mention its physical characteristics?

b) What is the mechanism of action?

c)What are the indications?

d) Method of administration?

e) Dose recommended in toxin ingestion

f) Name few contraindications?

g) In what toxins it is not beneficial?

h) Mention the complications?

i) Mechanism of action and method of administration of multiple doses?

6) A three year old boy was brought by the parents that the child had accidentally swallowed the aspirin tablets used by the grandmother and as a few used strips were found they could not tell how many tablets the child had taken. Child had vomited thrice before reaching the ER in two hours after ingestion.

O/E Child conscious, irritable, excessive sweating , HR 120/min RR 56/min afebrile BP-90 /70 mm Hg, dehydrated

PERLE Systemic examination normal.

a) What is the pathophysiology?

b) Clinical and laboratory manifestations of acute toxicity

c) What is the toxic effect?

d) What is the toxic dose?

e) What is the management ?

Answers

1a) Respiratory : Bradypnea, apnea, severe upper airway obstruction, pneumothorax

Cardiac : Cyanotic heart disease, cyanotic spell

Methemoglobinemia

b) Saturation gap - Low SpO2 and normal SaO2 suspect methemoglobinemia

MetHb level-35.8%

c) Diagnosis is acquired methemoglobinemia-toxin induced.

Common causes: Dapsone, local anesthetics, chloroquin, primaquin, sulphonamides, nitrates. naphthalene, certain pesticides

c) Management

Supportive care: High flow oxygen, removal of inciting agent

Treatment with IV Methylene blue

Initial dose is 1-2mg/kg IV bolus. Repeat dose may be given after 1 hour if Methemoglobin level is still >20%. Max dose is 7 mg/kg

Check G6PD level prior to therapy

2 a) Cake: Super warfarin

Paste: Yellow or white phosphorous

Powder: Zinc phosphide, thallium

b) Mechanism

Super warfarin: Interference with coagulation

Phosphorous: Corrosive, general cellular poison, cardiotoxic, decreases vascular tone and shock

Phosphide: Releases phosphine gas on contact with acid which results in altered sensorium, seizures, encephalopathy, hepatorenal and cardiovascular damage

Thallium: Mitochondrial poison

c) Supportive management.

Identify product and ingredient, monitoring,

One dose of activated charcoal

No gastric lavage in bleeding patient

N-Acetyl Cysteine infusion (150 mg /kg over one hour followed 10 mg/kg/hr for 24 to 72 hours based on serum transaminase levels, Vitamin K (children under 5 years 5- 10 mg and above 5 years 15-25 mg) and plasma exchange FFP, blood products for clinically significant active bleeding.

Early referral to tertiary care centre with PICU and hepatic support can improve the survival

d) ALF in poisoning: Paracetamol, rodenticide, valproate

3a) Clinical features: General- Fever, vomiting, diarrhea.

Cardiac - Tachyarrhythmia, cardiac failure

b) Decontamination procedure:Activated charcoal, cholestyramine to block enterohepatic circulation

c) Even up to 10 days- needs follow up as out patient or by telephone

d) Antidotes: Only with onset of symptoms.

i) Prednisolone (steroids) - Inhibits peripheral conversion of T4 to T3.

Alleviate the exaggerated adrenergic effects. Relative cortisol insufficiency in hypermetabolic hyperthyroid state, countered by steroids.

ii) Propanolol (beta blocker) effective in treating hypermetabolic symptoms, it antagonizes the beta receptor mediated effects of catecholamines.

iii) Iopanoic acid is a potent inhibitor of peripheral conversion of thyroxine(T4) to triiodotyronine (T3).

4a) Kerosene ingestion complicated with right sided pneumothorax

Pneumothorax develops as increased respiratory efforts occur as a result of aspiration and ingestion leading to lipoid pneumonitis which leads to air leak.

b) Air leak occurs due to increased transpulmonary pressure. Transpulmonary pressures that exceed the tensile strength of the non cartilageous terminal airways and alveolar saccules can damage the respiratory epithelium. Loss of epithelial integrity permits air to enter the interstitum, causing pulmonary interstitial emphysema. Persistent elevated transpulmonary pressure facilitates the dissection of air toward the visceral pleural and/or hilum via the peribronchial and perivascular spaces. Rupture of the pleural surface allows the adventitial air to decompress into the pleural space, causing pneumothorax. Other air leak syndromes also arise via this common mechanism.

c) Chemical pneumonitis, necrotizing pneumonia, atelectasis, pneumatoceles, air leak, secondary infection, lung abscess, empyema, lethargy seizures, rarely coma secondary to hypoxia, orogastric and intestinal irritation

d) Admitted in hospital for observation. Gastrointestinal decontamination procedures contraindicated

Humidified oxygen, monitoring saturation - if features of respiratory failure managed with NIV, CPAP, caution for mechanical ventilation as they are prone for air leak.

Seizures controlled with lorazepam, antibiotics if fever, respiratory distress persists beyond 48 hours as it suggests secondary infection

e) Chest X ray if symptomatic or after 6 hours if asymptomatic, radiological findings peak in 2 to 8 hours after aspiration, symptomatic patients must undergo CBC, ABG (initial ABG respiratory alkalosis with hypoxia, if hypoxia persists later metabolic acidosis), blood glucose, serum electrolytes, LFT and RFT in children exposed to halogenated hydrocarbons.

5a) Activated charcoal AC is fine, black, odourless, tasteless, pharmacologically inert and non-absorbable substance.

b) i.Activated charcoal adsorbs the toxic substance in the gastrointestinal tract thereby decreasing its systemic absorption. ii. It also enhances elimination through interruption of enterohepatic, enteroenteral recirculation, hence also called as enteral dialysis.

c) Indications: Phenobarbital, carbamazepine, dapsone, quinine, theophylline poisonings.

d) Method of administration: Charcoal powder can be mixed with water to form slurry. It can be given through NG tube or can be directly given along with juice or chocolate.

e) Dose: 1-2 g/kg body weight to a maximum of 100 g.

f) Contraindications: When airway protective reflexes are absent and the patient is not intubated, presence of ileus or when there is a need for endoscopy (Because AC is likely to impair visibility during endoscopy).

g) Pesticides, hydrocarbons/ heavy metals, alcohol/acids/ alkalis, iron, lithium, solvents (mneumonic - PHAILS) poisonings.

h) Complications: Vomiting, aspiration pneumonia, intestinal obstruction by bezoar formation and perforation if given erroneously in caustic ingestion.

i) Mechanism of action and method of administration of multiple dose activated charcoal: It prevents ongoing absorption of the toxin that persists in the GI tract e.g., phenytoin, digoxin, phenobarbital, carbamazepine, dapsone, quinine, theophylline. Initial dose: 1 g/kg and repeat dose 0.5 g/kg every 4-6 hrs for the next 24 hours.

6 a) Direct stimulation of respiratory center

Uncoupling of oxidative phosphorylation

Inhibition of tricarboxylic acid cycle

Stimulation of glycolysis and gluconeogenesis

Cerebral edema and acute lung injury

b) Early signs include nausea, vomiting, diaphoresis, tinnitus, tachypnea, hyperpnea, tachycardia, altered mental status, severe toxicity features include hyperthermia, coma and seizures.

Lab features include primary respiratory alkalosis, hyperglycemia, in early phase and later primary elevated anion gap metabolic acidosis and hypoglycemia.

c) Hepatotoxicity, direct stimulation of respiratory center, metabolic acidosis.

d) Toxic single dose is more than 150 mg/kg, fatal dose is more than 500mg/kg.

When serum levels exceed 30-50 mg/dL, more than 70 mg/dL is life threatening

e) Initial management includes correction of dehydration with isotonic fluids, gastric decontamination with activated charcoal, volume resuscitation, maintaining urine output at 2mL/kg/hr

Urinary alkalinization by administration of sodabicarbonate infusion two times the maintenance dose and urinary pH 7.5 - 8.5 and serum pH 7.45 -7.55. To stop alkalinisation when serum salicylate is less than 20 mg/dL

Hemodialysis when serum salicylate level is more than 70 mg/dL in acute ingestion

For further reading

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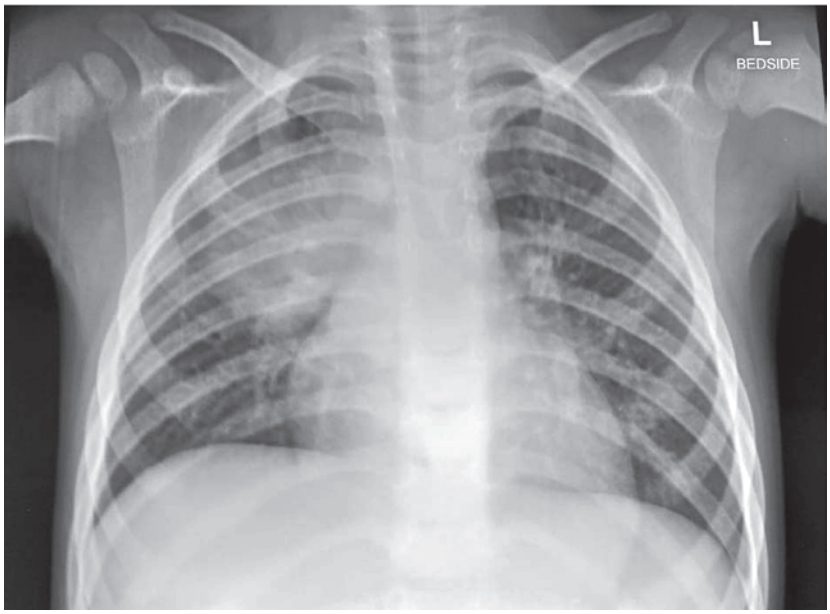
PICTURE QUIZ



Questions

1. Enumerate the findings in the X Ray chest and what is the interpretation?

2. What are the etiologies?

3. Any differential diagnoses?

4. Reason for this pathology to be preferentially seen in children?

5. What are the common sites of these lesions?

Answers

1. Round area of haziness with air bronchogram suggestive of 'round pneumonia'.

2. Commonly due to *Streptococcus pneumonia* , rarely *Klebsiella pneumonia* and *Hemophilus influenzae .M. pneumoniae*, fungi and mycobacterium in older children especially if immunocompromised.

3. Differential diagnosis: Lung abscess, tuberculosis, developmental pulmonary malformations [e.g. sequestration, bronchogenic cyst, congenital cystadenoid malformation (CCAM)], neoplasm (e.g., lymphoma, neuroblastoma), diaphragmatic hernia / eventration.

4. The pores of Kohn and channels Lambert function as collateral circulation and when collaterals are well developed in older children beyond 12 years, the infection and fluid can spread easily into adjacent alveolar sacs and throughout the lobe. With less developed collaterals, there is centrifugal spread, and the consolidation is spherical with sharp margins especially in children below 5 years.

5. Usually seen in posterior and lower lobes possibly resulting from gravity and supine position while sleeping.

Contributed by: Dr.N.C.Gowrishankar, Pediatric Pulmonologist, Mehta Multispeciality Hospitals, Chennai

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