Indian Journal for

# the Practising Doctor





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# INDIAN JOURNAL OF THE PRACTISING DOCTOR

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Editorial correspondence: ***P. O. Box: 673 (GPO), Srinagar, Kmr.***

[Phones: 951954-255042; 0194-2422987 Email: gaashb-10@yahoo.co.in]

# Contents:

Indian Journal for the Practising Doctor



**Editorial**

*The first two issues of the IJPD met an expectedly warm response. Both the doctors practicing in the field as well as students, both, have enthusiastically welcomed the issue. This has encouraged all those involved in the publication of the journal.*

*The journal, as promised, carries articles of direct relevance to the practising doctor.* ***Ascariasis*** *is one of the commonest infestations of the world, and contrary to the popular belief that it is a mild condition which could be ignored, research shows that roundworm infestation can prove disastrous, and even a single wandering worm could kill the victim. It implies that ascariasis should be treated whenever countered.*

*We know that water and food form the leading vehicle of infection in the developing world. Andt providing plenty of safe water, requiring huge monetary inputs, will continue to be a tall order for some time to come. Accordingly water- & foodborne infections will continue to haunt our place for a long time. We have included a guest article on* ***typhoid fever*** *from one of our colleagues currently working in Malaysia. This paper had been presented in an international seminar on gastrointestinal infections.*

***Diabetes in pregnancy*** *is a serious disorder which affects not only the mother but also the baby and continues its adversity throughout life. With the advent of newer antibiotics,* ***Penicillin*** *has become a forgotten antibiotic. However, we must remember that this cheap antibiotic has a place in the treatment which other antibiotics and chemotherapeutic agents may not be able to fill*

*Food provides nutrients, that is a universally known fact. But food can prevent such serious diseases as cancer is not known to all. For the benefit of doctors working in the field, we have included an article on the role of* ***non-nutrients on health****. This article has been condensed from an ICMR Bulletin.*

*Winter in northern India, particularly Kashmir ,is accompanied by a sharp increase in burn cases. We have included an article on* ***Burn care*** *which has been condensed from the British Medical Journal. Some of the articles on common medical and surgical conditions are carried for the health profession. The one on Chronic Obstructive Pulmonary Disease is included for the benefit of various health functionaries.*

*Brucellosis is a pressing problem for all countries which have adopted animal and sheep husbandry in a big way. Netherlands is one such country which has brucellosis and at the same time has a vast body of research-oriented knowledge on such zoonotic diseases. A guest article on Brucellosis from that country has been included for the benefit of the practitioner who finds it difficult to diagnose the disease.*

*Our own experience shows that doctors generally find it difficult to devise material for health education. Therefore, while writing articles for the medical profession, we have included special* ***health education material*** *which the practitioner can use for health instruction of their patients and family members. In this issue we have carried articles on asthma, COPD and Mongolism.*

*An original paper based on the research of the faculty members of the Institute is put for its direct relevance to the practitioner working in the field. The current issue carries an article titled* ***'Immunization Status of Infants in a Remote District'*** *which has already been published elsewhere.*

*A special supplement on the* ***Use of drugs in Renal Impairment*** *has been included for the benefit of the practising doctor.*

November 2004.

Bashir Gaash
**(Executive Editor)**

# *Contributors:*

**Henk L Smits, PhD.**
Molecular Biologist at the Department of KIT Biomedical Research, Royal Tropical Institute, Amsterdam, The Netherlands.

**M Yusuf Rathor, MD**. Associate Professor, General Medicine, International Islamic University of Malayasia, Malayasia.

**Rubina Shaheen**: Faculty member, Regional Institute of Health, Kashmir, is a postgraduate in Microbiology. She taught at the SKIMS before her new appointment.

**Rehana Kausar**: Faculty Member, Regional Institute of Health, Kashmir, is a postgraduate from SK Institute of Medical Sciences, Soura, Srinagar. Before joining RIHFW she has had a stint in the Department of Community Medicine, SK Institute of Medical Sciences, Srinagar.

**Farooq Fazilli**: Faculty Member, Regional Institute of Health, Kashmir, is a postgraduate from the SK Institute of Medical Sciences, Soura, Srinagar. Before joining the RIHFW, the doctor worked in the Department of Community Medicine, SK Institute of Medical Sciences, Srinagar.

**B A Qadri** is a Kashmir-born paediatrician currently working in Kuwait. He has graduated from the Government Medical College, Srinagar, and got his Fellowship in Genetics from Ohio.

**Ayaz Amin** is an Indonesian immunologist currently working in Michigan, USA.

**Manzoor A Kadri**: Trainer at the Regional Institute of Health, Kashmir, was a teacher at the Government Medical College, Srinagar (Department of Microbiology) before joining us.

**Rohini Bhan** is a trainer at the Regional Institute of Health, Kashmir.

**Shabnam Bashir** is a medical graduate from the Government Medical College, Srinagar.

**Bashir Gaash**; an International Fellow in Tropical Diseases, is a postgraduate in Social & Preventive Medicine and Health Administration, and currently is the Principal, Regional Institute of Health & Family Welfare, Kashmir.

**Muzaffar Ahmad**; MD in general Medicine, has a Fellowship in Emergency Medicine from USA, and currently is the Director Health Services, Kashmir.

# Diagnostic dilemma

**Medical Quiz: III**

A mother in England brought her daughter for the 2nd time in the last 24 hours to hospital, with abdominal pain and frequent passing of a soft stool in the last 2 days. The 4-year old was fit and well before this illness. She was sent home after she was assessed at hospital; she was not dehydrated and did not look septic. Two days later she presented with similar symptoms: headache, lethargy, more abdominal pain, malaise and a pain in her neck. Her mother said her temperature is going up every day, and today reached 40C for the first time. She also developed erythematous papular lesions, which measure about 2 mm in diameter. All members of her family are healthy and returned from a holiday in Kashmir 6 days ago. There is a 2cm splenomegaly, with no lymphadenopathy. Her heart rate is 77 beats/min and her respiratory rate 20/min.

Her lab profile showed:

| | |
|---|---|
| Na | 130 mmol/l |
| K | 3.9 mmol/l |
| Urea | 8.3 mmol/l |
| Creatinine | 76 mmol/l |
| ALT | 55 iu/l |
| Alkaline phosphatase | 290 iu/l |
| Bilirubin | 35 umol/l |
| Hb | 11.3 g/dl |
| TLC | 2.2 x $10^9$/l |
| DLC:N | 22% |
| L | 66% |
| Platelets | 90 x $10^9$/l |
| Midstream urine | Negative |
| Stool | Negative |
| Abdominal ultrasound | Large spleen only |

**Questions:**

**What is the most likely diagnosis?**
**Which 2 other tests are required to support the diagnosis?**
**What should the treatment be in this case?**

(Answers on page 75)

# Ascaris lumbricoides

***Bashir Gaash***

*Ascariasis is a very common infestation in Kashmir. Hardly anyone escapes it. However, doctors and parents tend to take the infection lightly. This essay is to underline the need for prompt treatment of even a single worm. Giving anthelminthics at periodic intervals to high-risk children with heavy burden is not irrational.*

Ascariasis is an extremely common infection; the number of people infected globally with *A. lumbricoides* is 2nd only to those infected with the pinworm (*Enterobius vermicularis*). Children have the highest prevalence, which varies with the socioeconomic status. Ascaris was well known in the ancient times; Romans called it *lumbricus teres*. The infestation is more prevalent in moist, warm climates. In most tropical countries, the average infection rates range up to 45%. Prevalence in Nigeria, the most populous African country Even North America is not free; foci of high prevalence among young children still persist in the southeastern United States.

**Life cycle**

Every person in the developing world has seen the adult worm and can instantly recognize it. Infection is acquired through ingestion of the embryonated eggs from contaminated soil. On ingestion the eggs hatch in the stomach and duodenum, where larvae actively penetrate the intestinal wall. Via the hepatic portal circulation, they are carried to the right heart, and thence into the pulmonary circulation where they are filtered out by the capillaries. After about 10 days of development in lungs, the larvae break into the alveoli, migrate via the bronchi till they reach the trachea, epiglottis, and pharynx, and then are swallowed. The larvae grow to 2mm and physiologically adapt to survive in the intestine, where the worms mature and mate, and produce eggs which are passed in stool. The number of eggs produced and passed daily can be as high as 2 lakh per day. The entire developmental process from ingestion of eggs to the subsequent passage of eggs takes 8-12 weeks. During her life span, which may extend to 1-2 years, the adult female can pass some 6 crore or more eggs!

| **Fertilized egg** | **Unfertilized egg** |
|---|---|
| Broadly oval | More oval |
| Size: 75 µm long x 50 µm wide | Size: 90µm x 45µm long |
| Thick mammilated coat, usually bile stained a golden brown. | Minimally mammilated layer |

The female lays eggs in the duodenum which are evacuated with faeces. Both unfertilized and fertilized eggs are passed in stool. Often only female worms are recovered from the intestine. Fertilized eggs passed in stool become infective within 2 weeks in warm, moist soil, where they can remain viable for months or even years. The total absence of fertilized eggs means that only female worms are present in the intestine.

**Clinical features**

Infection with A. lumbricoides continues to be a major public health problem in developing countries. Though behavioural aspects are behind the faeco-oral transmission, there is evidence of an individual predisposition to infection. In addition, genetic factors account for 30%-50% of the variation in worm burden.

| | |
|---|---|
| *Usual time to infective* | 2-3 weeks in soil; second stage larva in egg |

| | |
|---|---|
| *stage* | |
| *Mode of infection* | Ingestion of infective egg |
| *Development & location in Human host* | Obligatory larval migration through liver and lungs; adults in small intestine. |
| *Prepatent period* | 2 months |
| *Normal life span* | Up to 1 year or slightly longer |
| *Diagnosis by usual means* | Bile-stained, mammilated, thick-shelled eggs (45-75x35-50µm) in 1-cell stage in feces;<br>Infertile eggs (85-95x43-47 µm) have thinner shells & distorted mammilations;<br>Mature or immature adults may be found in feces or may spontaneously migrate out of the anus, mouth, or nares. |
| *Diagnostic problems* | Fertile eggs may lose outer mammillated layer (decorticate egs);<br>Infertile eggs may be difficult to recognize; also will not float in usual solution of zinc sulfate (sp gr 1.18) used for concentration. |
| *Clinical notes* | Owing to potential migration of adult worms, all infections should be treated.<br>Pulmonary symptoms may be present during larval migration (prior to egg recovery in stool).<br>Eosinophils present but not impressive. |

Ascariasis is an important and common cause of childhood morbidity; it may even cause mortality from intestinal obstruction or extra-intestinal complications. Infestation is particularly heavy in young children (probably because of their pica) and symptoms severe. In older children & adults, worm load is less and infection mild or subclinical. In such cases, passage of worm or ova may reveal infestation.

Pathogenesis is attributed to

i) the host immune response
ii) effects of larval migration
iii) mechanical effects of the adult worms and
iv) nutritional deficiencies caused by the presence of adult worms.

The first symptoms produced are respiratory, due to passage of larvae through the lungs leading to benign pneumonitis - Loeffler's syndrome. Main symptoms in children are abdominal pain, loss of appetite and failure to thrive.

***Loeffler's pneumonia***: *Initial* passage of larva through liver and lung generally produces no symptoms, pneumonitis occurs with very large number of larvae. *Subsequent* larval migrations lead to intense tissue reactions even with a smaller number of larvae. Pronounced tissue reactions around the larvae in liver and lungs, with infiltration of eosinophils, macrophages and epitheloid cells leads to ascaris pneumonitis, which is accompanied by allergic dyspnoea, dry or productive cough, wheeze, fever, transient eosinophilia, and an x-ray suggestive of viral pneumonia. The transient lung infiltrates clear within a few weeks. Sputum contains eosinophils, Charcot-Leyden crystals, and sometimes may even contain larvae. If needed gastric washings are more helpful in detection of larvae. Asthma and urticaria may continue during the intestinal phase of ascariasis.

Allergic manifestations (asthma, hives, peripheral eosinophilia) begin with the 10-day pulmonary phase but continue into the intestinal phase.

***Intestinal manifestations:*** The main symptoms in children are abdominal pain, anorexia and failure to thrive.

Heavy infestation may lead to protrusion of abdomen.

***Eosinophilic gastroentritis*** signifies the inflammatory disease characterized by eosinophilic infiltration of the gastrointestinal tract accompanied by varying abdominal symptoms and usually by peripheral eosinophilia.

***Nutritional complications***: In the under-five child heavy burden of worms may lead to severe nutritional impairment. Studies have shown increased loss of faecal fat and nitrogen and impaired carbohydrate absorption, which correspond to worm load. Lactose malabsorption is common.The long-term effect of impaired nutrition is growth retardation of growth & development.

***Educational achievement***: An association between helminthic infection and educational achievement has long been recognized. Antihelminthic treatment has resulted in improvement in test scores, learning ability, concentration, & eye-hand coordination in the affected children. Ascariasis has been shown to be associated with lower test scoes in language, social-, gross motor-, and fine motor-skills. Malnutrition associated with intestinal helminthiasis is an important contributory factor for increased prevalence of developmental disabilities in the developing world.

***Wandering worm***: Ascaris has a propensity to migrate from its usual habitat, duodenum, to other areas. Worm migration is stimulated by fever, general anesthesia, other abnormal conditions, or the need of the female worm to copulate or postmortem state of the worm.

1) They may enter the *stomach* and lead to vomting or traumatic bleeding. Worms may enter a nasogastric tube and block it.

2) Worms may ascend the *esophagus* and reach epiglottis and thence to upper respiratory tract leading to respiratory difficulty (stridor, cyanosis, dyspnoea). It has even caused cardiac arrest. Worms have come out of the nose or lachrymal duct. They may enter the Eustachian tube and lead to perforation of the tympanic membrane, and exit through the ear. Worms have strayed into paranasal sinuses.

3) Migration into *lower intestine* is the most frequent and most important complication. A tangled mass of worms moves from the duodenum to lodge in the ileocaecal valve, especially in the under-fives. This leads to vomiting, abdominal pain and distension, constipation, and partial or total obstruction on plain x-ray abdomen. They may enter the appendix or Meckel's diverticulum and lead to obstruction, symptoms & signs of appendicitis, sometimes with perforation & peritonitis.

Intestinal obstruction is the single most common complication accounting for 38%-88% of all complications. The complication is commoner in young children. Case fatality ranges widely, and may exceed 8%.

4) *Pancreatic duct* is easily accessed, leading to pancreatitis with severe, acute abdominal pain, tenderness, and raised serum amylase levels. Pancreatic strictures may occur.

5) Worms can enter the *bile duct*, the gall bladder and the intrahepatic biliary tree. They may cause biliary lithiasis, acute cholecystitis or acute cholangitis. They may reach the *liver parenchyma*, and cause hepatic ascariasis. They may carry various pathogens on their surface which may prove disastrous in immuno-compromised host. Liver abscesses may perforate into the pleural cavity, the lungs and the pericardium. In one case, 60 adult worms were surgically removed from the liver of a patient suffering from

acute obstructive cholangitis. In endemic areas, ascariasis should be considered in any child with hepatobiliary symptoms.

6) The worm may move to the *peritoneal cavity* through intestinal ulcerations. Rarely the worm may itself perforate the intestine. The female worm lays eggs which produce a granulomatous inflammation, and itself dies leading to a large abscess. Clinically it presents as a tumourlike mass anywhere in the abdomen. Peritonitis is often fatal since there is secondary bacterial infection. Post-surgery they may wander into the peritoneal cavity or come out of the sutures of the skin wound.

7) *Unusual migrations*: Worms may enter any tube or opening. They have entered nasogastric tubes, T-tubes, fistulas between intestine & the ureter, sinus tracts in the gluteal region, fistula of ulcerated inguinal hernia, etc. They may pass out from the mouth, nose, ear, or even eye. They have been found to pass into the placenta and even recovered from the intestine of he delivered baby.

8) *Postmortem migrations*: After its death the worm can go to any place it could visit during life. However, absence of inflammatory changes in the visited organ exclude premortem migration.

Inside the intestine, adult worms when scant usually cause no difficulty. However, because of the tendency of the adult worm to migrate, even a single worm can cause serious sequelae.. Wandering worms may move to any organ of the gastrointestinal system (including liver, biliary tract, gall bladder, pancreatic duct, appendix) or to the peritoneal cavity. They may come out of the anus, mouth, nose. Unexpected body sites as kidney or pleural cavity have been involved.

**Diagnosis:**

In the larval migration phase, diagnosis can be made from detection of larvae in sputum, or more commonly in gastric washings. The typical Loeffler's syndrome is more likely to be seen in areas where transmission is seasonal.

In the intestinal phase, diagnosis is made by finding the eggs or adult worms in the stool. The eggs are most easily seen on a direct wet smear or a wet preparation of the concentration sediment.

***Burden of ascariasis in developing countries (1990s)***

Population: 2500 million
People infected with ascaris: 1000 million
Daily faecal output with ascaris eggs: 2.00 lakh tons
*(Average daily output of stool/person, 200g)*
Daily discharge of eggs: $2 \times 10^{14}$ eggs
*(Average 1000 ascaris eggs per gram of stool)*
DALYs lost to ascaris: 10.5 million

Adapted from: Coombs I, Crompton, DWT. How much human helminthiasis is there in the world? J Parasitol 85:397-403, 1999

Intestinal disease can often be diagnosed from radiographic studies of the gastrointestinal tract, where the worm displaces the barium and looks dark. This may be particularly obvious when two worms are lying parallel (trolley car lines).

Specific symptoms may indicate the sites involved as bowel obstruction, biliary or pancreatic duct block, appendicitis, or peritonitis.

**Treatment:**

Newer anthelminthics, unlike the older remedies, do not require pre or post-treatment purging or fasting. In the USA, mebendazole is considered the drug of choice for both children and adults; other good alternatives pyrantel pamoate and albendazole are not used as commonly. These drugs are

effective in eliminating the adult worm but there is no conclusive evidence that they are effective in the larval migration phase. For other body sites, surgery is required.

Worms are easily eliminated from the intestine, and prognosis is excellent. On the contrary, the prognosis may be extremely poor in case of massive larval migration through the lungs. Prognosis may be unfavourable if there is perforation or need for surgery.

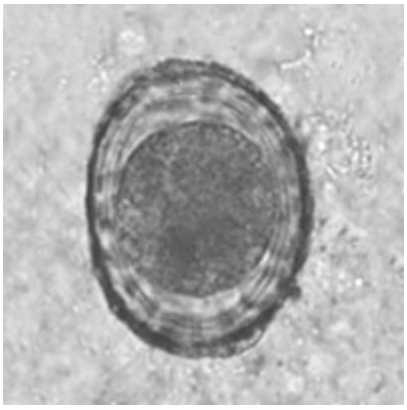
Some individuals are susceptible to heavy infections while others are not. This too has been seen that deworming has a greater impact on the intensity of infection than on its prevalence and that mass chemotherapy is likely to be a more effective means of controlling morbidity than is selective treatment of heavily infected individuals only. Targetted approaches (child targeted treatment) is also as effective and both these approaches are more cost effective than the selective approach.

**Prevention & Control:**

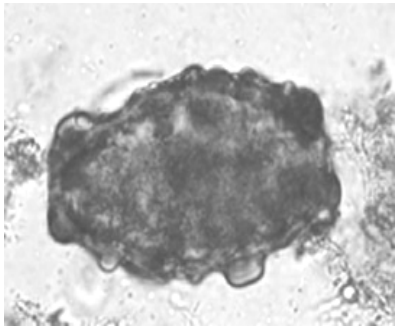
The ultimate transmission of ascaris depends on contamination of the soil by the egg-laden faeces. Therefore, provision of proper sanitary facilities, coupled with hygiene education, is the best means of prevention and control. There is no practical means of killing the eggs in clay soil under favourable conditions of warmth and moisture.

In endemic areas where re-infection rates are high, mass or targeted treatment plans have been quite successful.

Human faeces should not be used for fertilizing crops, and no vegetable or fruit from such a field should be eaten raw. It must be noted that even with proper pretreatment of night soil, ascaris eggs retain viability and infectivity than otrher helminthic eggs. It has been reorted that upto 90% of ascaris eggs survived sludge treatment for upto 30 weeks and were able to develop motile larvae.



Fertilized egg of A. lumbricoides



Unfertilized egg of A. lumbricoides

¤ Both the eggs are still at the unicellular stage. Eggs are normally at this stage when passed in the stool. Complete development of the larva requires 18 days under favorable conditions.

**Laboratory diagnosis of ascariasis***

Helminthic eggs are often easier to find and identify because of their size and their distinctive morphological features. While direct smears of fresh faeces will often demonstrate helminth eggs, it is usually more efficient for laboratories to do a simple concentration to avoid overlooking parasites that may be present in very small numbers.

## Direct faecal smears – saline and iodine wet mount preparations

**Procedure**

1). With a wax pencil or other marker, write the patient's name or identification number and the date at the left hand side.
2). Place a drop of saline in the centre of the left half of the slide and place a drop of iodine solution in the centre of the right half of the slide.

## Materials & reagents

- Wooden applicator sticks or matches
- Microscope slides (75x25 mm)
- Coverslips
- Pens or markers for indelible marking
- Dropping bottles containing: Isotonic saline solution (0.85%; 8.5g/l)
- Lugol's iodine (1% solution)

3). With an applicator stick or match, pick up a small portion of faeces (approximately 2 mg which is about the size of a match head) and add it to the drop of saline: add a similar portion to the drop of iodine. Mix the faeces with the drops to form suspensions.
4). Cover each drop with a cover slip by holding the coverslip at an angle, touching the edge of the drop, and gently lowering the coverslip onto the slide so that air bubbles are not produced.
5). Examine the preparation with the 10X objective in a systematic manner (either up and down or laterally) so that the entire coverslip area is observed. When organisms are seen, switch to higher magnification top see the more detailed morphology of the object in question. [* Based on the WHO recommendations]

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# Typhoid Fever

*(M Yusouf Rathor)*

Typhoid fever is an acute, systemic, febrile illness caused by S. typhi, S. paratyphi A, S. paratyphi B and occasionally S. typhimurium. Many clinicians prefer to call it enteric fever.

Typhoid is a worldwide health problem, especially in developing countries, which is attributable to poor sanitation, poor standards of personal hygiene, and frequent contamination of food. Delay in diagnosis, emergence of antibiotic-resistant strains, the lack of availability of a safe, effective and cheap vaccine are contributing factors.

In developed countries, the infection is acquired from abroad or from chronic carriers who handle food. In 1989, a large outbreak occurred in a New York hotel because of contamination of orange juice. *S typhi* was isolated from the stool of an asymptomatic typhoid carrier who handled orange juice.

**Epidemiology**

***Incidence***: According to the World Health Organization, globally some 16 million cases occur annually resulting in more than 600,000 deaths. More than 62% of the global cases occur in Asia, of which, 7 million occur annually in South East Asia. Other countries with a high incidence include Central & South America, Africa and Papua New Guinea.

- ***Age group***: In endemic countries, typhoid is predominantly a disease of school children and young adults. In an outbreak of 649 cases in Penang (Malayasia) in 1987, 52% of cases were between the ages of 1-24 years. In Indonesia, 3-19-year-age group accounted for 91% of typhoid cases.
- **Typhoid & HIV**: In endemic regions, the rate of clinical typhoid among the 15-35 year age group is approximately 25 times higher in HIV positive cases than in the HIV –ve individuals.

**Pathogenesis**

Human beings are the only reservoir for *S. typhi*. The infection is transmitted by faecally-contaminated water and food in endemic areas and by chronic carriers handling food in developed countries. The bacteria can survive several months in soil or water.

Infection is dose-related - size of the inoculum and the type of vehicle in which the organisms are ingested will influence both the attack rate and the incubation period. A dose of $10^9$ organisms will induce infection in most cases, whereas a dose of $10^3$ or less organisms will rarely produce symptoms in otherwise healthy individuals.

*S. typhi* virulence is complex requiring several virulence factors for full expression of pathogenicity. Host factors, e.g. gastric hypoacidity, may increase the attack rate as gastric acid kills most of the bacilli that have been ingested with food or water.

The two most important sites normally affected are the Peyer's patches

in the small intestine and the gall bladder.

**Clinical Features**

The average incubation period is 10-14 days, (a range of 3 – 60 days has been reported). The duration of illness, on an average, is approximately 4 week (may range between 4 to 8 weeks).

- ***First week***: The disease classically presents with step-ladder fashion rise in temperature (40 – 41°C) over 4 to 5 days, accompanied by headache, vague abdominal pain, and constipation.
- ***Second week*: B**etween the 7th - 10th day of illness, mild hepato-splenomegally occurs in majority of patients. Relative bradycardia may occur and rose-spots may be seen.
- ***Third week*:** The patient will appear in the "typhoid state" which is a state of prolonged apathy, toxaemia, delirium, disorientation and/or coma. Diarrhoea will then become apparent. If left untreated by this time, there is a high risk (5-10%) of intestinal haemorrhage and perforation.
- Patients with multi-drug resistant typhoid fever (MDR-TF) are more toxic at admission and have a higher risk of life-threatening complications such as endotoxic shock, disseminated intravascular coagulation, encephalopathy, myocarditis and paralytic ileus.

The course of paratyphoid fever tends to be shorter and milder than typhoid & onset is often abrupt with acute entritis.

Following recovery, 5 % of patients become long term (chronic) asymptomatic carriers. The likelihood of becoming a chronic carrier increases with age, especially in women often associated with cholecystitis and gallstones.

**Complications**

Gastrointestinal complications are the commonest – haemorrhage towards the end of the 2nd week, and intestinal perforation in 3rd week may occur in 3-5% of patients. Ileal perforation, with a mortality of about 40%, is frequently seen in young men.

Other complications include cardiovascular insufficiency, myocarditis, meningitis, hepatic involvement (10%), cholecystitis, thrombophelibitis and pulmonary embolism, pneumonia, parotitis, thyroiditis, osteitis, arthritis, osteomylitis, orchitis and nephritis. Rarer complications include endotoxic shock, disseminated intravascular coagulation, encephalopathy, myocarditis and paralytic ileus.

Complications are commoner with multi-drug resistant typhoid, and frequency of all complications, except relapse, is reduced by prompt antibiotic therapy.

**TYPHOID AND CANCER:** A study of cancer risk in chronic typhoid and paratyphoid carriers showed an increased incidence of cancer of gall bladder, pancreas, colorectum, & lung and various other neoplasms.

**Diagnosis**

- Typhoid should be considered in any patient with prolonged unexplained fever in endemic

areas and in those with a history of recent travel to endemic area.

- Prolonged fever, rose spots, relative bradycardia and leucopenia make typhoid strongly suggestive. About 25% of patients show leucopenia and neutropenia.
- Widal test measures titres of serum agglutinins against somatic (O) and flagellar (H) antigens which usually begin to appear during the 2nd week. In the absence of recent immunization, a high titre of antibody to O antigen > 1:640 is suggestive but not specific.
- Polymerase chain reaction (PCR) can be performed on peripheral mononuclear cells. The test is more sensitive than blood culture alone (92% compared with 50-70%) but requires significant technical expertise.
- Several new serologic tests have been developed to aid in the diagnosis of typhoid fever.

**Definitive diagnosis** of typhoid is by isolation of organisms.

- Blood cultures are positive in 70-80% of cases during the *1st week.*
- Stool and urine cultures are usually positive (45-75%) during the *2nd-3rd week.*
- Bone marrow aspirate cultures give the best confirmation (85-95%) and are positive even after brief antimicrobial treatment.

**Immuno-chromatographic test for rapid diagnosis of Typhoid**

Various rapid tests have been developed for diagnosing typhoid:

- **Typhidot** test that detects presence of IgM & IgG in one hour (sensitivity>95%, Specificity 75%)
- **Typhidot**-M, that detects IgM only (sensitivity 90% & specificity 93%)
- **Typhidot** rapid (sensitivity 85% & Specificity 99%) is a rapid 15 minute immunochromatographic test to detect IgM.

# Treatment

**Time-tested, Traditional Treatment**

- Chloramphenicol has been the antimicrobial gold standard for treatment of typhoid. Clinical response is apparent usually within 24 to 48 hrs of treatment. Treatment is started with a dose of 50 – 75 mg/kg bodyweight/day and reduced to 30 mg/kg per day once the patient is afebrile. The total course takes some 2 weeks.
- Ampicillin/ Amoxillin (750 mg 6 hrly) may be used as an alternative.
- Trimethoprim-Sulphamethoxazole (TMP-SMZ), 2 tablets or IV equivalent 12 hrly.

**Short course therapy**

Efficacy of both fluoroquinolones and third-generation cephalosporins has been evaluated. (cure rates have been shown to be 90-100%). Ceftriaxone has been shown to be the most effective short-term drug and rivals Chloramphenicol in rapidity of defervecenc, and at the same time relapse rate is less. Ciprofloxin is widely used in doses of 500mg 12 hrly. Relapse responds to same antimicrobials as given earlier.

Salicylates should be avoided. Role of steroids is controversial.

**Table I: Treatment of Typhoid Fever using Third-Generation Cephalosporins**

| First Author (Year) | Drug | Dose | Duration (Days) | No. of Patients | Clinical Cure (%) | Number of Patients who Relapsed n (%) |
|---|---|---|---|---|---|---|
| **Acharya (1995)** | Chloramphenicol<br>Ceftriaxone | 40-60mg/kg/d<br>2g/d | 14<br>3 | 23<br>23 | 83<br>87 | 0<br>0 |

**Table II: Treatment of Typhoid Fever using Fluoroquinolones**

| First Author (Year) | Drug | Dose | Duration (Days) | No. of Patients | Efficacy Rate (%) | FCT* (Days) Mean (SD) or range | Number of Patients who Relapsed n (%) | MDR-ST |
|---|---|---|---|---|---|---|---|---|
| **Uwaydah (1992)** | Ciprofloxacin | 500mg bd<br>750mg bd | 7-10<br>7-10 | 34<br>28 | 100<br>100 | 4.9<br>5.2 | 0<br>1 (4) | 43.5% |
| **Wallace (1993)** | Ciprofloxacin<br>Ceftriaxone | 500mg bd<br>3gm/d | 7<br>7 | 20<br>22 | 100<br>73 | 4<br>5.2 | 0<br>1 (5) | 50% |
| **Alam (1995)** | Ciprofloxacin | 500mg bd<br>500mg bd | 10<br>14 | 35<br>34 | 100<br>100 | 4.2<br>4.9 | 0<br>2 (6) | 52% |
| **Smith (1994)** | Ofloxacin<br>Ceftriaxone | 200mg bd<br>3gm/d | 5<br>3 | 22<br>25 | 100<br>72 | 3.4<br>8.2 | 0<br>1 (4) | 63% |
| **Hien TT (1995)** | Ofloxacin | 15mg/kg/d<br>10mg/kg/d | 3<br>5 | 118<br>110 | 100<br>100 | 2.5<br>3.0 | 0<br>1 (1) | 91% |
| **Vinh H (1996)** | Ofloxacin | 15mg/kg/d | 2<br>3 | 53<br>47 | 89<br>96 | 4.2<br>4.4 | 0<br>1 (4) | 86% |

**Managing MDR-TF:**

- Either oral ciprofloxacin or IV Ceftriaxone can achieve a 95% cure rate with low relapse and carrier rates following clinical cure of TF
- The advantages of fluoroquinolones are low toxicity profiles, its ability to penetrate into macrophages (site of Salmonella replication), the low risk of plasmid-mediated resistance and the fact that it can be given orally.

**Treatment of Typhoid fever in Children**

Third generation cephalosporins have been found to be very safe, but have to be given parenterally.

Quinolones (ciprofloxacin, oflaxacin, gatifloxacin) are advised to be avoided in younger children as as they are potentially toxic to the growing plate and thus may retard growth. A recent study, however, showed no evidence of acute joint toxicity in 326 children, aged 1-14 years, treated with single short courses of fluoroquinolones, compared to their age-matched controls.

Newer drugs that have been studied for the treatment of MDR-TF are Aztreonam, Azithromycin and Furazolidine. None of them has been well accepted as alternatives and further studies are awaited.

**Prevention**

- Environmental Sanitation, sewage disposal and safe water supplies.
- Improvement in personal hygiene
- Immunization for travelers
- Eradication of carrier state. (4 weeks of ciprofloxacin, along with cholecystectomy in presence of gall stones).
- Early diagnosis and treatment.

**Differential Diagnosis**

- Differential diagnosis of typhoid includes all infections associated with prolonged fever such as
  - Rickettsioses
  - Leptospirosis,
  - Infectious Mononucleosis
  - Malaria.
  - Miliary TB,
  - Viral Hepatitis
- Non-infectious cause – Lymphoma.

**Rickettsial Infections:** Infections caused by *Rickettsia* are vector-borne illnesses that occur worldwide. *Rocky Mountain spotted fever, caused* by *Rickettsia rickettsii*, occurs most commonly in North America. It is transmitted by ticks. After an average incubation period of 7 days (range, 2 to 14 days) following a tick bite that may go unnoticed, fever, malaise, myalgias, headache, and nausea and vomiting develop.

- The typical rash consists of macules on the wrists and ankles that appear between the second and sixth day, subsequently spread to include palms and soles, and become hemorrhagic.
- Complications include non-cardiogenic pulmonary edema, renal failure, and encephalitis.

**Tick typhus (Mediterranean spotted fever, boutonneuse fever)**

Tick typhus is endemic in southern Europe and the Middle East, where it is caused by *R. conorii*, and in southern Africa, where *R. africae* is the causative agent. In other countries, it is the most common imported rickettsial disease .

A 5- to 7-day incubation period is followed by fever and nonspecific symptoms that are generally mild and self-limited. A maculopapular rash involving palms, soles, and face and an eschar with regional lymphadenopathy are valuable clues to the diagnosis. Diagnosis is confirmed serologically.

- Treatment is as for Rocky Mountain spotted fever; ciprofloxacin is an alternative therapy for tick typhus.

**Typhus:** Transmitted by the body louse, typhus is both endemic and epidemic in mountain regions and highlands of Mexico, Guatemala, Africa, in the Himalayas and Afghanistan.

The infection is caused by *R. prowazeckii* through scratching over infected faeces of human body louse. The usual incubation period 8- to 12-days is followed by high fever and other nonspecific symptoms.

Severe headache is common. A maculopapular rash that generally spares the palms and soles appears between $4^{th}$ and $7^{th}$ day and in severe cases may become hemorrhagic.

Hypotension, altered mental status, and renal failure are poor prognostic signs.

Untreated, mortality is as high as 60% ; in survivors, defervescence occurs in 2 to 3 weeks, but recovery is prolonged.

The most effective preventive measure is to eliminate lice.

**Murine or flea-borne (endemic) typhus,** caused by *R. typhi,* occurs throughout the world, with high endemicity in Central and South America, parts of Africa, Malaysia, Thiland, Myanmar and Australia.

Infection results from percutaneous inoculation or inhalation of infected feces of the rat flea. Humans are infected when while scratching they introduce the faeces of a crushed flea which has fed on an infected rat.

Fever 39-40°C, headache ( most common), photophobia, conjunctival suffusion are common but less severe. Neck rigidity and spasticity suggest meningitis but CSF is normal except raised pressure and few lymphocytes.

Illness is similar to but much less severe than that of louse-borne typhus, and mortality is low.

**Scrub typhus or mite borne typhus:**
Endemic in areas of Asia and nearby Pacific islands, India, and northeastern Australia, Pakistan , Myanmar, Thailand, Bangladesh, Indonesia, the infection is caused by *R. tsutsumaguch* which is transmitted by mites (chiggers).

Infection leads to fever, headache, and myalgias in 10-14 days; an eschar with regional lymphadenopathy and an erythematous maculopapular rash usually develop during this time. With treatment, mortality is low. Temperature continues in a remittent fashion until it falls by lyses on 12-18 day. In severe cases patient is prostated with cough , confusion, and deafness. Cardiac failure, renal failure, and haemorrhage may develop.

**Diagnosis** is clinical, and serologic tests are confirmatory.

Rapid diagnostic tests, such as Rickettsial isolation in cell culture and immunofluorescence staining of skin lesions, are sensitive but are not widely available. With an immunoflorescence test, Rickettsia can be can be identified in a skin biopsy specimen as early as 4 th day of illness.

The Weil- Felix reaction is the nonspecific agglutination reaction. A fourfold rise in titer is diagnostic.

Doxycilline is the treatment of choice; Chloramphenicol is an alternative. Death may occur within 2 weeks of onset of illness if untreated. Prompt treatment significantly reduces mortality. Therapy should be continued for at least 5 days and for 48 hours after defervecence.

**Leptospirosis**

Leptospirosis is the most widespread zoonotic infection in the world. It is common in tropical and subtropical climates and is the result of mucous membrane or percutaneous exposure to fresh water contaminated by the spirochete *Leptospira interrogans.*

Most cases are sporadic, but epidemics have been reported. Incubation period – 2 – 20 days (average 10 days).

Leptospirosis is a typically biphasic illness: In the first phase, Leptospira are present in the blood and CSF. Onset is typically abrupt with chills followed by high spiking temperature , myalgias (especially thighs & lumber areas) with pain on palpation and headache . Involvement of one organ system may predominate, often leading to initial misdiagnosis. Examination reveals an acutely ill, febrile patient, with relative bradycardia .Disturbance of sensorium in 25% cases,1/2 with icteric disease .The most characteristic sign is conjunctival suffusion on 3rd or 4th day . Less common findings are pharyngeal injection, skin rashes and cutaneous haemorrhages, splenomegally, hepatomegally and lymphadenopathy. Symptoms resolve in 4 to 7 days, only to be followed several days later by second phase.

Second ("Immune") phase correlates with the appearance of circulating IgM antibodies. After a relatively asymptomatic period of 1-3 days, fever and earlier symptoms recur and aseptic meningitis develops . Pleocytosis not initially present now rapidly develops. CSF protein may exceed 1g/L. Xanthochromic

CSF has been observed in the presence of jaundice.

The illness is self-limited, although treatment does reduce the severity and duration of symptoms and may prevent the second phase of disease.

Icteric disease (Weil's syndrome) is more severe form of leptospirosis with hepatic, renal, and vascular involvement, and has a 5% to 10% mortality rate.

Hemorrhagic leptospirosis has also been described, with a presentation similar to other viral hemorrhagic fevers.

**Diagnosis:** Isolation of leptospires from blood or cerebrospinal fluid is diagnostic, but requires prolonged incubation. The diagnosis is usually made retrospectively by serology. Increased titers of leptospiral antibodies( Four fold or greater rise) are seen after 2 weeks. An IgM specific dot- ELISA has been effective in diagnosing leptospirosis in endemic areas.

Mild disease responds to oral amoxicillin or doxycycline, whereas more severe illness requires intravenous penicillin or Ampicillin.

- Jarisch-Herxheimer reactions have occurred with penicillin.

**Infectious Mononucleosis:** Caused by the Epstein-Barr virus (EBV), most infections are sub clinical and occur before age of 5 or through adolescence .

EBV, is a member of the herpes virus family and one of the most common human viruses, and most people become infected with it sometime during their lives. Clinical expression is most often seen in adolescence or young adulthood. Symptoms are fever, sore throat, and lymphadenopathy. Posterior and /or anterior cervical adenopathy is noted in 90 % cases. Hepatomegally is infrequent. Splenomegally which is usually maximal in 2nd or 3rd week is seen in ½ of patients.

Administration of Ampicillin results in a pruritic, maculopapular eruption in 90 – 100 % of patients of infectious mononucleosis.

Rarely autoimmune hemolytic anemia, thrombocytopenia, aseptic meningitis, hepatitis, G . B syndrome and splenic rupture can occur

Transmission of EBV requires intimate contact with the saliva of an infected person; less commonly it may be contracted by blood transfusion. EBV is shed from the oropharynx for up to 18 months following primary infection. Asymptomatic shedding of EBV by healthy individuals accounts for most of the spread to uninfected members of the population.

The incubation period,, ranges from 4 to 6 weeks

Clinical diagnosis can be made from the characteristic triad of fever, pharyngitis, and lymphadenopathy lasting for 1 to 4 weeks and atypical lymphocytosis.

Three fourths of patients present with absolute lymphocytosis (greater than 10% atypical lymphocytes), normal to moderately elevated white blood cell count, and a positive reaction to a "mono spot" test help in diagnosis. A positive Paul-Bunnell heterophile antibody test result is diagnostic, and no further testing is necessary. Moderate-to-high levels of heterophile antibodies are seen during the first month of illness and decrease rapidly after week 4. However "mono spot" test has largely replaced it, because it is rapid, sensitive and specific.

**Clinically** infectious mononucleosis is a self limited illness in vast majority of cases. There is no specific treatment**,** other than symptomatic. No antiviral drugs or vaccines are available. Acyclovir has been studied with mixed results. The role of corticosteroids remains controversial and are not indicated for usual use. However 60 – 80 mg of prednisolone daily for short periods may be beneficial for patients with severe tonsillopharyngitis, thrombocytopenia & hemolytic anemia. They have also been reported to decrease the overall length and severity of illness, but these reports have not been published.

**Miliary Tuberculosis:** Results from hematogenous dessimation of Myco tuberculosis and chiefly occurs in children and young adults. It presents with a high persistent fever and drenching sweats, marked tachycardia, loss of weight, and progressive anemia with hepato splenomegally. Cough and breathlessness only occasionally present with no abnormal physical signs in lungs

**Diagnosis**: Chest x-ray shows characteristic miliary mottling symmetrically distributed throughout both lung fields. Choroidal tubercles may be seen on ophthalmoscopy. Bacteriological confirmation is done by culture of sputum, urine, or bone marrow. Liver biopsy is diagnostic in difficult cases. Tuberculin test is usually positive, but a negative test does not rule out miliary TB since sensitivity is depressed in later stages of illness.

If chemotherapy is not given, death takes place within days or weeks.

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The highly successful COX2 inhibitor, rafecoxib, widely used for osteoarthritis and rheumatoid arthritis, and studied for use in gut polyposis, has been withdrawn from the market by Merck, after reports proved that use of this drug for periods exceeding 18 months doubled the risk of myocardial infarction. The drug has been shown to greatly increase the risk of thrombo-embolism in chronic users.

Typhoid is known for its multisytsem involvement – the common presenting features being fever and gastrointestinal symptoms.

Some of the features – headache, vomiting, drowsiness, toxicity - and complications - as perforation, bleeding, sepsis – are widely recognized and reported., However, there are some complications which are only rarely reported. One of such infrequently recognized and reported complication is ascites. Patients present with fever, diffuse tender, distended abdomen with sluggish bowel habits. Liver function tests show some hepatic dysfunction.

Serum albumin may be normal or nor so low as to account for acites. Ultrasonography of the abdomen reveals free fluid. Ascitic tap shows sterile exudate – caused by generalized inflammation of peritoneal serous layer (as a part of polyserositis found in enteric fever). Most of the times presence of ascites is not clinically suspected. The signs & symptoms including ascites responded to ceftriaxone or ciprofoloxacin. (Ed)

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# ADVERSE REACTIONS TO TRANSFUSION

***S M Kadri***

Human beings are complex machineries and blood is not a simple fluid; it is a vibrant organ system which is unique to every individual. Thus adverse reactions should be expected with each and every pint of blood that is transfused. The best recourse is no transfusion; the next best is transfusion given only sparsely, when no other choice is left.

Strict testing and cross-matching is to ensure that no serious reaction occurs. The most common immediate adverse sequelae to transfusion of blood and blood components are fever, chills and urticaria. The most common potentially serious reactions include *acute and delayed hemolytic transfusion reactions and bacterial contamination of blood components*, which are described in some detail below. Less common severe reactions, such as anaphylaxis due to anti-IgA, transfusion-related volume overload, acute lung injury, or post-transfusion purpura, are managed in consultation with the medical staff of the blood bank.

Any adverse reaction to the transfusion of blood or blood components should be reported to blood bank personnel as soon as possible. Speed is essential in such situations because of the possible life-threatening nature of acute transfusion reactions. The evaluation of all adverse reactions to transfusion is the responsibility of the medical staff of the blood bank and the notification of such a reaction by the patient-unit serves as a request for blood bank physician consultation. In the USA, the blood bank is required to report any death resulting from transfusion to the Food and Drug Administration (FDA).

These reactions may be separated into reactions that present in proximity to the transfusion and those that present at some time subsequent to the transfusion. Suspected post-transfusion disease, which may present after a considerable time following transfusion, must also be reported to the blood bank. Investigation of these reports may result in identification of "carrier" donors who are removed from the donor pool.

## FEBRILE REACTIONS

Febrile reactions (chill-fever) to blood transfusion are common and are thought to be caused, in some cases, by recipient antibodies to leukocyte antigens reacting with leukocytes or leukocyte fragments contained in the transfused component. Such reactions are most commonly encountered in patients with a history of multiple blood transfusions or pregnancies, both of which can stimulate the development of leukocyte antibodies. Approximately 1 out of 8 patients who have such reactions will have similar reactions to subsequent transfusions. Fever may also result from pyrogenic cytokines generated during storage of blood components.

Febrile reactions usually present during transfusion or in the immediate post-transfusion period and must be distinguished from fever related to the underlying disease or infection. Thus, documentation of a pre-transfusion baseline temperature is extremely important. A temperature rise of 1.5° F (1.0° C) from the baseline is considered significant. The usual treatment, and

pre- transfusion prophylaxis, is with an antipyretic (non-aspirin containing medication). Diphenhydramine hydrochloride (Benadryl) is not appropriate for such treatment. In some patients these reactions present as severe rigor (shaking chills).

Fever is also the most frequent manifestation of acute hemolytic transfusion reactions. Therefore, it is important to rule out this potentially life-threatening reaction through proper evaluation. Notification to the blood bank of all adverse reactions is necessary to provide the patient with the most appropriate blood component.

**ALLERGIC (URTICARIAL) REACTIONS**

The appearance of urticaria during and immediately after the transfusion of blood components is seen in approximately 1% of recipients. This reaction is caused by foreign plasma proteins. On rare occasions, such allergic reactions may be associated with laryngeal edema and bronchospasm.

A mild urticarial reaction is generally innocuous. If coupled with another sign, such as fever, evaluation for a hemolytic reaction may be indicated.

If the allergic symptoms, such as urticaria, are bothersome, an antihistamine may be administered before the blood transfusion is restarted.

In the case of a mild urticarial reaction, with no other signs or symptoms attributable to blood transfusion, it is not necessary to submit post transfusion blood specimens. It may also be possible to reinitiate the blood transfusion. Such a decision must be arrived at through consultation between the physician reporting the reaction and the Blood Bank physician.

**SEVERE ALLERGIC (ANAPHYLACTIC) REACTIONS**

In addition to the signs of typical milder allergic reactions, anaphylactic or anaphylactoid reactions manifest cardiovascular instability that includes hypotension, tachycardia, and loss of consciousness, cardiac arrhythmia, shock and cardiac arrest. Respiratory involvement with dyspnoea or stridor may be more pronounced than is usually seen in typical allergic reactions. Patients with IgA deficiency who develop anti-IgA can have anaphylactic reactions. A blood bank physician should be consulted regarding the evaluation of patients with severe allergic reactions, as well as selection of appropriate blood components for future transfusion.

**ACUTE HEMOLYTIC REACTIONS**

The most dreaded complication of blood transfusion is the acute hemolytic reaction in which transfused red cells react with circulating antibody in the recipient with resultant intravascular hemolysis. Such a reaction is most likely to occur when a group O patient is ABO-incompatible marrow or stem cell transplant with sufficient red cell content will likely develop an acute hemolytic reaction.

Most acute hemolytic reactions are the result of human error, such as the transfusion of properly labeled blood to the wrong person, improper identification of pre-transfusion blood

samples, or clerical errors occurring within the blood bank.

**Symptoms of an acute hemolytic reaction may include**

- chills and fever,
- the feeling of heat along the vein in which the blood is being transfused,
- pain in the lumbar region,
- constricting pain in the chest,
- tachycardia,
- hypotension, and
- hemoglobinemia with subsequent hemoglobinuria and hyperbilirubinemia.

Uncontrollable bleeding due to disseminated intravascular coagulation may be the only sign of a hemolytic transfusion reaction in an unconscious or anesthetized patient. Such a reaction may not be accompanied by hypotension.

## HYPOTENSIVE REACTIONS

Transfusion associated hypotension is defined as hypotension occurring during transfusion in the absence of signs or symptoms of other transfusion reactions such as fever, chills, dyspnoea, urticaria, or flushing. A drop of at least 10 mm Hg in systolic or diastolic arterial blood pressure from the pre-transfusion baseline is typical of a hypotensive reaction. However, if the immediate pre-transfusion blood pressure is elevated from the patient's typical blood pressure, and the arterial pressure does not fall below the patient's usual blood pressure, it should not be considered a hypotensive reaction. The onset of hypotension is during the transfusion, and resolves quickly with discontinuation of the transfusion. If hypotension persists beyond 30 minutes after discontinuing the transfusion, another diagnosis should be strongly considered. Hypotensive reactions have been associated with red cell and platelet transfusions. Some reactions have been associated with angiotensin converting enzyme (ACE) inhibitor drugs or the use of leukocyte reduction filters.

## NON-IMMUNE HEMOLYSIS

Lysis of red cells can occur in conditions of improper storage, handling, or transfusion. The clinical signs are usually hemoglobinemia and hemoglobinuria. Transient hemodynamic, pulmonary and renal impairment may occur. Hyperkalemia may occur, particularly in patients with renal failure. The most significant complications of nonimmune hemolysis are cardiac arrhythmia due to hyperkalemia, and renal failure. Differentiation of non-immune hemolysis from a hemolytic transfusion reaction may be impossible unless the contents of the blood bags are available for study. Therefore, the blood bag together with attached tubing and intravenous fluids should be saved for further investigations.

## POST-TRANSFUSION PURPURA

Post-transfusion purpura (PTP) presents as thrombocytopenia typically 5 to 21 days after transfusion. In PTP, the patient makes an allo-antibody in response to platelet antigens in the transfused blood that for a period of time causes destruction of autologous

antigen-negative platelets. The signs and symptoms are thrombocytopenia that is frequently profound, purpura, or bleeding. Febrile reactions have been reported retrospectively with the implicated transfusion. The thrombocytopenia is self-limited in PTP, with recovery occurring within 7-48 days. PTP must be differentiated from the far more common allo-immunization to platelet antigens. This may be problematic when the patient has an underlying cause of thrombocytopenia. Consultation with a blood bank physician is recommended in evaluating such patients.

Platelet transfusion is of very little value in PTP; however, therapeutic plasma exchange may be beneficial. Since autologous platelets do not survive in circulation, there is no expectation that transfused platelets regardless of antigen matching will do any better. Platelet transfusion should be reserved for patients with active bleeding.

**DELAYED HEMOLYTIC REACTION**

Not all hemolytic reactions occur during or shortly after blood transfusion. The so-called "delayed" hemolytic reaction commonly occurs about 4-8 days after blood transfusion, but may develop up to one month later. The most common signs of such a reaction are a falling hematocrit (a manifestation of extra vascular destruction of the transfused red blood cells) and a positive direct antiglobulin (Coomb's) test (DAT). There may also be hemoglobinuria and a mild elevation of the serum bilirubin. Many delayed hemolytic reactions will go undetected because the red cell destruction occurs slowly. Symptomatic patients may manifest fever and leukocytosis thus appearing to have an occult infection.

Delayed hemolytic reactions occur in patients who have developed antibodies from previous transfusion or pregnancy but, at the time of pre-transfusion testing, the antibody in question is too weak to be detected by standard procedures. Subsequent transfusion with red cells having the corresponding antigen results in an anamnestic antibody response and hemolysis of transfused red cells.

Notify the blood bank at the time the reaction is suspected, to allow prompt investigation. Care must be taken that subsequently transfused red cells lack the antigen corresponding to the patient's antibody.

**GRAFT vs HOST DISEASE (GVHD)**

GVHD is associated with bone marrow transplantation. Transfusion associated GVHD occurs when viable T lymphocytes in blood components are transfused engraft and react against the recipient's tissues and the recipient is unable to reject the donor lymphocytes because of immunodeficiency, severe immunosuppression, or shared HLA antigens. It typically presents 3-4 weeks after transfusion with rash, fever, diarrhea, pancytopenia and liver dysfunction. Transfusion associated GVHD carries a very poor prognosis. Irradiation is the recommended method of preventing this complication. The blood bank must be appraised of the immune status, or diagnosis, of the patient so that cellular components intended for transfusion of immunocompromised patients and blood components from designated

donors will be irradiated. Irradiation of blood red cell containing components decreases the red cell survival and increases the potassium of the component. There is no apparent effect on platelet survival. Fresh Frozen Plasma (FFP) and cryoprecipitated AHG (CRYO) need not be irradiated because these components do not contain enough viable lymphocytes to cause GVHD.

### BACTERIAL CONTAMINATION OF BLOOD COMPONENTS

Bacterial contamination occurs when a small number of bacteria enter a blood component during collection or processing. During storage, bacteria may proliferate, resulting in a large number of organisms, and possible endotoxin, being given with the transfusion. Bacterial contamination is rare, but difficult to detect prior to transfusion. The organisms that contaminate red blood cells are often Yersinia and Pseudomonas, which grow at 4° C and metabolize citrate. Autologous blood may be contaminated with bacteria, particularly if the patient had an active infection at the time of donation. Organisms that contaminate platelets are typically Gram negative rods and Gram positive cocci. Symptoms that indicate bacterial contamination include hypotension, shock, fever and chills, nausea and vomiting, and respiratory distress. These symptoms may also indicate a hemolytic transfusion reaction. Suspected transfusion reactions due to bacterial contamination should be reported promptly to the blood bank. Diagnosis is established by Gram stain and blood culture of both the blood component and the recipient.

### TRANSFUSION RELATED ACUTE LUNG INJURY (TRALI)

TRALI is a rare though under-recognized complication of transfusion manifested by abrupt onset of non-cardiogenic pulmonary edema. Severe cases may require assisted ventilation with high $FIO_2$. Most cases of TRALI resolve within 72 hours although fatalities may occur in approximately 10% of cases. TRALI has been associated with the presence of antibodies in the donor plasma reactive to recipient leukocyte antigens or with the production of inflammatory mediators during storage of cellular blood components. Prompt notification of the blood bank when TRALI is suspected will assist in evaluation and appropriate blood component selection for future transfusions.

**IF A TRANSFUSION REACTION IS SUSPECTED**

**Stop** the transfusion immediately!

**Disconnect the intravenous line** from the needle. Attach a new IV set and prime with saline, or flush the line with the normal saline used to initiate the transfusion and reconnect the line. Open the line to a slow drip. In certain cases, such as a mild urticarial reaction or the presence of repeated chill-fever reactions, it may be possible to restart the blood transfusion after evaluation and treatment of the patient. To reinitiate the transfusion using new IV tubing set, enter the second port to reduce the chance of bacterial contamination.

**Seek medical attention** immed- iately

**Check** to ensure that the patient name and registration number on the blood bag label matches exactly with information on the patient's identification

***DO NOT BYPASS THIS STEP BY ASSUMING THAT THE PATIENT'S TRUE IDENTITY IS KNOWN.***

**Do not discard the unit of blood** that has been discontinued because it may be necessary for the investigation of the transfusion reaction.

## When a Reaction Occurs!

Notify Blood Bank personnel that a transfusion reaction has occurred and briefly describe the nature of the reaction. Delay the transfusion of additional units until the possibility of serological incompatibility has been investigated.

Consult a Blood Bank physician if there is an urgent need for transfusion. Initiate the Transfusion Reaction Report Form after Blood Bank personnel have been notified of a transfusion reaction. It is essential that this form be filled out completely, including the unit numbers of all blood transfused. The form will serve as a written request for investigation of the reaction by a Blood Bank physician.

In the case of a **suspected hemolytic transfusion reaction** (not urticaria alone), the following items should be submitted promptly to the Blood Bank:

- Completed Transfusion Reaction Form (all copies),
- Post transfusion blood specimens and
- Incriminated unit(s) of blood and attached tubing.

The necessary specimens, blood bag and attached tubing should be sent to the Blood Bank unless the Blood Bank physician, after review of the clinical information, believes the transfusion can be restarted. The latter may apply to patients who might manifest urticarial reactions or repeated chill-fever reactions.

Additional blood specimens may be requested, depending on the serological findings. The venipuncture to obtain these blood specimens must not be traumatic. Small lumen catheters should not be used to collect blood specimens for a transfusion reaction investigation. If red cells are hemolyzed during the venipuncture or collection, the serum will turn pink and it may be erroneously concluded that intravascular hemolysis has occurred.

The IV tubing used to transfuse the blood components should be clamped and sent *without the needle attached*. A urine sample is not required for the routine evaluation of a transfusion reaction, but may be requested by the Blood Bank physician in the course of further assessment.

Patient care personnel will be notified by telephone of significant findings of the reaction evaluation as soon as possible. A written report of the investigation, on the Blood Transfusion Reaction Form, will be returned to the patient care unit at a later date for inclusion in the patient's chart.

## TREATMENT OF TRANSFUSION REACTIONS

The following guidelines should be tailored to suit individual cases.

### ACUTE HEMOLYTIC REACTIONS

### Diuretic therapy:

Initially, give 40-80 mg Frusomide (Lasix) intravenously. This dose can be repeated once. Lack of response to frusomide in 2-3 hours indicates the presence of acute renal failure. Pediatric dose: 1-2 mg/kg/dose. May repeat once at 2-4 mg/kg.

### Water loading:

The patient should be hydrated to maintain urinary output of at least 100 ml/hr. Infuse a loading dose of 0.9% sodium chloride or 5% dextrose in 0.45% sodium chloride. Chart hourly urine output. Maintain the urine output by administering intravenous fluid at 100 ml/hour until the urine is free of hemoglobin. If the patient's urinary output does not increase with this hydration, any additional fluids should be infused with caution. Pediatric patients should receive a smaller loading volume of fluid in proportion to their body surface area.

Treat shock and disseminated intravascular coagulation with appropriate measures if and when they appear.

### DELAYED HEMOLYTIC TRANSFUSION REACTIONS

Specific treatment generally is not necessary. Supplemental transfusion of blood lacking the antigen corresponding to the offending antibody may be necessary to compensate for the transfused cells that have been removed from the circulation.

### ALLERGIC TRANSFUSION REACTIONS

***Antihistamines*** Give 50-100 mg orally or intravenously. If urticaria develops slowly, antihistamines may be given orally. Pediatric dose: 1-2 mg/kg im or iv; 25-50 mg per average dose. Routine use of an antihistaminic as premedication for all transfusions, regardless of a history of allergic reactions, is discouraged.

***Aminophylline*** for wheezing, at a dose of 125-250 mg iv slowly over a period of about 5 minutes. Pediatric dose: 3 mg/kg/dose in iv drip over a period of 20 minutes.

***Epinephrine*** for severe, acute reactions including laryngeal edema or bronchospasm. Give 0.1-0.5 mg (0.1-0.5 ml of a 1:1000 solution) subcutaneously. Subcutaneous dose may be repeated at 10-15 minute intervals. The total subcutaneous dose in a 24-hour period, with rare exceptions, should not exceed 5 mg. Pediatric dose: 0.03 $mL/M^2$ (0.03 $mg/M^2$ of a 1:1000 solution) given subcutaneously. A single pediatric dose should not exceed 0.3 mg.

### FEBRILE TRANSFUSION REACTIONS

Premedicate the patient with acetaminophen or other antipyretic agents when previous reactions have been extremely bothersome. Pediatric dose: 10 mg/kg to a maximum of 600 mg. Aspirin will adversely affect the patient's platelet function, so non-aspirin antipyretic agents are preferable.

**Severe shaking chills** (rigors) can be controlled by the sedative effect of antihistaminic (25-50 mg given im or iv). Some prefer an opiate as Demerol which may cause acute respiratory arrest. An opiate antagonist should be immediately available.

For patients with a *history of severe repeated well-documented febrile reactions,* transfusion with leukocyte-poor components may be indicated to reduce the transfused load of white blood cells. Leukocyte-reduced components are transfused routinely to patients with hematologic malignancy and to patients receiving outpatient transfusion.

**SEPSIS DUE TO BACTERIAL CONTAMINATION OF DONOR BLOOD**

Treatment of septic shock includes: terminating the suspected transfusion immediately, cardiovascular and respiratory support, blood culture of the patient, and administration of broad spectrum antibiotics including anti-pseudomonas coverage if the blood component involved is red blood cells**.**

**PREMEDICATION FOR RECIPIENTS OF GRANULOCYTES**

It is suggested that patients receiving granulocytes who have a history of febrile reactions to blood components be pretreated with antipyretic agents if there are no contraindications to the use of these drugs. In general, transfusion of granulocytes should be terminated only for such complications as severe flank pain, chest pain, hemoglobinemia and hemoglobinuria, hypotension, laryngospasm, or acute pulmonary injury.

**POSTTRANSFUSION DISEASES**

All cases of suspected posttransfusion disease transmission encountered among inpatients or outpatients, in any context, must be reported to the Blood Bank so that they can be investigated. This way blood donors who are thought to be infectious can be excluded from the list of eligible donors. Because of the risk of posttransfusion infection, the benefits associated with blood transfusion must always be weighed against possible risks. In addition patients must be informed of the risks of transfusion and of alternative strategies. Under extremely rare circumstances it may be necessary to transfuse blood or a blood component to a patient before all the screening tests for disease transmission have been completed. In such situations, the physician treating the patient should be made aware of the available options by Blood Bank medical staff and will be informed of the test results as soon as they are available.

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Studies have shown that fast foods when consumed regularly lead to obesity. Public consciousness in the UK has led to mounting pressure on fast food manufacturers to alter the composition of such foods which are generally high-salt, high-calorie snacks, and fast-food joints to serve such healthy foods as salads, organic milk and juices.

Two school girls in New York have filed suits against the world-famous fast-food giant, McDonalds, claiming their food made them overweight and sick.

Our place long known for traditional food habits is adopting fast-food style to its detriment. It is the need of the hour to make our youngsters aware of the dangers of fast-food culture.

## Patient Education

# Asthma

Asthma is a chronic airway disease that involves episodic attacks of breathing difficulty, wheezing, coughing, or tightness in the chest. Just what triggers these attacks varies from one person to another, but allergies probably account for the majority of symptoms in people with susceptible airways. Other influences can include cold air, respiratory infections (including colds), smoke and environmental pollutants, sudden changes in temperature or humidity, and strenuous exercise. Only rarely is asthma attributed to emotional or psychological distress, although for many years this was considered one of the prime triggers.

During an asthma attack the muscles tighten around the tubes inside and leading to the lungs (the bronchi), and the lining of the tubes becomes swollen and inflamed. Often thick mucus accumulates in the airways as well. In all cases airflow is restricted, and emptying the lungs of air becomes particularly difficult. These attacks can last anywhere from several minutes to several days. Although severely restricted airflow can be life-threatening, in most cases the attacks are mild or moderate. In fact, by avoiding triggers and using appropriate medications, most people with asthma can lead active, healthy lives.

Asthma has become increasingly common in early childhood, affecting as many as 10 percent of all children, probably because of a rise in both outdoor and indoor pollution. Up to the age of 10, boys are twice as likely as girls to have asthma, but by the preteen years the numbers even out. By age 20, as well as throughout the remainder of life, women are about 3 times more likely than men to be diagnosed with asthma. They are also more likely to be hospitalized for asthma and to die of an attack.

Some of the differences in diagnoses are undoubtedly attributable to the greater propensity of women to seek medical attention for any condition. The differences may also be related to the fact that asthma in men is often misdiagnosed as some other respiratory condition, such as chronic obstructive lung disease or emphysema. Even so, there is now some intriguing evidence that at least some of the explanation for women's susceptibility lies in hormonal differences. Also, women frequently have conditions (such as arthritis, menstrual cramps, and headaches) that lead them to use aspirin and other anti-inflammatory drugs which, in rare cases, may trigger asthma attacks. In addition, women may be exposed more frequently than men to certain inhaled allergens, such as the mites that grow in house dust and other indoor pollutants. Despite the many strides made in sharing household duties, a woman allergic to dust mites still is much more likely to be the one who does the vacuuming than a man with similar susceptibilities.

There is no evidence that asthma attacks become more severe or more frequent during pregnancy, but asthma can pose particular problems for a woman expecting a baby. This is because restricted airflow to the mother can potentially deprive the fetus of oxygen. During pregnancy many women who do not have asthma notice changes in breathing patterns or difficulty breathing because the growing uterus changes the shape of the chest cavity. In pregnant women with asthma, these body changes can make asthma attacks more difficult to control than normal. Still, most women with asthma can expect to stay healthy and have healthy babies if they continue to take their medications under the supervision of a clinician who is aware of their pregnancy.

**Who is likely to develop asthma?**

The susceptibility to asthma appears to be inherited, and people with allergies are particularly likely to develop it at some point. Among the allergens that trigger attacks in people with susceptible airways are dust mites, molds, pollens, animal dander, and certain foods. As much as 8 percent of the population is also allergic to food additives called sulfites (whitening agents), and they may experience an almost immediate asthma attack after eating foods containing these chemicals. Sulfites are often found in dried fruits and vegetables, wine, beer, potatoes, dehydrated seafood soups, baking mixes, fruit drinks, and certain soft drinks.

Susceptible people exposed to large amounts of smoke (whether from cigarettes or wood-burning stoves), gasoline fumes, fresh paint, and other environmental pollutants may have frequent attacks of asthma.

**What are the symptoms?**

The classic symptoms of an asthma attack are wheezing (noisy breathing), coughing (especially at night), tightness in the chest, shortness of breath, and labored breathing. Symptoms may begin upon exposure to the offending trigger or may develop slowly over many hours. Often attacks develop in the middle of the night.

In a severe attack breathing becomes rapid and shallow, heartbeat quickens, and the skin pales or takes on a bluish cast. It may be necessary to use accessory neck and abdominal muscles in order to support breathing. Sometimes a person with longstanding asthma becomes barrel-chested as the chest expands to accommodate enlarged lungs -the body's way of compensating for constricted airways.

**How is the condition evaluated?**

Usually asthma is diagnosed by a clinician only after several attacks have occurred. Various tests including pulmonary function tests can help differentiate asthma from other respiratory diseases. Once asthma has been diagnosed, the clinician may suggest seeing an allergist, who can do skin tests to see if there are any identifiable allergens underlying the attacks. The clinician may also suggest keeping a diary to help determine if the attacks can be linked to any particular substances or situations.

**How is asthma treated?**

Active asthma attacks are usually treated with a short-acting bronchodilator, such as albuterol, which opens the airways by relaxing smooth muscle. Corticosteroid medication in an inhaler or in oral form, such as prednisolone or prednisone, reduces inflammation, which is a key mechanism of asthma attacks. Because it takes at least 6 hours for corticosteroids to take effect even if inhaled, bronchodilators are used to provide immediate relief of symptoms.

Once the attack is under control, the physician may prescribe maintenance medications, such as cromolyn, which reduce the chances that the airways will become inflamed. Corticosteroids are usually continued on a maintenance basis, in the inhalable form; long-term treatment with oral preparations is avoided if possible because they are associated with adverse side effects.

Many asthma medications are available in aerosol form and can be inhaled into the lungs in specific amounts through a device called a metered-dose inhaler. The medications are also available as tablets and syrups. The aerosol inhalers fit inside a purse and should be carried at all times to stave off emergency attacks. Bronchodilators are also available in a solution for use in an electric nebulizer, which produces a mist that the patient

breathes through a hand-held inhaler attached by tubing to the machine. The mist may provide added relief at home during prolonged attacks. Bronchodilators can also be taken systemically if necessary. Nose sprays can help dry up the stuffy or runny nose which often accompanies allergic asthma.

Although some asthma medications are available over the counter, the condition should be evaluated by a clinician before these are tried.

Most asthma drugs are considered safe for use during pregnancy. If antibiotics are prescribed to treat the upper respiratory infections that can trigger asthma, tetracycline or sulfa drugs should be avoided because of adverse effects on the fetus. Corticosteroids used in inhaled form are preferred over oral forms during pregnancy, since relatively little drug can reach the fetus through this route. But because severe asthma attacks can be life-threatening to the pregnant woman and so potentially damaging to the fetus, systemic steroids are considered an appropriate tradeoff for pregnant women with severe asthma, even though their safety for the fetus has not yet been proved or disproved.

In the past, people with known allergies received desensitization shots to reduce susceptibility to allergens. Today, however, allergists often advocate eliminating or reducing exposure to the allergen as a first course of action, partly because desensitization shots must be taken quite frequently, are not always effective, and are uncomfortable and expensive.

Anyone with asthma needs to be under the regular care of a clinician. This is because it often takes a good deal of trial and error before the right combination of medications and preventive steps can be determined.

**How can asthma be prevented?**

Although the underlying physical cause of asthma cannot be prevented, minimizing the frequency of asthma attacks boils down to eliminating or reducing exposure to anything known to trigger them. This is not always easy and is sometimes impossible, in which case the only recourse is heavy reliance on medications. The many asthma attacks that develop for no apparent reason obviously cannot be prevented either. Anyone who suspects certain allergens or environmental sources can try one or more of the following tactics.

**Minimize dust and other household allergens**

Ordinary household dust consists of a number of different materials that trigger asthma attacks, including the feces of dust mites and cockroaches, pet dander, and microscopic fabric fibers. Frequent dusting and vacuuming can minimize dust exposure over the long run, but often these well-intentioned efforts only stir some of the lighter-weight particles into the air, where they are readily inhaled. For this reason, someone other than the allergic person should be assigned these dust-busting tasks and the allergic person should stay out of the room for at least half an hour after cleaning.

An alternative is to invest in a double-filtered vacuum cleaner or, better yet, a so-called high-efficiency particulate arresting (HEPA) vacuum cleaner. HEPA air cleaners are a good investment for the bedroom, if not the whole house, because so much time is spent in that room during sleep. Many allergists also recommend more extreme measures such as ripping out carpeting,

eliminating all stuffed and upholstered furniture, and removing books and dust-catching knickknacks, but not all people are willing or able to take these steps (nor do they necessarily help). Perhaps a more practical alternative is to cover the affected person's mattress and pillowcase with airtight rubber covers, wipe these down with water on a weekly basis, wash bedding frequently in very hot water, and keep the bedroom in particular as dust-free as possible. If there is a forced-air heating system in the home (which disperses dust even more than other heating systems), it should be equipped with an effective air filter to trap offending particles.

Various steps can be taken against specific allergens found in dust. If dust mites are the problem, for example, agents lethal to the mites, called acaricides, can be applied to carpeting although these are probably not safe for use in the home of a pregnant woman. A cockroach problem may be reduced by having the house or apartment fumigated regularly by an exterminator. As for animal dander, the best solution is clearly to avoid owning a dog, cat, or other furry pet and to avoid long stays at homes inhabited by these animals. If this is impossible, having someone who is not allergic wash the pet on a weekly basis can be a significant help.

**Avoid molds and pollens**

Because many of these substances are prevalent only during certain seasons, the best tactic for those unable to exile themselves temporarily to another climate may be to stay indoors as much as possible, preferably in a home, car, or office with air-conditioned or filtered air. At all times of the year, shampoos and skin creams should be checked to make sure they do not contain extracts of cottonseed, flaxseed, or other natural substances that are sometimes allergenic. Those allergic to mold and dust mites in particular may want to invest in a dehumidifier, since humidity above 20 percent encourages the growth of these organisms. Adding a few drops of chlorine bleach to cut flower arrangements and changing the water daily can also help prevent mold. Also, because soil and water can foster the growth of molds, it is a good idea to keep indoor plants to a minimum. If there is a humidifier in the home, it needs to be cleaned regularly to prevent the growth of molds and other allergens.

**Exercise with care**

Even though exercise often triggers asthma attacks, there is no reason people with asthma should have to forgo an activity so important to health and well-being. In fact, regular exercise that develops lung capacity is generally recommended. Just what steps need to be taken to keep exercise safe, however, will vary with the individual.

If exercise itself triggers attacks, it is often sufficient to inhale a bronchodilator before beginning the exercise. If cold or rapid temperature changes trigger attacks, it is best to restrict exercise to places with warm, humidified air (such as swimming pools or gymnasiums). If it is necessary to walk in the cold air, problems can be reduced by wearing a warm scarf or mask around the mouth and nose and breathing through the nose in order to warm, filter, and humidify the air before it reaches the lungs. If pollen plays a role

as well as exercise, it makes sense to exercise indoors during allergy season.

**Be wary of aspirin and other anti-inflammatory drugs**

Because many drugs used to reduce pain seem to promote asthma attacks, anyone with asthma should use these drugs with caution until she is certain they do not pose a problem for her. Aspirin (acetylsalicylic acid), which is sold under a variety of brand names, is a common culprit. Other analgesics that often cause problems are ibuprofen and other non-steroidal anti-inflammatory drugs (NSAIDs).

**Avoid smoke and other pollutants**

Anyone with asthma should cut out cigarettes and steer clear of other people's smoke whether it is secondhand smoke from a cigarette or smoke from a woodstove, burning leaves, or an industrial chimney. It is also advisable to stay inside during pollution or ozone alerts in urban areas and to avoid breathing fumes from fresh paint, turpentine, insecticides, deodorants, chlorine, cleaning fluid, and other irritants.

**Eliminate foods that cause problems**

If the problem is a solitary food such as peanuts, this is relatively easy to avoid. It can be quite an ordeal, however, when the allergy is to eggs, milk, or flour ingredients that are often hidden in processed foods or foods prepared in restaurants. Anyone who reacts to sulfites needs to be particularly careful in restaurants and should routinely check all labels on packaged foods eaten at home. The Food and Drug Administration (FDA) recently banned the use of these agents on fresh fruits and vegetables and made it mandatory for manufacturers to include a notice on labels if detectable amounts of sulfites are present in a food.

**Consider getting a flu shot**

If asthma is triggered by respiratory infections, it is a good idea to have a flu vaccination every year. Other household members might also consider getting shots, to minimize the chances that they will bring an infection home. Also, if at all possible, contact with people who have viral infections (including colds) should be avoided.

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## Expected breakup of 135 cases of TB under RNTCP

New smear-positive: New smear-negative
[ 50 : 50]

New smear-positive (CAT I): Retreatment smear-positive (CAT II)
[50 : 25 (initially)]

New smear-positive: Extra-pulmonary
[50 : 10]

Non-seriously ill smear-negative: Seriously ill smear-negative
[40 : 10]

Non-seriously ill extra-pulmonary: Seriously ill extra-pulmonary
[8 : 2]

| Treatment Category | Smear positive | Smear negative | Extra Pulm. | Total |
|---|---|---|---|---|
| I | 50 Seriously ill | 10 Seriously ill | 2 Seriously ill | 62 |
| II | 25 | Nil | Nil | 25 |
| III | 0 | 40 | 8 | 48 |
| Tota; | 75 | 50 | 10 | 135 |

# Airborne infections Epidemiology & Control

***Farooq Fazilli***

Acute respiratory infections (ARI) range, in spectrum, from mild colds & coughs to life-threatening pneumonias. ARI is the most common cause of morbidity and mortality among young children; of the estimated 15 million deaths in Indian children under 5 years of age, 1/3rd are due to ARI. Among these, 1 million deaths are due to result of measles and diphtheria both vaccine preventable diseases. Hospital-based statistics shows that 13% inpatients pediatric deaths are attributable to pneumonia. ARI is more common in urban than in rural areas. On an average, a child in an urban area gets 5-9 episodes of ARI annually during the first 5 years of life, each episode lasting for a mean duration of 7-9 days. In rural areas, the annual incidence per child is 1-3 episodes. Estimatedly, one in every 30—50 episodes of cough develop into pneumonia and without treatment 10—20% will die. Vaccine preventable diseases like measles, whooping cough & diphtheria together account for 15-25% of all deaths. Without adequate treatment, the child may die within 4-5 days of the onset of illness. Morbidity is equal in both developing and developed countries, but the mortality is 30 times greater in the developing countries.

In 50-60% of children, the causative agents in lower respiratory tract infection (LRTI) are bacterial agents – the common bacteria being *H. influnzae, S. pneumoniae* and *Staphylococci* . All these are sensitive to anti bacterials like Co-trimoxazole, which is a safe, effective and cheap therapy and if started early and provided adequately, can save many lives.

**Deaths from ARI occur because:**

- *Children do not come for treatment at all.*
- *Children come for treatment, but too late.*
- *Children come for treatment but receive inadequate treatment*.

## What is ARI ?

ARI is an acute infection of any part of respiratory tract & related structures including paranasal sinuses, middle ear, and pleural cavity. For qualifying as ARI, the duration of acute illness must be less than 30 days except in the case of acute suppurative otitis media (ASOM) where duration may be less than14 days.

**Classification of ARI**

1. Upper respiratory tract infections (AURI) include: common cold, pharyngitis, laryngitis, tracheitis, epiglotitis and otitis media .
2. Lower respiratory tract infections (ALRI) include: bronchitis, bronchiolitis, and pneumonias.

## Mode of presentation

Children with pneumonia generally present with symptoms of cough or/ and difficult breathing. For practical purposes, the cases are classified as: *no pneumonia, pneumonia, severe pneumonia, and very severe illness*. Acute lower respiratory tract infection (e. g. pneumonia) is a serious life threatening illness with high mortality . This mortality can be reduced by timely diagnosis, adequate and

effective management with relatively cheap and effective antibiotics and good nutrition, health education as well as good hygiene.

## Clinical assessment

**History taking**:
Ask about

- Age,
- If coughing, for how long?
- About feeding; is child able to drink?
- Did the child has antecedent history of measles ?
- History of diarrhea / and or fever,
- Drowsiness and seizers
- Convulsions
- Fast breathing ,chest in-drawing and abnormal sounds like stridor, grunting

**look / listen for:**

- Whether the child is calm,
- How many breaths/m,
- Chest in-drawing,
- Stridor, wheeze,
- Drowsy,
- Febrile, hypothermia,
- Severe malnutrition

**Physical examination**

***Fast breathing*:** Count the respiratory rate for one minute. Expose the chest and abdomen before the counting. Use the second-hand of wrist watch. Count the respiratory rate by looking at abdominal/lower chest wall movements. Count only when the baby is quite and calm or sleeping.

Fast breathing is considered if:

*Respiratory rate is*
*60 or more in a 2 month old child*
*50 or more in 2-12 months child*
*40 or more in 12 -60 months child*

***Chest in-drawing*** means inward movement of lower chest wall /(intercostal & subcostal) while breathing in (inspiratory indrawing). Look for the chest in- drawing when the child is quite/calm or sleeping. Crying may mask chest indrawings.

In children below 2 months of age, presence of any of the following indicates severe disease:

- Fever (38$^{o}$C or more)
- Convulsions
- Abnormal sleepy or difficult to wake
- Stridor in calm child
- Wheezing
- Not feeding
- Tachypnea
- Chest indrawing
- Altered sensorium
- Central cyanosis
- Grunting
- Apnoeic spells or
- Distended abdomen.

Such children should be referred to hospital for admission and treatment with injectable antibiotic like gentamycin, ampicillin or any other feasible antibiotic. Supportive care must be continued.

## Management

*A)* ***No Pneumonia:***

Home care should be given to the children with common cold, cough and fever (ie children with no pneumonia). These children do not require treatment with antibiotics because

- Majority are viral, where antibiotic is not effective.
- May produce side effects with no clinical effects.
- May produce resistance strains.

- Unnecessary financial loss.

Mothers should do the following:

- Continue feeding as before. If the child is unwilling to take food, give small quantities frequently.
- Continue breast-feeding in breast-fed children.
- Give enough fluids orally.
- Give Paracetamol for fever.
- If nose is blocked with nasal secretions, then clean the nose with normal saline drops.
- Do not use medicated nasal drops which may be harmful.
- For cough and cold may give honey, ginger, tulsi etc. but not to the baby below two months of age.
- Mothers should be aware about the danger signs of pneumonia like; *breathlessness, intercostals recession, convulsions and irritability etc.* so that she brings the child immediately for the treatment.

***B) Pneumonia;***

In developing countries, bacterial pneumonia like streptococcal pneumonia and Hemophilus influenzae type b are most common in the age group of 2 months to 5 years, followed by viral pneumonia. The former organisms are sensitive to Co-trimoxazole, which is the drug of choice for the treatment of pneumonia. The efficacy of Cotrimoxazole is similar to ampicillin and procaine penicillin and cure rate is about 95%. At the same time, cotrimoxazole is also less expensive and cost- effective.

The children suffering from pneumonia should be given treatment as in table:

*Severe pneumonia:*

In severe pneumonia, there is chest indrawing in addition to fast breathing. The children in the age group of 2 months to 5 years should be treated as follows:

**Table IV: Dose Frequency and Rate of Administration of Antibiotics in Severe Pneumonia.**

| Antibiotics<br>First 48 hours | ***Dose*** | Interval | Mode |
|---|---|---|---|
| Benzyl Penicillin<br>Or Ampicillin Or<br>Chloramphenicol | 50000 IU/Kg<br>50 mg/Kg<br>25 mg/Kg | 6 hrly<br>6 hrly<br>6hrly | IM<br>IM<br>IM |
| *If condition improves, continue for next 3 days* | | | |
| Procaine penicillin Or<br>***Ampicillin Or***<br>Chloramphenicol | 50000/kg (max 4 lakh)<br>50 mg /kg dose<br>25 mg/kg dose | Once daily<br>6 hourly<br>6 hourly | IM<br>Oral<br>Oral |
| *If there is no improvement over the next 3 days* | | | |
| ➢ Change to chloramphenicol IM, if Ampicillin was started initially | | | |
| ➢ Change to Cloxacillin 25 mg /kg/dose 6hrly IM with Gentamycin 2.5mgm /kg/dose 8hrly IM, if chloramphenicol was started initially | | | |
| ➢ If condition improves, continue chloramphenicol only | | | |
| *Symptomatic treatment for fever and wheeze if required.* | | | |
| *Regulate fluid and food intake.* | | | |
| On discharge advise the mother to continue home treatment. | | | |

Treatment with antibiotics should be continued for at least 5 days. Continue treatment for at least 3 days after the child recovers.

**Table II: Antibiotic Dosage in Pneumonia**

| **Age / weight** | **Co-trimoxazole twice daily orally.** | | | *Amoxicillin thrice Daily orally* | | *Procaine penicillin* |
|---|---|---|---|---|---|---|
| | **†Ad.Tb Syrup**** | **Pd Tb*** | | **Tb. syrup** *250mg* | *5ml* | **IM once daily** |
| <2 months <5Kg | ¼ | 1 | 2.5ml | ¼ | 2.5ml | 200000 IU |
| 2—12 months 6—9 Kg | ½ | 2 | 5ml | ½ | 5ml | 400000 IU |
| 1—5 yrs 10—19 Kg | 1 | 3 | 7.5ml | 1 | 10ml | 800000 IU |

*†Ad.Tb. Sulphamethoxazole 400mg & Trimethoprim 80 mg*
**Pediatric tablet: Sulphamethoxazole 100mg & Trimethoprim 20 mg*
***Pediatric syrup. Each TSF (5ml) Sulphamethoxazole 200mg & Trimethoprim 40 mg*

- Cotrimoxazole should not be given to premature babies and in cases of neonatal jaundice.
- Less than two months child with rapid breathing and drowsiness should be treated as a case of severe disease/pneumonia
- The tablets are crushed and mixed with water. The mixture should be given to the child with a spoon.
- Cotrimoxazole should be given for 48 hours initially followed by the re-assessment of the child.
- If there is improvement, continue same treatment for further 3 days; and
- If there is no improvement or the condition deteriorates, the child should be brought for revaluation and new treatment started as per the type of pneumonia.

If cloxacillin and gentamycin are started, they should be continued at least for 3 weeks.

***Very severe illness*:**

The child is too sick if s/he is not able to drink/feed, is having convulsions, is sleepy, and is having stridor when calm with severe chest indrawing and severe malnutrition. It may be because of meningitis, encephalitis, and severe pneumonia etc. thus there is need of appropriate diagnosis and treatment. If there is difficulty in diagnosis and treatment, the children should be referred to FRU.

The child with very severe illness must be treated in a hospital with facilities of oxygen and intensive care as well as invasive facilities.

| Antibiotics | Dosage | Frequency | | Route |
|---|---|---|---|---|
| | | *Age< 7days* | *7d-2month* | |
| Inj. Benzyl penicillin or | 50000 IU/Kg/dose | 12 hrly | 6 hrly | IV/IM |
| Inj. Ampicillin and | 50mgm/Kg/dose | 12 hrly | 8 hrly | IV/IM |
| Inj. gentamycin | 2.5 mgm/Kg/dose | 12 hrly | 8 hrly | IV/IM |

*If the condition does not improve /or deteriorates after 48 hours*

- Change over from chloramphenicol to IM cloxacillin and gentamycin IM.
- On improvement continue for 3 weeks.

## Treatment of a childless than 2 months

Cough, running nose and fever are not the usual features in young infants with pneumonia. There may be only fast breathing/ indrawing of chest. The pneumonia is always severe in the young infant and the low birth weight baby may die from cold stress/ hypothermia even in hot climate. In such conditions, it is very difficult to differentiate between severe pneumonia, septicemia, and meningitis. But whatever it may be, **treatment is same**.

These children must be hospitalized and treated with injectable benzyl penicillin or injection penicillin and gentamycin. *Here chloramphenicol is not the drug of choice.*

- ►Maintain the body temperature.
- Treat associated complications if any.
- Continue exclusive breast feeding and home care.

### *Wheezing*

Wheezing is referred to high-pitch whistling sounds audible without auscultation by the stethoscope. About 30-50 % of all children suffer from one or more bouts of wheezy chest during the first decade of life, causing considerable anxiety to the parents. Wheezing is due to the obstruction of flow of air in the small air ways, which might be due to inflammation caused by infection as in pneumonia or allergy as in bronchial asthma. Pressure from outside the bronchi may also be responsible in some cases. Thus, all that wheezes is not asthma.

*Causes:*

I. Wheeze associated with lower respiratory tract infection (WLRI).
II. Bronchiolitis
III. Bronchial asthma
IV. Tropical eosinophilia
V. Loeffler's syndrome
VI. Hypersensitivity pneumonitis
VII. Rare causes like inhaled foreign bodies
VIII. Pressure from large mediastinal nodes
IX. Pressure from anomalous left pulmonary artery
X. Cystic fibrosis of the lungs
XI. Pulmonary hemosiderosis
XII. Tuberculous lymph glands
XIII. Mediastinal cysts and tumors

*Presentation*

Wheezing child may present as:

- Wheezing without associated respiratory distress.
- Wheezing with respiratory distress.
- Recurrent wheezing.

***Management***

*I. Management of wheezing without associated respiratory distress.*

- Give oral salbutamol in the following doses:

1. Child less than 10 Kg body weight, give 1 mg 8 hourly orally after food.
2. Child weighing 11-19 Kg, give 2 mg 8 hourly orally after food.
3. Salbutamol is given only for few days.

II. *Management of wheezing associated with respiratory distress and recurrent wheezing.*

Here rapidly acting bronchodilators are required to be given as follows:

| **Rapid-acting bronchodilator** | |
|---|---|
| Nebulized salbutamol (5mg/ml) | In the dose of 0.5ml SBM plus 2.0ml of sterile water may repeat after 20 minutes. |
| Subcutaneous Epinephrine (Adrenaline) 1:1000=0.1% Subcutaneous terbutaline | `In the dose of 0.01ml/kg body weight, may repeat after 20 minutes `0.1 mgm/Kg body wt. may be repeated after 30 minutes upto maximum of 3 times (total 0.3 mgm) |

Wait for 30 minutes after the last dose of administration; if the child responds well, treat at home with oral salbutamol. If there is no improvement, refer the child for hospitalization.

*Children with Recurrent Wheezing (Asthma)*

Give rapid acting bronchodilator as mentioned above.

Asses the child's condition 30 minutes later:

If respiratory distress or any danger sign is present, treat for severe pneumonia or severe disease (refer)

If there is fast breathing but no respiratory distress, treat for pneumonia, give oral SBM

If No respiratory distress and no fast breathing then treat for 'no pneumonia', cough or cold; give oral SBM.

***Dosage of oral salbutamol*** *(*Oral salbutamol three times daily)

| *Age /weight* | *2mg tablet* | *4 mg. tablet* |
|---|---|---|
| 2 months upto 12 months (<10 Kg) | ½ * * * | ¼ * * * |
| 12 months upto 5 years (10-19 kg) | 1 * * * | ½ * * * |

**Advice to mothers**

Mothers play a key role in the management of illnesses in infants and children. Majority of cases of pneumonia are to be treated at home, therefore mothers must be advised on:

- How to give antibiotics to the child in proper dosages.
- Continue adequate feeding including breast –feeding in small quantities and at frequent intervals, as the child may not be willing to take feed.
- Mothers should know and understand the signs whether the child is improving or worsening.
- Danger signs should be explained to the mother so that she immediately recognizes the worsening condition of the child and brings her for treatment; failure to do so may cost the child her life.

Various danger signs are:

- *Difficult and rapid breathing.*
- *Chest indrawings*
- *Refusal of feeds.*
- *Eating and drinking poorly excessive sleeping/ drowsiness.*
- *Convulsions.*
- *Cyanosis.*

*Precautions to be taken by the mother:*

- Keep young infants warm and away from the draught.

- ❖ Exclusive breast feeding upto 6 months
- ❖ Complete immunization on scheduled dates
- ❖ Prophylactic Vit. A
- ❖ Hand-washing before feeding and touching the child especially young infants.
- ❖ Smoke- and dust-free environment.

*Mothers of sick children are themselves of poor health and anemic, so they should be advised about their nutrition and birth spacing. Counsel them to adopt birth spacing in the interest of her and her child's health.*

***Fever***

Fever is defined as an elevation of body temperature in response to any pathological stimulus.

American College of Emergency Physicians has published a clinical policy on febrile illness in children that chooses a rectal temperature of ≥38◦c (100.4◦F) as the most widely used definition of fever.

Fever is a sign that the body is fighting an infection. The main reason to treat the child is to make him or her feel better. When the child is achy and fussy, he/she may need some medicine.

Common cold, pharyngitis, acute otitis media, mastoiditis and pneumonia are the usual acute respiratory illnesses leading to fever in children. These are often viral in etiology. Throat should always be examined to exclude follicular tonsillitis and diphtheria. Other important area to be examined is ear, where acute supparative otitis media is a common cause of fever among children.

***Treatment:***

Fever and infection in children are not synonymous; antimicrobial agents should not be used as antipyretics and empirical trails of medication should thus be avoided.

Fever with temperatures less than 39º C in healthy children usually does not require treatment. However, as the temperatures become higher, patients tend to become more uncomfortable and administration of antipyretics often makes patient feel better. Other than providing symptomatic relief antipyretics do not change the course of the infectious disease. Hyper-pyrexia (>41º C) indicates greater risk of severe infection, hypothalamic disorders, or CNS hemorrhage, and should always be treated with antipyretics.

Aspirin, acetaminophen and ibuprofen are inhibitors of hypothalamic cyclo-oxigenase, thus inhibiting PGE-2 synthesis. These all drugs are equally effective antipyretics. Acetaminophen 10-15 mg/kg orally *every 4 hours* is not associated with significant adverse affects; however prolonged use may be associated with renal injury and massive overdose may be hepatotoxic. Ibuprofen, 5-10 mg /kg orally every 6-8 hours may cause dyspepsia, gastrointestinal bleed, reduced renal blood flow, and rarely aseptic meningitis & aplastic anemia.

***Treat fever***

- if Fever is high (≥39°C), give Paracetamol
- If fever is not high (38-39°C), advise the mother to give more fluids

If fever continues for more than five days, refer the patient to a hospital for further assessment.

*Fever alone is not the reason to give an antibiotic except in a young infant (age < 2 months)*

***Paracetamol dosage***

| Age or weight | 100 mg tablet | 500 mg tablet |
|---|---|---|
| 2 months up to 3 years (6-14 Kg) | 1 | ¼ |
| 3 years up to 5 years (15-19 Kg) | 1 ½ | ½ |

**Other ways to help the child feel better**

- Give the child plenty to drink to prevent dehydration and help the body cool itself.
- Keep the child still and quiet.
- Keep the room temperature at about 70°F to 74°F.
- Dress the child in light cotton pajamas so that body heat can escape.
- If the child is chilled, put on an extra blanket but remove it when the chills stop.

**********

Microorganisms, which as part of their evolution chose to be human pathogens, have adapted themselves to thrive and multiply more efficiently at a temperature of 37C° - ie the human body's normal internal temperature. When they invade the body with the expectation of finding an optimal temperature, the body increases its temperature (fever) so as to deprive them of such cozy atmosphere. Thus fever is the body's defence to microbial invasion.

Body has its own mechanisms of fighting which require boost only when in danger of being overwhelmed. Most of the times our body can ward off the invading microorganisms on its own.

Reducing fever by giving antipyretics for all fevers is simply to over-drugging children. It is only when the temperature exceeds 104°, the patient is in discomfort, or when there is previous history of febrile convulsions, should pharmacologic antipyresis be a part of the drug regimen.

Parents should be advised to offer lukewarm sponging or bathing as a good alternative. Also, the patient should sufficiently be hydrated orally (if needed, intravenously) to provide enough water for perspiration and evaporation.

When advised, antipyretics should be prescribed in full dose and at recommended intervals. The dose of paracetamol is 325 per dose every 4 hourly, with a maximum of 5-6 doses in 24 hours. The dose of ibuprofen is 200mg/400 mg every 6-8 hourly.

Appropriate antibiotic theray is the mainstay of treatment in bacterial infections. In viral infections temperature is symptomatic.(Ed)

# DIABETES IN PREGNANCY

***Rehana Kausar***

Before insulin was discovered, patients of reproductive age group usually died within 1-2 years of onset of illness and pregnancy was very rare. Despite the immediate improvements in maternal survival that occurred when insulin became available, perinatal outcome remained poor. Pregnancy in the diabetic woman was complicated by a high rate of fetal malformations, sudden fetal death in late pregnancy, pre-eclampsia and eclampsia, death from prematurity and fetal injury and death from macrosomia. During the past three decades, a great deal has been learned about the important relationship between maternal glycemic control before and during pregnancy and fetal outcome. The perinatal mortality has simultaneously improved as an improved and an intensive approach to the diabetic pregnancy has become the standard. A true shift in the therapeutic paradigm has occurred. Whereas simple maternal and fetal survival used to be the primary goal in the diabetic pregnancy, today's chief concern is to approximate the clinical outcomes of non-diabetic pregnancy.

An essential concept that has evolved from years of epidemiologic observation is the differential effect of diabetic control during preconception and the early first trimester (which practically encompasses the period of organogenesis) from that during the final two trimesters. Glycemic control in the early phase primarily affects the risk of fetal congenital malformations, whereas maternal gestational outcomes , the risk of fetal macrosomia (and its attendant obstetric complications) and much of the risk of perinatal complications are influenced by the latter phase.

Table 1: White Classification of Diabetes During Pregnancy

| Class | Description |
|---|---|
| A | Abnormal glucose tolerance test (asymptomatic ; normal glucose levels achieved with diet only) |
| B | Adult onset diabetes (age > 20) and short disease duration (<10 yrs) |
| C | Youth onset diabetes ( age 1-19) or relatively long disease duration (10-19 yrs) |
| D | Childhood onset (age <10 ) , very long disease duration (>20yrs) , or evidence of background retinopathy |
| E | Any diabetes with evidence of vascular disease in the pelvis (diagnosed by plain radiograph) |
| F | Any diabetes with the presence of renal disease |
| R | Any diabetes with the presence of retinopathy |
| RF | Any diabetes with the presence of both renal disease and proliferative retinopathy |
| G | Any diabetes with history of multiple failures during pregnancy |
| H | Any diabetes with atherosclerotic heart disease |
| T | Any diabetes post-renal transplantation |

## Classification

The White Classification of Diabetic Pregnancy is given below. Although this classification is widely used, it makes no attempt to take into account the degree of glycemic control during or before pregnancy. Many centres prefer to use a simpler classification which places diabetes primarily in the context of pregnancy (ie as a pre-existing condition) or one that was acquired during gestation (table 2) .Patients with either type I or type II diabetes have *pre-gestational diabetes.* Those women with diabetes diagnosed during pregnancy itself have *gestational diabetes*

Table 2: Alternative Classification of Diabetes in Pregnancy

| |
|---|
| *Overt diabetes* |
| Type I diabetes |
| Complicated by retinopathy |
| Complicated by nephropathy |
| Complicated by coronary heart disease |
| Type II diabetes |
| Complicated by retinopathy |
| Complicated by nephropathy |
| Complicated by coronary artery disease |
| *Gestational diabetes* |
| Diet controlled |
| Insulin requiring |

## Epidemiology

The incidence of diabetes mellitus in pregnancy is less than 0.5%. Many surveys report an incidence of pre-gestational diabetes of 2 per 1000 pregnancies.

## Screening

Despite more than 30 years of research, there is lack of consensus regarding the optimal approach to screening for gestational diabetes. The best time for diabetes screening is between 24 and 28 weeks' gestation because peripheral insulin resistance and insulin response to a glucose load start to increase at that time. While some advocate screening for all expectant mothers, others reserve it for potential candidates. Such patients include those with

- Family history of diabetes
- Marked obesity
- Prior gestational diabetes
- Glucosuria
- History of poor obstetric outcome
- Having a previous birth of a macrosomic baby
- Age over 30
- Presence of polyhydramnios or recurrent vaginal candidiasis in present pregnancy

| **Criteria for diagnosis of gestational diabetes with 100 gm of oral glucose tolerance test** | | |
|---|---|---|
| *Time* | *Whole blood(mg%)* | *Plasma (g%)* `` |
| Fasting | 90 | 105 |
| 1hour | 165 | 190 |
| 2hours | 145 | 165 |
| 3hours | 125 | 145<br><br>*if any two or more values are elevated , the GTT must be considered abnormal* |

| **Criteria for diagnosis of impaired glucose tolerance and diabetes with 75 g (WHO) oral glucose** | | | |
|---|---|---|---|
| *Time* | *Normal* | *Impaired glucose tolerance* | *Diabetes* |
| Fasting | <105 | 105-<140 | >140 |
| 2 hour post glucose | <160 | 160 to<200 | >200 |

Evaluation for diabetes may be done in one or two steps. In the *two step procedure***,** a 50gm oral glucose challenge test is followed by a diagnostic 100g oral glucose test if results exceed a predetermined plasma glucose concentration. Plasma glucose is measured 1 hour after a 50g load without regard to the time of the day or time of last meal. A cut-off value of 140mg is used. In the *one step test*, the diagnostic 100g test is used without the preceding 50g test. .The WHO (1985) recommends the 75g 2-hour oral glucose tolerance test ie *the one step diagnostic procedure* and this approach is often used in Europe**.** *The criteria are the same as those of non-pregnant individuals, with the important modification that impaired glucose tolerance (2-hour plasma glucose>140mg) be treated in pregnancy as diabetes.*

**Pre-gestational diabetes**

In diabetic women with fair to good glycemic control, fertility is well maintained. As a result, pregnancy occurs commonly in women of child bearing age. Generally speaking, the fetal risks associated with both types of diabetes are similar. However, the maternal risks are more closely aligned with the presence of end-organ complications, which tend to be

associated with the established duration of diabetes. For this reason, and because of their absolute lack of endogenous insulin production (which predisposes them to ketosis and more erratic glycemic control), women with type 1 pre-gestational diabetes tend to have more difficult courses.

***Effects on the fetus*:** The abnormal metabolic milieu of the diabetic pregnancy has substantial deleterious effects on the fetus. The diabetic pregnancy is associated with multiple potential complications for the fetus-neonate, which directly or indirectly result from the maternal metabolic derangements:

- *Congenital anomalies (6-8%):* The incidence of congenital malformations is 2-4 times more than the expected frequency. There is a substantial positive correlation between the degree of maternal hyperglycemia present at conception and /or first trimester . Overall the rate of congenital malformations may approach 10% when no specific preconception glycemic goals are attained. The various congenital malformations are listed in table 3. Early intensive diabetes management has been shown to be advantageous for fetal and maternal health and also very cost-effective.

**Early detection of fetal anomalies**
Estimation of glycosylated hemoglobin A (HbA1c) before 14 weeks can predict affection of the fetus. Mothers with Hba1c values <=8.5% have got least chance of severe malformations . Chances increase if value rises to 9.5% or more. Maternal serum alpha protein level at 16 weeks and a detailed USG at 20 weeks are recommended.

- *Early pregnancy loss*: The risk of spontaneous abortions is increased. As in the case of fetal malformations, maternal HbA1 at the end of first trimester is positively correlated with this risk. The exact explanation for the effects of diabetes on fetal complications is unclear but presumably involves several factors e.g hyperosmolarity, ketosis, disruption of glycolysis, DNA glycosylation, inhibition of various growth factors, the generation of free radicals, altered myoinositol metabolism, cell membrane lipid peroxidation and decreased prostaglandin concentration.

Table 3: Congenital abnormalities found more frequently in infants of mothers with pre-gestational diabetes

| | |
|---|---|
| *cardiac*<br>transposition of the great vessels<br>atrial septal defects<br>ventricular septal defects | *gastrointestinal*<br>anal/rectal atresia |
| *spinal /central nervous system*<br>spina bifida<br>anencephaly<br>hydrocephalus | *genitourinary*<br>renal agenesis<br>cystic kidney<br>ureteral duplex |
| *other*<br>caudal regression syndrome<br>situs inversus | |

- *Hyperinsulinemia and macrosomia*: Poor glycemic control spurs fetal growth during the second and third trimesters, as excess nutrients (glucose, aminoacids, free fatty acids) are delivered to the fetus. Excess glucose from the maternal circulation stimulates fetal beta-cells, leading to increased anabolic processes, including the deposition of excess calories as fetal fat. This fetal fat is deposited in the insulin dependent

tissues e.g liver, intra-abdominal, and thigh adipose stores.

- *Birth injuries* are associated with prolonged labour and shoulder dystocia, due to an oversized baby. The injuries include shoulder dystocia, brachial plexus injury (Erb's palsy), fractures of the clavicle and humerus, cerebral injury, and increased requirements for both cesarean and forceps delivery.
- *Late fetal demise*: Stillbirth rate in diabetic pregnancy is reported to be 0-4% with good diabetic control. These fetal deaths are without any identifiable cause such as placental insufficiency, abruption, fetal growth restriction and oligo-hydramnios. These infants are typically large for age and die before labour, usually at 35 weeks or later. It may be due to impaired placental oxygen transfer due to placental vasculopathy, fetal acidosis, and villous hydrops.

*Neonatal complications include:*

Respiratory distress syndrome
Neonatal hypoglycemia
Neonatal hypocalcemia
Polycythemia
Neonatal hyperbilirubinemia
Cardiac hypertrophy

The risk of future type 1 diabetes in the off-spring of mothers with type 1 diabetes is 1.3%; for those having fathers with this type is 6%. There is a greater genetic predisposition in type 2 diabetes, with the risk being approximately 15% with one affected parent and as high as 60% to 75% when both parents are affected.

***Maternal Effects***

In patients with pregestational diabetes, the progressive insulin resistance of pregnancy results in increased insulin requirements, typically 2-3 fold their prepregnancy dose. The increase in insulin requirements is directly related to the maternal weight gain in pregnancy. Diabetic women are also more prone to hypoglycemia and ketosis in pregnancy.

- *Hypertensive disorders*: The incidence of pregnancy-induced hypertension in pre-gestational diabetes is 15% ie two to four fold higher than in normal pregnancies. In more advanced diabetes, the incidence is 30%. Hypertensive disorders are more common when glycemic control is poor.
- *Preterm labour* complicates 10-30% of pre-gestational diabetic pregnancies and this rate also increases with worsening severity of disease, elevated plasma glucose levels and presence of uro-genital infections.
- *Hydramnios* is seen in 16% of all diabetic pregnancies, with comparatively higher rates in pre-gestational diabetes. Increased fetal urinary flow, and altered amniotic fluid osmolarity have been postulated in the patho-physiology.
- *Pyelonephritis* is reported in 4% of diabetic pregnancies.
- *Cesarean section* is two times more common in diabetic mothers than their non-diabetic counterparts, mainly due to increased rates of macrosomia.
- *Vascular changes* such as retinopathy, nephropathy, coronary artery disease, and neuropathy may be worsened during pregnancy.

**Management**

1. *Preconceptional screening*: The theme of diabetic control in pregnancy is to approximate the non-diabetic state; ie to lower blood glucose levels into a range as close to normal as possible. Such care requires the joint efforts of an obstetrician, internist, diabetologist and neonatologist. It is imperative that all women with pre-gestational diabetes attain strict glycemic control as soon as possible upon discovery of pregnancy if such control is not achieved during the preconception phase. This may require a brief hospitalization to assess the effectiveness of therapy. Treatment options for women with diabetes during pregnancy include a variety of insulin combinations. The most common combinations include mixtures of intermediate-insulin, such as NPH or lente with short-acting insulin (Regular insulin).
2. There is frequent change in insulin need in pregnancy and changes in dosage should be made in small increments at a time. Glycemic goals are shown in table 4. Frequent blood sugar estimation should be done. The aim is to maintain blood sugar within normal range without causing troublesome hypoglycemia. Oral hypoglycemics are not used in pregnancy as they can cause fetal teratogenesis. Changes in insulin dosage should be made at no more frequent intervals than every 3 to 4 days, so that trends in glycemia are addressed.
3. For patients receiving two injections daily , two thirds of the dose should be given in the morning before breakfast, with the remainder being given before the evening meal. For patients taking a mixture of intermediate- and short-acting insulin the usual ratio is 2:1 0f N:R (NPH:regular) before breakfast and 1:1 before supper.
4. If the blood glucose level is high and ketones are present, the patient requires more insulin. If ketones are present and blood glucose is normal, the patient requires extra calories, particularly before bedtime.
5. The diet should contain 30-35 kcal/kg, consisting of three meals and a bedtime snack, comprising 50-60% carbohydrates, and less than 30% fat, with adequate amount of dietary fibre.
6. A graded exercise programme should be considered because it improves insulin sensitivity and glucose levels in both pregnant and non-pregnant patients.
7. Antenatal visits should be scheduled every 1-2 weeks during gestation to ensure proper glycemic control throughout pregnancy. This is more important in the last trimester of pregnancy because insulin resistance increases and most of the insulin dosage adjustments are required.
8. HbA1c levels as an index of recent glycemic control should be monitored every 4-6 weeks.
9. Blood pressure and urinary albumin excretion should be monitored closely
10. A retinal evaluation should be done in every trimester in those without known eye disease and every 1 to2 months in those with established retinopathy.
11. Sonogaphic evaluation of the fetus is done to rule out any congenital abnormalities and to detect fetal macrosomia or growth retardation.
12. Fetal well-being is assessed from 32 weeks onwards. This is done by various methods including fetal heart rate testing, non-stress test or contraction stress test and the

biophysical score. These should be done bi-weekly between 26-36 weeks.

13. It is essential to obtain accurate dates in diabetic pregnancies; USG should be performed in first trimester before macrosomia becomes established.
14. Alfa-fetoprotein concentrations should be monitored between 16-21 weeks.
15. **Timing of delivery**: A universal guideline has not been formulated. The possibility of fetal demise in a potentially hostile environment needs to be weighed against the risk of potential premature lung development. But the fact that majority of fetal deaths occur in the last two weeks of pregnancy, the termination of pregnancy should be done after 37 completed weeks. If adequate glycemic control is achieved and the pregnancy has been otherwise uncomplicated, there is little reason to alter the natural course of pregnancy. In these situations a vaginal delivery should be planned. However, many experts still recommend elective induction between 36 to 38 weeks.
16. Women whose pregnancies are complicated by poor glycemic control or who have other high-risk characteristics, should be delivered once fetal lung maturation has been achieved.
17. Early delivery, usually by cesarean, is recommended in the situation of a macrosomic infant. Generally, fetal weight more than 4500g is a strong indication for a cesarean delivery, and should be considered for fetuses weighing 4000 to 4500g.
18. **Methods for normal delivery**: Prior to the day of induction, the usual dose of insulin is administered. No breakfast is given. Induction is done by low rupture of membranes. Oxytocin drip is started, if not contraindicated. An intravenous drip with 5% dextrose is started with 10 units of soluble insulin. An infusion rate of 100-125 ml/hr (1-1.25 units/hr) will maintain a glucose level of 100mg/dl. Blood glucose levels are measured hourly using dextrostix and insulin dosage is adjusted accordingly. If the labour fails to start within 6-8 hours or progress of labor is unsatisfactory, cesarean section should be performed.
19. **Procedure for cesarean**: Cesarean is scheduled for morning. On the day of operation, breakfast and insulin-dose are omitted. A 5% dextrose drip is started. The maintenance of dextrose and insulin dosage are the same as mentioned above. The insulin requirement falls suddenly after delivery and after the omission of the drip, pre-pregnant dose of insulin is given. Epidural or spinal anaesthesia is administered.

Table 4. Glycemic goals for intensive management of diabetes during pregnancy

| *Criteria* | *Goals (mg/dl)* | |
|---|---|---|
| | Preconception and first trimester | 2nd and 3rd trimester |
| Preprandial glucose | 70-110 | 60-90 |
| Postprandial glucose at 2 hrs | <140 | <120 |

## GESTATIONAL DIABETES MELLITUS (GDM)

Diabetes diagnosed during pregnancy is called gestational diabetes mellitus. This category includes both diabetes that first appears during pregnancy and that which is first recognized during pregnancy. GDM is 10

times more common than pre-gestational diabetes. Its diagnosis is made routinely by oral GTT as described above. Specific risk categories have been described as above. Treatment consists of diet and exercise; a few patients will require insulin. GDM is associated with significant risks to both mother and fetus, although most series have shown no increase in congenital malformations. There is no increase in rates of early fetal demise and risk of congenital malformations; presumably because hyperglycemia has not become established till late second trimester - well after the period of organogenesis. The woman with GDM is at risk of recurrence in later pregnancies and for type 2 diabetes in later life. Many believe that GDM is and type 2 diabetes mellitus are nothing more than variations of the same general disease process or an unmasking of type 2 diabetes in pregnancy. Recurrence rates between 20-50 % have been reported in future pregnancies.

***Complications of GDM:***

1. Fetal macrosomia
2. Traumatic delivery
3. Neonatal complications related to hyperglycemia (hypoglycemia, hypocalcemia, hypomagnesemia, polycythemia, hyperbilirubinemia) increased perinatal mortality

***Pathogenesis***: Like type 2 diabetes, GDM is marked by a variable combination of decreased insulin production and decreased insulin action due to peripheral insulin resistance.

**Management:**

- Treatment goals are similar to patients with type 2 diabetes. Oral hypoglycemics are contraindicated. About 20% patients will require insulin. During 2nd and 3d trimesters maintain preprandial blood sugar <90 mg/dl and postprandial levels below120 mg/dl.
- Initially a diet consisting of 30-32 kcal/kg per day is recommended for the non-obese woman with GDM. In an obese woman further restriction, as low as 25kcal/kg per day, is warranted.
- Diet should contain 50-60% carbohydrate, and less than 30% fat and adequate fiber (25gm/1000kcal).
- Daily caloric intake should be divided equally between three meals and one or two snacks. A bedtime snack is important to prevent fasting ketosis.
- Insulin therapy is needed for women who are not able to maintain their plasma glucose at or below 105mg/dl or their 2 hr postprandial glucose at or below 120mg/dl.
- Others recommend the use of insulin using the 1-hr postprandial glucose reading of less than 140mg/dl as threshold.

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Studies across 25 countries have shown that involvement in *bullying* (as a bully or a victim) is associated with negative social adjustment in later life. This manifests as poorer relationships with classmates, with bullies resorting to alcohol abuse and weapon carrying.

# Food & Cancer Prevention

***Shabnam Bashir***

Cancer is a multi-factorial, multi-faceted and multi-mechanistic disease requiring a multi-dimensional approach for its treatment, control and prevention. Cancer involves fundamental biological processes concerning disorganized cell replication, cell death and disorganization of organ structure. For India, the annual estimate of cancer for the year 2001 was 9.8 lakh, while the annual mortality in 2000 was 7 lakh. The incidence of cancer is on the rise, with multiple risk factors that involve an interplay between genetic and environmental components. Diet is a major environmental risk factor. The contribution of diet and nutrition status to cancer risk and conversely to the prevention and treatment of cancer has been a major focus of research as well as public health policy.

Several epidemiological studies highlighted the role of vegetables and fruits in reducing the risk of cancer in a variety of organs and tissues. Nutrients which show modulatory effects in experimental cancers include macronutrients such as fat, carbohydrates, proteins, fibre and micronutrients such as vitamins - folic acid, riboflavin, β-carotene, retinol, α-tocopherol, vitamin $B_{12}$ and minerals such as selenium, zinc, magnesium and calcium. Recently, however, the focus and emphasis has shifted to a number of non-nutritional components in our diet which possess anticarcinogenic and antimutagenic properties. These are also known as bioactive compounds or chemopreventers. Chemoprevention is considered as a strategy to block or reverse carcinogenesis from the very early stages. It has been suggested that chemoprevention should be considered as an inexpensive, cost effective and easily applicable approach to cancer control.

**Table I. Food sources of phytochemicals**.

In 1981 Doll and Peto attempted the first relative quantification of the environmental contributions of a variety of factors such as diets, alcohol, tobacco, occupation and radiation. Diet is not only a source of antimutagens/ anticarcinogens but also a source of mutagens. The carcinogens in the diet may be exogenous in origin or formed as a result of the interaction of components of foods endogenously eg heterocyclic amines.

Doll and Peto also estimated the contribution of diet, and identified some specific agents to have preventive influences on cancer. Throughout the 1930s and 1940s, the modifying effects of diet on cancer induced in animals by chemicals were very well demonstrated. Many hypotheses proposed centered on nutritional deficiencies, which were believed to be provoked by carcinogenic compounds.

**CHEMOPREVENTERS** (Phytochemicals)

Cereals, vegetables, fruits, pulses, spices and other plant foods contain many micro- constituents other than vitamins and minerals that are known to be biologically active (Table I). The chemopreventers belong to over 25 classes of chemicals. They are safe and have low or no toxicity.

**Nutritive Chemo-preventers**

A number of micronutrients in diet have cancer preventive properties. These include vitamins A, C and E, β-carotene, selenium and calcium. Most of these

| ***Phytochemicals*** | ***Food source*** |
|---|---|
| Fiber (macronutrients) | Cereals (grains) fruits and vegetables |
| Caroterioids | Yellow/orange vegetables. fruits and dark-green leafy vegetables |
| Allium compounds | Qnion, garlic, chives, leeks |
| Dithiolthiones/ glucosinolates | Cruciferous vegetables |
| Isothiocyanates | Cruciferous vegetables |
| Terpenoids | Oil of citrus fruit peel |
| Phytoestrogens | Cereals, pulses. sorghum. millets, soyabeans, fruits and berries |
| Protease inhibitors | Cereals. barley, wheat. oats. rye, soyabeans, kidneybeans and chick peas |
| Phytic acid | Cereals, nuts, seeds, seasame seeds, lima beans, peanuts, and soyabeans |
| Flavonoids | Fruits and vegetables |
| Phenolic compounds | Fruits, vegetables and tea |
| Plant sterols | Vegetables |
| Saponins | Soyabeans, yam and colacasia |

agents are antioxidants. Epidemiological studies have shown that the incidence of certain forms of cancer is highest in people with a low dietary intake of the above nutrients.

**Non-nutritive chemo-preventers**

There are many non-nutrients in diet with plausible cancer preventive effects. During the past few years, research on the relationship between diet and cancer has shown that cereals, vegetables, fruits, and certain beverages contain a variety of potential cancer preventing substances.

**Sources of Non-nutritive Chemo-preventers**

***Cereals***

Cereals like wheat, rice, maize, millet, sorghum are principle constituents of food. They provide protein, vitamins, trace elements and varying amounts of non-starch polysaccharide (NSP)/dietary fibre. Although dietary fibre is not a supplier of calories or essential nutrients, it is important for intestinal functioning. The dietary fibre lowers the intestinal pH, binds to bile acid and shortens the intestinal transit time. Bile acids are believed to be one of the factors involved in colon carcinogenesis by regulating gene expression II. The prevalence of colon cancer in India is much lower as compared to Western population, probably because of higher unprocessed cereal intake with more fibre.

***Vegetables***

Green leafy vegetables, beans of all varieties, cruciferous vegetables namely cabbage, brussels sprouts, cauliflower and broccoli are rich in anti-carcinogens. Umbelliferae vegetables like carrots, celery, parsnips, alliums namely onions, garlic and chives, solanaceaous vegetables like potato, tomato and brinjal have significant levels of cancer protecting non-nutrients .

***Fruits***

All the citrus fruits, grapes, apples, strawberries, plums, pineapple, melons have high levels of protective phyto-chemicals. All the other fruits and dried fruits also possess some amounts of anticancer agents.

***Spice***

Spices and condiments which are a part of the Indian diet have chemical constituents which have antioxidant, anti-mutagenic and anti-carcinogenic properties. Some of them have many other beneficial effects like hypo-cholesterolaemic, hypoglycaemic, anti-inflammatory and antimicrobial properties. Turmeric, cloves, ginger, thyme, mustard and cinnamon have been reported to have antioxidant and anti-mutagenic properties.

**********

**Table II. Nonnutrient chemopreventers - Mechanism of action**

| ***Category*** | ***Mechanism*** |
|---|---|
| Inhibitors of carcinogen formation Caffeic acid, ferulic acid | Inhibit formation of carcinogen eg nitrosamines formation |
| Blocking agents Isothiocyanates, diallylsulphide, ellagic acid, ferulic acid, dithiocarbamates | Inhibit the activity of enzymes (cytochrom P 450) which convert procarcinogens to carcinogens |
| Inducing agents Isothiocyanates. sulpharaphane d-limonene, terpenoids, curcumin | Stimulate enzymatic system which are involved in detoxification of carcinogens |
| Trapping agents Ellagic acid. N-acetylcysteine | Physically react with carcinogens and detoxify them |
| Suppressing agents/ selenium, soya products Isotlavones, phytoestrogens, epigallocatechin gallate (EGCG) | Suppress different steps in metabolic pathways required for tumour development |

**Mechanisms of Action of Chemo-preventers**

The mechanism of action of chemo-preventers is complex. It appears that most chemopreventers act primarily as antioxidants, anti-mutagens, immuno-modulators and anticarcinogens" (Table II).

Broadly, the chemo-preventers may act through detoxification mechanism or by antimutagenic processes at both the initiation and promotion steps of carcinogenesis.

***Detoxificants***

These phyto-chemicals induce drug metabolizing enzymes in the body and act by detoxifying the harmful substances capable of producing harmful effects. The anti-neoplastic effects of inducing and inhibiting agents in foods focus on specific mono-oxygenases like the aryl hydrocarbon hydroxylase (AHH), uridine diphosphate - glucuronyl transferase (UDPGT), and glutathione S-transferases I.

***Antimutagens***

Carcinogens bind to the cell macromolecules namely, DNA, RNA and proteins, and result in mutagenic events leading to cell transformation and neoplastic changes. Some phytochemicals prevent these changes from occurring either by directly binding to the carcinogens/ their metabolites or by metabolizing toxic xenobiotics. These are known as antimutagens/ anticarcinogens.

At the National Institute of Nutrition (NIN), Hyderabad, extensive research has been carried out on some of the non-nutritive chemo-preventers such as garlic, onion, turmeric, green leafy vegetables (spinach, amaranth) and cabbage. Some results of the NIN studies are highlighted here.

**Turmeric as Anticancer Agent**

Among the spices, turmeric is the most extensively used for its colour, taste and flavour. It is also added to foods as a preservative. In traditional medicine, turmeric has been used as a potent anti-inflammatory agent, carminative and antiseptic agent. Curcumin, the active principle in turmeric, has strong antioxidant and anti-inflammatory potency. The NIN studies on turmeric consisted of its in vivo and in vitro evaluation as a potential chemo-preventive agent. Its potent anti-mutagenic effects were demonstrated against well known carcinogens. In order to understand the underlying mechanisms. experiments were conducted to study the levels of tissue xenobiotic metabolising enzymes in animals fed turmeric through diet. The results suggested that there was stimulation of detoxifying enzymes glutathione-S-transferases (GSTs) and UDP glucuronyl transferases (UDPGT). Although drug metabolising enzymes are important in the carcinogen activation/deactivation pathway, the propensity of DNA to bind itself to the toxic metabolites of carcinogens is equally important. Turmeric/curcumin feeding to rats for 4 weeks prior to carcinogen exposure decreased the binding of liver DNA to the carcinogen benzo(a)pyrene.

As oral cancers occur commonly in India, the effects of curcumin and turmeric were assessed in experimental tumourigenesis. Cheek pouches of certain animals were painted with the carcinogen, dimethyl-benanthracene (DMBA) with or without turmeric/ curcumin for induction or retardation of tumours along with feeding turmeric/ curcumin through diet. At the end of 14 weeks, it was found that the animals .given turmeric/ curcumin through diet or painted with curcumin had a lower percentage of microscopic tumours as

compared to controls which did not receive turmeric through diet. In animals which received curcumin, most of the tumours did not go beyond grade I. The binding of tissue DNA to carcinogen was found to be significantly reduced in the experimental groups given turmeric/curcumin either through diet or locally painted. These findings suggest that *turmeric/curcumin may act as anti-proliferators and anti-promoters.*

### *Turmeric anti-initiator or anti-promoter*

To know exactly at what stage turmeric acts, tumours were induced by benzo(a)pyrine in mice which were simultaneously fed turmeric/curcumin during the various stages of carcinogenesis. While turmeric and curcumin treatment during initiation inhibited papillomas by 67 and 50% respectively, the inhibition was 50 to 100% post-initiation. *While turmeric can act in the both phases (initiation & postinitiation),* curcumin can act only in post-initiation process..

### *Curcumin on DNA repair*

DNA repair is one of the important mechanisms of protecting the system from the onslaught of genotoxic agents. Therefore, the effect of curcumin was studied on the single strand breaks (ssb) in the DNA of yeast, Saccharomyces cerevisiae, exposed to UV radiation, 8-methoxypsoralen and benzo(a)pyrene. The single strand breaks in DNA were found to be reduced in yeast cells in the presence of curcumin.

Studies to assess the repair capacity of curcumin against DNA damage induced by carcinogens in lymphocytes of smoking and non-smoking men and in women, showed that it was effectively counteracted suggesting *that in addition to anti-initiating, detoxifying and antioxidant activities, curcumin also has the ability to repair DNA.*

### *Turmeric as antimutagen in humans*

Anti-mutagenicity effect of turmeric was evaluated in human smokers who are known to excrete mutagens. The excretion of urinary mutagens was reduced at the end of 15 days of turmeric ingestion (1.5 g/day orally for 30 days). The liver and kidney function tests were not altered. A clinical trial in reverse-smokers who are at a high risk of palatal cancers in a specific areas of Andhra Pradesh showed that turmeric administration (Ig/day for 9 months) had a significant impact on the regression of precancerous lesions such as red and white patches over the palatal regions, and decreased the micronuclei and DNA adducts in oral epithelial cells which are markers for genomic damage.

### *Turmeric /curcumin as antioxidant*

Turmeric and curcumin have been shown to be antioxidants. Studies in the animal model where oxidant damage was induced by paracetamol and DMBA showed that the levels of TBARS and SGOT and SGPT were reduced in liver of carcinogen-treated rats, demonstrating its antioxidant property.

### *Effect of cooking oil on turmeric/curcumin*

As turmeric in the Indian culinary practices is usually boiled or fried, it was considered essential to assess its anti-mutagenic properties after heating or frying. A short term assay was used to measure the genotoxic response to a commonly present food mutagen, 4-nitroquinoline oxide in E.coli, PQ37. In

the presence of boiled or fried curcumin, this response was decreased indicating that *cooking conditions are unlikely to destroy the antimutagenic property of turmeric.*

**Turmeric as a functional food**

In view of its wide spectrum of action, turmeric is an ideal functional food for prevention of cancer. Toxicological studies on turmeric have indicated that curcumin taken orally in doses of 40-1800 mg/day for 1 to 3 months does not produce toxic effects. From mutagenicity and other studies, the protective consumption levels can be extrapolated for humans. A daily intake of 0.5 to 1.0 g can be consumed without any adverse effect.

## Alliums

Among the vegetables, those belonging to the allium family have received increased attention in recent times. Onion and garlic are commonly consumed through the diet. They contain sulphur compounds like diallyl-sulphide and diallyl-disulphide. Wistar rats fed garlic- (0.1,0.5, 1 %) or onion- (1 and 5%) containing diet for one month when exposed to either B(a)P or 3MC showed reduction in the excretion of urinary mutagens,

**Effect on drug metabolising enzymes**

Stimulation of activity of liver cytosolic glutathione S-transferase enzyme was seen on garlic feeding. The activity of the antioxidant enzyme quinone reductase in the liver and lung microsomes was elevated in animals fed garlic containing diets. In onion fed rats there was stimulation in the GST and GSTMu activity in the stomach and liver tissues.

The reduction in the excretion of carcinogen derived mutagens in garlic/onion fed rats suggested that endogenously present mutagens could be countered by protective substances. Enhancement in the levels of tissue detoxification enzymes could be another important mechanism through which these dietary agents could confer their protective effects. Garlic at 0.1 and 0.5% and onion 1 and 5% were fed through diet in these experiments. These quantities of alliums can be easily consumed through diet.

## Mustard

Mustard is a spice used for flavouring and as a source of edible oil in India. The leaves of this plant are consumed as vegetable. Mustard belongs to cruciferous family, other members of which are cabbage, broccoli, cauliflower, etc. The active principle of mustard is dithiolthione. NIN studies have shown that mustard has antimutagenic property. In rats fed 10% mustard powder-containing diet, significant reduction in the activity of carcinogen activation enzyme, aryl hydrocarbon hydroxylase and stimulation in the activities of carcinogen-detoxification enzymes namely UDPGT and glutathione-S-transferases were observed.

## Vegetables

**Induction of Protective Enzymes by Vegetables**

Induction of hepatic microsomal and cytosolic xenobiotic metabolising enzymes by commonly consumed vegetables such as spinach, amaranth, **gogll,** cabbage etc was studied in rats fed at 20% level. Stimulation of the microsomal aryl hydrocarbon hydroxylase was observed only in animals fed **gogu,** while the activities of UDP glucuronyl transferase and glutathione-S-transferase were significantly elevated in the groups fed cabbage. Benzopyrene binding to hepatic DNA

in vivo, a measure of carcinogen activation, tended to decrease in the groups fed **gogll,** onion and mustard.

**Other Evidences for Non-nutrients as Chemopreventers**

***a) Experimental***

Phenolic compounds in grains, fruits and vegetables, lignans, and flavonoids have shown chemopreventive effects in experimental animals. These have been shown to exert antimutagenic activity. Turmeric and curcumin have been shown to inhibit tumours in skin, breast, oral cavity and forestomach in initiation and promotion models in many species including mice, rats and hamsters.

Diallyl-sulphide (DAS), an active component present in garlic, has been shown to inhibit DNA carcinogen adduct formation in rat tissue. It was found to reduce forestomach tumour frequency in hamster buccal pouch and rat oesophagus. Garlic oil has been shown to inhibit promotion of chemically-induced skin cancers.

Isothiocyanates, present in cruciferrous vegetables, have been shown to block tumours induced by chemical carcinogens. Tumours of the mammary gland, digestive system, and nitrosamine-induced lung tumours have been shown to occur at reduced frequency in laboratory animals fed thiocyanates prior to carcinogen exposure.

Short term tests and experiments on animals are used to establish the anti-genotoxic potential of phyto-chemicals and unequivocal evidence is available to demonstrate the anticancer property of these agents. However epidemiological studies need to be conducted to establish the diet-cancer relationship in humans.

***b) Epidemiological***

Epidemiological studies indicate that fruits and vegetables have health-promoting factors particularly against cardiovascular diseases and cancer. Possible plant nutrients providing this protection include micronutrient and non-nutrient components of the diet. According to National Nutrition Monitoring Bureau (NNMB) surveys in 10 states of India, there is poor consumption of green leafy vegetables and poor intake of micronutrients.

Oral cancer is one of the ten most common cancers in the world and in India accounts for a third of all cancers. A case control study was conducted by the NIN to examine the role of diet in oral and oropharyngeal cancers. Dietary intakes and nutrient estimates were obtained through diet history collected by oral questionnaire. The results suggested poor dietary intake of vegetables and fruits coupled with low estimated intake of micronutrients.

Cancer of the colon and rectum is the fourth most common cancer and cause of death from cancer, throughout the world. Cross-sectional comparisons, case control studies and trends in food intake show high rates of colorectal cancer in populations consuming diets high in meat and fat and low in fibre and vegetables. In prospective cohort studies, an association between consumption of vegetables and fruits with reduced risk of lung, oesophagus, stomach and pancreatic cancer was observed .

An epidemiological study was conducted in Jiangsu province, China, where gastric cancer is low and in Yangzhong which is a high risk area for gastric cancer using a questionnaire and adjusting for ecological and life-style factors and age and sex. The

study reports that allium vegetables were consumed in .the low risk area more frequently, with high consumption of raw vegetables, fruits, tomatoes, kidney beans and soyabean products. The results suggest that frequent consumption of allium vegetables, in addition to other anticancer foods may be a factor for low mortality due to gastric cancer in the low risk area.

From several reports it emerges that, assessment of individual nutrient intake, as opposed to fruit and vegetable consumption, does not increase the protective association of these components. However, changes in the diet that would increase consumption of fruits and vegetables would be beneficial as such a diet is unequivocally associated with cancer protection. Based on available information, it seems prudent to advocate a diet rich in fruits and vegetables, rather than consumption of a specific nutrient or non-nutrient in order to decrease the risk of developing cancer of organs such as colon, stomach, oesophageal, breast and prostrate.

An interventional trial supplementing micronutrients such as vitamin A, riboflavin, zinc and selenium to a group of reverse smokers indicated that the cocktail of nutrients given as a prescriptive approach could result in regression of pre-neoplastic lesions in the oral cavity. The nutrients also prevented the deterioration of lesions and the appearance of new lesions in the non lesion group. Similarly in tobacco-chewers administration of beta-carotene and vitamin A lead to disappearance of leukoplakia. Biomarkers such as DNA adducts and micronuclei were significantly reduced in the treated groups. In another intervention study on tobacco-chewers in Kerala, administration of spirulina for a year resulted in complete regression of leukoplakia in 45%. Similar observations on chemoprevention have been noted in China where a high prevalence of oesophageal and stomach cancers exists. Intervention trials using antioxidants in various doses and combinations have yielded inconsistent results for protection against lung cancer in smokers, invasive cervical cancer, oesophageal and gastric cancers and colorectal polyps.

Dietary Modification Studies Women's Health Initiative (WHI) 10 year trial was started in 1993 to assess the effect of diet low in fat and high in fruits, vegetables and fibre on cancer incidence among more than 50,000 post menopau'sal women. Women's Intervention Nutrition Study (WINS) is a 5 year clinical trial designed to test whether dietary fat reduction will reduce breast cancer recurrence and increase survival among 2000 women breast cancer patients. Can dietary intervention with increased fruit and vegetable consumption provide the key answer? A recent study has demonstrated that a group of healthy individuals who consumed increased quantities of fruits and vegetables for 2 weeks had elevated plasma levels of antioxidant nutrients as compared to basal values; the levels of a tocopherol and retinol did not show elevation.

In another recent study, a group of subjects on normal diet, except vegetables high in carotenoids for 2 weeks, were supplemented with tomato juice (weeks 3 and 4), carrot juice (weeks 5 and 6) or spinach (weeks 7 and 8). The supplementation resulted in a significant decrease in the endogenous levels of strand breaks in lymphocytes DNA as measured by comet assay; oxidative damage was significantly reduced by carrot juice.

High intake of cruciferous vegetables associated with reduced risk for colorectal cancer have been shown to induce GST in human plasma and lymphocytes following consumption of brussel,s sprouts. This stimulation has been shown in plasma GST-α and rectal GST-α and GST–α in humans after one week of consuming brussels sprouts. This is supported by another intervention study in fried meat consumers in whom a two-fold reduction. in urinary mutagenicity was observed.

In a dietary-intervention study, a group of subjects with non-melanoma skin cancer was placed on low fat diets for 2 years. The incidence of both premalignant lesions (actinic keratoses) as well as skin cancer per se was reduced significanty. An intervention study is currently underway to investigate the effect of wheat bran fibre. However, in studies of this kind a double blind regimen is not possible where the intervention comprises a diet high in fibre and low in fat. Cancer as an unambiguous end point needs prolonged duration of study.

## Conclusions

Prescriptive and proscriptive approaches for cancer prevention in relation to diet are important to reduce the incidence of cancer particularly that of the aero-digestive system and cervical cancer in India. The current focus is on cost-effective health care strategies of which dietary change is one. Beside the nutrients, the non-nutrient components of diet are gaining importance in studies pertaining to diet-cancer relationship. Plant foods including vegetables, fruits and spices possess phyto-chemicals which have antioxidant activity. Spices such as turmeric, onion and garlic were shown to be potent antimutagens in in vitro and in vivo conditions. These were also shown to induce the drug metabolizing enzymes involved in detoxification of harmful substances in the tissues. Studies on turmeric have established. its anti-carcinogenic potential in animals. In humans, turmeric and curcumin reduced urinary mutagens excretion by smokers, and the precancerous lesions in reverse smokers.

Evidence from epidemiological studies indicates that diets high in fruits and vegetables with phytonutrients and low in certain types of fat, along with moderate caloric intake and fibre-rich food are associated with reduced cancer risk. Results from clinical trials with nutrients/ nonnutrients as supplements have not given conclusive evidence for protective effects against cancer. It is important to realize that a supplement of any nutrient or nutrients against the backdrop of a poor diet can hardly be expected to produce the desired outcome. A more appropriate approach should be a food based one, rather than nutrient-based. Beside the protective effects of nutrients and non-nutrients their synergistic effect is also an important point to be considered. Therefore, dietary preventive measures or promotion of healthy dietary habits and life styles, though demanding, are perhaps the right answer for cancer prevention.

(Condensed from ICMR Bulletin)

# Brucellosis

***Henk L. Smits & Manzoor Kadri***

*Brucellosis is a severe zoonotic disease that leads to considerable morbidity and loss of man-days across the globe and thus perpetuates poverty. Brucellosis presents as an acute or persistent febrile illness with a diversity of clinical manifestations. Untreated patients may develop severe complications and suffer from prolonged disability. Early diagnosis and prompt treatment with a full course of appropriate antibiotics is essential to prevent relapse. For early diagnosis, alertness of the physician with awareness of many non-specific presentations is essential. Brucellosis cannot be diagnosed with certainty without laboratory testing. The Rose Bengal test may be used as a simple and rapid screening test but should be confirmed with the serum agglutination test or ELISA.*

**Introduction.** Brucellosis is endemic in all states of India and is a significant and increasing veterinarian and public health problem.[1] As it is a particularly severe disease that often is overlooked or misdiagnosed, it requires close attention by the practitioner.[2,3]

Brucellosis is a bacterial disease caused by gram-negative coccobacillae, of which *Brucella abortus, B. melitensis* and *B. suis* are pathogenic for man. Of main concern in India are *B. melitensis* and *B. abortus. B. melitensis* is transmitted mainly by goats and sheep, and is the most virulent strain for man; it causes severe and prolonged disease with a high risk of disability. *B. abortus* is the dominant species in cattle and is widespread in India. Although the evolution of disease caused by *B. abortus* often follows a milder pattern, serious complications may occur as well.

**Epidemiology.** Brucellosis is an important disease of farmers, veterinarians and butchers. They may contract the disease when working with infected animals and animal products. Brucellosis is also transmitted through the ingestion of unpasteurized raw milk and dairy products. Dairy products prepared from unpasteurized milk such as soft cheeses, yoghurts and ice-creams, may contain high concentration of the bacteria and consumption of these is an important cause of brucellosis.[4] Brucellosis is common in rural areas because farmers live in close contact with their animals and often consume fresh unpasteurized dairy. However, the vending of dairy products may also bring the disease to urban areas.

**Clinical aspects.** Human brucellosis usually manifests as an acute or sub-acute febrile illness, which may persist and progress to a chronically incapacitating disease with severe complications. The intermittent or remittent fever may be accompanied by malaise, anorexia and prostration. Complaints may persist for weeks or months in the absence of specific treatment. Typically, no or few objective signs are apparent that specifically point to brucellosis. Thus, to the unaware physician, the diagnosis of brucellosis can be problematic.

Brucellosis is acute in about half the cases, with an incubation period of two to three weeks. In the other half, the onset is insidious, developing over a period of weeks to months. Fever, chills, sweats, aches, lack of energy, joint and back pain, headache and loss of appetite are

observed in majority of the patients.[5] Arthritis, constipation, abdominal pain and sleep disturbance are seen in about half of them. Cough, testicular pain (from epididymo-orchitis), rash, ill-appearance, pallor, vaginal bleeding, hepatomegaly, splenomegaly, lymphadenopathy are somewhat less common. Other symptoms such as diarrhoea, jaundice, central nervous system abnormalities, cardiac murmurs and pneumonia are rare. Although symptoms and signs often occur in various combinations, one study reported fever as the only sign in 44% of patients with a positive blood culture for *B. melitensis* and fever with arthritis in another 42%.[6] Arthritis may affect all major joints including hip, back, knee, sacroiliac and knee. Sometimes more than one joint is affected.

To a doctor with no suspicion, brucellosis is a typical example of a difficult-to-diagnose disease. It may present as a very mild, self-limiting affliction to a chronic incapacitating disease. The patient may present as mild fever or debilitating psychosis. It is very difficult for a doctor to diagnose it in a non-endemic area; s/he needs a high degree of suspicion. In endemic areas, it is relatively easier to diagnose. In the hyperendemic areas, as Mediterranean region & the Gulf, practitioners take every case of prolonged fever as brucellosis unless proved otherwise. (Ed)

Acute brucellosis may progress to a more persistent disease. Persistent infections often are localised to one specific organ or site. Osteoarticular, gastrointestinal, hepatobiliary, respiratory, genitourinary complications are observed. Bone and joint complications are the most frequent complications. These include sacroiliitis, spondylitis, peripheral arthritis, osteomyelitis and bursitis. Complaints of back pain with radiation down to the legs and refusal of children to walk or carry loads are indicative. The liver is commonly involved in brucellosis even though liver function tests are normal or only slightly elevated. Orchitis and epididymitis are the most frequent genitourinary complications in men and may be confused with testicular cancer or tuberculosis. Infection during pregnancy carries the risk of abortion or intrauterine transmission to the infant. Meningitis and meningo-encephalitis are the most common complications seen in neurobrucellosis. The central nervous system is affected in about 5% of the cases of *B. melitensis* infection and often occurs at a late stage as the main presenting manifestation. It should be noted that brucellosis may affect essentially any organ at any site and that the list of rare and unusual complications is much longer than those mentioned here. Complications of the cardiovascular system are rare but important as they have a high degree of mortality. Other examples of rare complications are those of skin and eyes.

**Laboratory diagnosis**. Culture from the blood of a patient provides definite proof of brucellosis but is too slow to provide a quick diagnosis.[7] For this reason, one often resorts to serological testing.[8] The classical Rose Bengal test is often used as a rapid screening test. This test is performed by mixing on a glass plate a drop of reagent with an equal volume of serum and agglutination is read after 2 or 4 minutes. The sensitivity of Rose Bengal is very high (>99%) but the specificity is disappointingly low. Therefore, a positive test result should be confirmed with a more specific test such as the serum agglutination test (SAT) also known as Wright's SAT is performed by mixing serial dilutions of serum, usually 1:20 through 1:2,560, with *Brucella* antigen in test tubes or in ELISA plates. After overnight incubation, agglutination is read either by the unaided

eye or under a binocular. As a guide, agglutination at titres of 1:160 or above is considered of diagnostic value as long as the patient has signs and symptoms of disease. In endemic areas the diagnostic threshold value will have to be set at least one titre step higher (1:320) to provide a sufficiently high specificity as many asymptomatic individuals will have titres equal to the lower threshold level of 1:160. Under endemic conditions titres of 1:320 and above in general provide conclusive evidence for brucellosis. Lower titres are inconclusive and land the clinician in a diagnostic dilemma. The use of the higher threshold level thus restricts the sensitivity and clinical importance of the test.

Sometimes SAT is performed in the presence of reducing agent, which destroys the agglutinating activity of immunoglobulin M (IgM) leaving IgG intact. This 2-ME (2-mercaptoethanol) test is used to increase the specificity of the reaction by looking at IgG only, which is important in patients with a more persistent infection.

In brucellosis, specific IgM antibodies dominate during the acute phase of the disease. Specific IgG antibodies are present in the serum of patients at a more persistent phase and in the serum of relapsing patients. ELISA is used to discriminate between the presence of specific IgM and IgG antibodies and to roughly assess the stage of illness. SAT and the 2-ME test also may be used for this purpose but are less accurate.

**Treatment.** Uncomplicated acute brucellosis almost invariably responds well to appropriate antibiotic treatment.[11,12] In those patients with complications, additional treatment, including in some cases surgical intervention will be necessary. To prevent disease progression and the development of complications, treatment should start as early as possible also in patients showing signs of spontaneous improvement. In all cases it is important that the patient finishes the full course of medication because the risk of incomplete recovery and relapse is otherwise considerably increased.[13] The standard treatment of uncomplicated cases in adults and children 8 years of age and older is 100 mg doxycycline twice a day for 6 weeks plus 1 g streptomycin daily for 2 to 3 weeks. Instead of streptomycin, rifampicin may be given in combination with doxycycline (200 mg/day orally for 6 weeks) at a dose of 600-900 mg for 6 weeks. Treatment of complications such as spondylitis and osteomyelitis, neurobrucellosis and brucella endocarditis may require prolonged therapy ie for at least 8 weeks. The optimal therapy for brucellosis during pregnancy has not been established. Co-trimoxazole has been used successfully. Alternatively, rifampicin for at least 45 days may be used. The optimal therapy for infants and children less than 8 years of age remains to be established as well. As for pregnant women doxycycline is contraindicated because of possible permanent staining of deciduous teeth and inhibition of bone growth of the baby. Suggested therapies include trimethoprim-sulfamethoxazole (TMP/SMZ) 8/40 mg/kg/day twice daily orally for 6 weeks plus streptomycin 30 mg/kg/day once daily intramuscularly for 3 weeks or gentamycin 5 mg/kg/day once daily intravenously or intramuscularly for 7 to 10 days. Another alternative is TMP/SMZ plus rifampicin 15 mg/kg/day orally for 6 weeks.

**Brucellosis in Jammu & Kashmir and prospects.** Brucellosis has not been studied in any detail in the State of Jammu & Kashmir. Rearing of sheep and cattle is common among villagers in the State and most villagers live in close contact with their animals or handle animal products regularly.

Veterinary services are not high grade; most of the live stock remains unexamined and unimmunized. Consequently, most of the animals, flesh or milch, remain ill. There are no abattoirs, and slaughtered animals are not examined pre- or post-mortem. In addition, the consumption of raw dairy is common practice. In the absence of effective measures to control and prevent brucellosis such as vaccination of livestock, farm sanitation and food hygiene brucellosis could be easily transmitted to the human population. In the absence of laboratory testing, many patients with febrile illness are classified by practitioners, registered as well as unregistered, as pyrexia of unknown origin (PUO), some of whom could very well be suffering from brucellosis. Serum agglutination test (Wright) has often detected presence of brucellosis in patients admitted to the SMHS hospital as PUO.[14] Retrospective examination with SAT of 3,532 cases of PUO referred for diagnosis to the Department of Clinical Microbiology, Government Medical College, Srinagar, revealed a serum prevalence of 0.8% at a threshold value of 1:160[15].

To improve the diagnosis of brucellosis the authors intend to examine the clinical utility of the *Brucella* IgM/IgG flow assay as a point-of-care test for brucellosis in hospitals and health care centres. The *Brucella* IgM/IgG flow assay is a simplified version of ELISA and is simply performed by the addition of a drop of serum and some running fluid to the sample well of a plastic assay device. The test result is read after 10-15 minutes by visual inspection for staining of the detection line.[16] The *Brucella* IgM/IgG flow assay is easy to perform and to read and may be performed by a nurse or a medical assistant. The sensitivity and specificity of the *Brucella* IgM/IgG flow assay is very high and a positive test result is highly consistent with active brucellosis.[17] The use of this test will provide clinicians with a means to confirm the diagnosis of brucellosis at first presentation of the patient and to start treatment immediately.

## Conclusions

- Brucellosis is a severe and debilitating febrile illness.
- It is very deceptive disease; physicians should be aware of the diverse and non-specific clinical manifestations.
- Laboratory testing is indispensable for diagnosis.
- The Rose Bengal test is a rapid and simple screening test but should be confirmed with a more specific test.
- A high titre in the SAT (Wright's test) is consistent with brucellosis; a low titre at or around the threshold value suggests but does not prove brucellosis.
- Uncomplicated brucellosis responds well to antibiotic treatment.
- Early diagnosis and prompt treatment is essential to prevent complications and relapse.
- Use of the *Brucella* IgM/IgG flow assay will allow physicians to diagnosis and treat patients with brucellosis promptly.

Dr. S. Manzoor Kadri, from the Regional Institute of Health, Kashmir, and Dr. H.L. Smits, a molecular biologist at the department of KIT Biomedical Research of the Royal Tropical Institute in Amsterdam, The Netherlands, are investigating the clinical utility of a simple and rapid "point-of care" test, the *Brucella* IgM/IgG flow assay, for use by general practitioners to improve the diagnosis and treatment of patients with clinical suspicion of brucellosis. The *Brucella* IgM/IgG flow assay was developed at the Royal Tropical Institute and studies performed in Spain and Turkey showed a high sensitivity and specificity. The study also will be used to determine the main risk factors for brucellosis. (Ed)

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**A leaf from the history of medicine**

# Fleming

**[Sir Alexander Fleming]**

Fleming (1881-1955) was a British bacteriologist and Nobel laureate, best known for his discovery of penicillin. Born in Lochfield, Ayr (now part of Strathclyde), Scotland, Fleming had a brief military career before a small legacy enabled him to begin studying medicine in 1901 at St Mary's Hospital Medical School of the University of London. He remained associated with St Mary's throughout his career, ending as Director of what (from 1948) was called the Wright-Fleming Institute of Pathology and Research. (The Institute was originally the Inoculation Department of St Mary's Hospital and was under the direction of Sir Almroth Wright, with whom Fleming worked closely).

In addition to a number of routine contributions to bacteriology and chemotherapy, Fleming made two important observations about antibiotic substances. In 1921, he noticed that his own nasal secretions lysed (dissolved) a colony of common bacteria on a Petri dish. He named the active substance lysozyme and discovered that it was also contained in other body fluids and in some plants. Lysozyme had no clinical application, however, as it was difficult to obtain in concentrated amounts and was ineffective against disease-causing bacteria.

**Discovery of Penicillin**

The research of Alexander Fleming in 1928 led to the accidental discovery of penicillin, the life-saving antibiotic derived from the mould *Penicillium notatum.* Penicillin is effective against a wide range of disease-causing bacteria and acts by killing bacteria directly or by inhibiting their growth.

In 1928, Fleming observed that a mould (later identified as *Penicillium notatum*) lysed colonies of the bacteria staphylococci, a common cause of wound infections. His paper describing this phenomenon mentioned the potential clinical importance of the substance, but he was unable to obtain penicillin in a sufficiently pure form to produce reliable results in patients with infections, and he abandoned his work in this area in the early 1930s. It was taken up again in World War II by a group at Oxford University, including the pathologist Howard Florey and the chemist Ernst Chain. This group succeeded in producing small amounts of penicillin and in demonstrating its effectiveness against a number of bacterial diseases. Industrial production methods were developed in the United States during the War.

Fleming, who was knighted in 1944, shared the 1945 Nobel Prize for Medicine or Physiology with Florey and Chain. Primarily through the publicity

activities of Wright, Fleming received most of the popular acclaim for penicillin's discovery.

## Chain [Ernst Boris Chain]

Chain (1906-1979), was a German-born British biochemist, pathologist, and Nobel laureate, born in Berlin and educated at the University of Berlin. Because he was Jewish, he left Germany for England after Hitler's accession to power in 1933. He engaged in research on enzymes at the Universities of Cambridge and Oxford, where he collaborated with the Australian pathologist Sir Howard Walter Florey in the investigation of antibiotic substances produced by moulds. By 1941, this investigation had resulted in the small-scale production of penicillin. After 1950, Chain worked at the Higher Institute of Health in Rome, and in 1961 he became Professor of Biochemistry at the University of London. Chain shared the 1945 Nobel Prize for Physiology or Medicine with Florey and the British bacteriologist Sir Alexander Fleming.

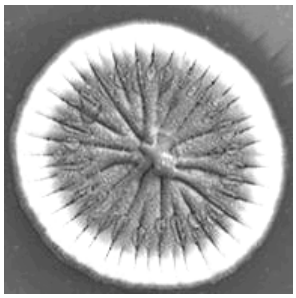
## Florey

**[Sir Howard Walter, Baron]**

Florey (1898-1968) was an Australian pathologist, co-discoverer of penicillin, and Nobel laureate. Born in Adelaide, Australia, and educated in medicine at the University of Adelaide, he later studied and taught in England. In 1935 he was appointed director of the Dunn School of Pathology, University of Oxford. Florey studied naturally occurring antibacterials, of which the *Penicillium* mould discovered by Alexander Fleming seemed the most promising. In 1939 Florey and the German-born British biochemist Ernst Boris Chain isolated the active agent, penicillin, from a fraction of the mould and formulated procedures for extraction and production. With British industries affected by World War II, Florey took his process to the United States, where private and government laboratories produced sufficient quantities to combat bacterial infection in wounded soldiers. For his work he was knighted in 1944, shared the Nobel Prize for Physiology or Medicine in 1945 with Chain and Fleming, was elected president of the Royal Society in 1960, and was created a life peer in 1965.

## Penicillin

Penicillin is a widely known antibiotic derived from the mould *Penicillium notatum.* The action of this antibiotic was first observed in 1928 by the British bacteriologist Sir Alexander Fleming, but it was another ten years before penicillin was concentrated and studied by the British biochemist Ernst Chain, the Australian pathologist Sir Howard Florey, and other scientists.



***Penicillium* Mould**
Penicillin is an important antibiotic derived from the mould *Penicillium notatum* pictured here. It is effective against a wide range of disease-causing bacteria, which it kills directly or by inhibiting their growth.

Penicillin acts both by killing bacteria and by inhibiting their growth. It does not kill organisms in the resting stage but *only those that are growing and reproducing (ie the actively growing microbes)*. It is effective against a wide range of pathogenic micro-organisms, including pneumococci, streptococci, gonococci, meningococci, the clostridium of tetanus, and the syphilis spirochaete. The drug has been successfully employed to treat such deadly diseases as subacute bacterial endocarditis, septicaemia, gas gangrene, gonorrhoea, and scarlet fever. Toxic symptoms produced by penicillin are limited largely to allergic reactions which can be determined by scratch tests before administration of the drug.

SEMI-SYNTHETIC PENICILLIN

Despite the effectiveness displayed by penicillin in curing a wide range of diseases, infections caused by certain strains of staphylococci could not be cured by the antibiotic as a result of the ability of the organism to produce an enzyme, penicillinase, capable of destroying the antibiotic. In addition, enterococci and many gram-negative bacilli known to cause respiratory and urinary-tract infections were found to be intrinsically-resistant to the action of penicillin. Appropriate chemical treatment of a biological precursor to penicillin, isolated from bacterial cultures, resulted in the formation of a number of so-called semi-synthetic penicillins. The most important of these are methicillin and ampicillin. Methicillin is remarkably effective against penicillinase-producing staphylococci and ampicillin/amoxycillin are not only active against all organisms normally killed by penicillin, but also inhibits enterococci and most gram-negative bacilli.

DOSAGES

The strength and dosage of penicillin are measured in terms of international units. Each of these units is equal to 0.0006 g of the crystalline fraction of penicillin called penicillin G. In the early days of penicillin therapy, the drug was administered every three hours in small doses. More recently a preparation called benzathine penicillin G has been produced that provides detectable levels of antibiotic for as long as four weeks after a single intramuscular injection. It is useful for treatment of syphilis and strep throat. Bacterial resistance to penicillin has increased over the years, causing a need for alternative drugs and increases in penicillin dosage.

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With the advent of new antibiotics, penicillin has fallen from grace in our place for three simple reasons:

1) Newer antibiotics are more fashionable; since penicillin has been around for long and is still one of the cheapest available, parents feel that it is inferior to other costlier antimicrobials,

2) Practitioners either don't want to take chance or have lost faith in penicillin.

3) Retailers don't stock and sell penicillin, mainly because it is too cheap to deal in. (Ed)

# Penicillins

***Rubina Shaheen***

Benzylpenicillin remains an important and useful antibiotic but it is inactivated by bacterial beta-lactamases. It is effective for many streptococcal, (including pneumococcal), gonococcal and meningococcal infections and also for anthrax, diphtheria, gas gangrene, leptospirosis, tetanus and treatment of Lyme disease in children. Pneumococci, meningococci and gonococci often have decreased sensitivity to penicillin and benzylpenicillin is no longer the first choice for pneumococcal meningitis. Benzylpenicillin is given by injection as it is inactivated by gastric acid and absorption from the intestinal tract is low.

Depot preparations are used when therapeutic concentrations need to be sustained for several hours. Benzathine benzylpenicillin or procaine benzylpenicillin provides a tissue depot from which the drug is slowly absorbed over a period of 12 hours to several days. They are the preferred choice for the treatment of syphilis
or yaws.

Phenoxymethylpenicillin is suitable for oral administration; it has a similar spectrum of activity but is less effective than benzylpenicillin. It should not be used for
serious infections because absorption can be unpredictable and plasma concentrations variable.

# Benzylpenicillin

**Availability**: Injection (Powder for solution), benzylpenicillin sodium,
600-mg vial (1 million units),
3-g vial (5 million units)

**Uses**: Benzylpenicillin is useful for pneumonia; throat infections; otitis media; Lyme disease in children; streptococcal endocarditis; meningococcal meningitis; necrotizing enterocolitis; necrotizing fasciitis; leptospirosis; neurosyphilis; anthrax; actinomycosis; brain abscess; gas gangrene; cellulitis; osteomyelitis

**Contra-indications**: Penicillin hypersensitivity; avoid intrathecal route.

**Precautions**: History of allergy; renal failure; heart failure; pregnancy and breastfeeding; interactions.

**Dose**:
i) *Mild to moderate infections* due to sensitive organisms, by intramuscular injection or by slow intravenous injection or by intravenous infusion ,
ADULT: 0.6-2.4 g daily in 2-4 divided doses, with higher doses in severe infections and duration of treatment depending on disease;
CHILD 1 month to 12 years, 100 mg/kg daily in 4 divided doses, with higher doses in severe infections. (Infant 1 to 4 weeks, 75 mg/kg daily in 3 divided doses; neonate 50 mg/kg daily in 2 divided doses)
ii) *Bacterial endocarditis*, by slow intravenous injection or by intravenous infusion, ADULT up to 7.2 g daily in 6 divided doses
iii) *Meningococcal meningitis*, by slow intravenous injection or by intravenous

infusion, ADULT up to 14.4 g daily in divided doses; premature infant and neonate 100 mg/kg daily in 2 divided doses; infant 150 mg/kg daily in 3 divided doses; CHILD 1 month to 12 years, 180-300 mg/kg daily in 4-6 divided doses

iv) *Suspected meningococcal disease* (before transfer to hospital), by intramuscular injection or by slow intravenous injection , ADULT and CHILD over 10 years, 1.2 g; CHILD 1 to 9 years, 600 mg; CHILD under 1 year, 300 mg

v) *Neurosyphilis*, by slow intravenous injection , ADULT 1.8-2.4 g every 4 hours for 2 weeks.

vi) *Congenital syphilis*, by intramuscular injection or by slow intravenous injection , CHILD up to 2 years, 30 mg/kg daily in 2 divided doses for 10 days; CHILD over 2 years, 120-180 mg/kg (to a maximum of 1.44 g) daily in divided doses for 14 days

(Reconstitution & administration is done according to manufacturer' s directions)

**Adverse-effects**:

. Hypersensitivity reactions including urticaria, fever, joint pains, rashes, angioedema, anaphylaxis, serum sickness-like reactions, haemolytic anaemia, interstitial nephritis;

. Diarrhoea, antibiotic-associated colitis;

.Neutropenia, thrombocytopenia, coagulation disorders, central nervous system toxicity, including convulsions, coma, and encephalopathy (associated with high dosage, or severe renal failure);

. Electrolyte disturbances;

.Jarisch-Herxheimer reaction (during treatment for syphilis and other spirochaete infections, probably due to release of endotoxins);

. Inflammation, phlebitis or thrombophlebitis at injection sites

# Benzathine benzylpenicillin

**Availibility**: Injection (Powder for solution for injection), benzathine benzylpenicillin, 1.8-g vial (equivalent to benzylpenicillin 1.44 g, 2.4 million units)

**Uses:** Streptococcal pharyngitis; diphtheria carrier state; syphilis and other treponemal infections (yaws, pinta, bejel); rheumatic fever prophylaxis.

**Contra-indications**: Penicillin hypersensitivity; intravascular injection; neurosyphilis

**Precautions**: History of allergy; renal failure; pregnancy and breastfeeding; interactions.

**Dose:**

i) *Streptococcal pharyngitis*; primary prophylaxis of rheumatic fever, by deep intramuscular injection , ADULT and CHILD over 30 kg body-weight, 900 mg as a single dose; CHILD under 30 kg body-weight, 450-675 mg as a single dose

ii) Secondary prophylaxis of rheumatic fever, by deep intramuscular injection , ADULT and CHILD over 30 kg body-weight, 900 mg once every 3-4 weeks; CHILD under 30 kg body-weight, 450 mg once every 3-4 weeks

iii) *Early syphilis*, by deep intramuscular injection , ADULT 1.8 g as a single dose, divided between 2 sites
iv) *Late syphilis*, by deep intramuscular injection , ADULT 1.8 g, divided between two sites, once weekly for 3 consecutive weeks
v) *Congenital syphilis* (where no evidence of CSF involvement), by deep intramuscular injection , CHILD up to 2 years, 37.5 mg/kg as a single dose
vi) *Yaws, pinta, and bejel*, by deep intramuscular injection , ADULT 900 mg as a single dose; CHILD 450 mg as a single dose

(Reconstitution & administration is done according to manufacturer' s directions)

**Adverse-effects**:
. Hypersensitivity reactions including urticaria, fever, joint pains, rashes, angioedema, anaphylaxis, serum sickness-like reaction, haemolytic anaemia, interstitial nephritis;
. Neutropenia, thrombocytopenia, coagulation disorders and central nervous system toxicity (associated with high dosage or severe renal failure);

. Jarisch-Herxheimer reaction (during treatment for syphilis and other spirochaete infections, probably due to release of endotoxins);
. Rarely, non-allergic (embolic-toxic) reactions; pain and inflammation at injection site

## Mechanism of action:

Penicillins are bactericidal agents that inhibit bacterial cell wall synthesis & induce a bacterial autolytic effect.

i) *Inhibition of bacterial cell wall synthesis*: Penicillins exert their bactericidal activity primarily by inhibiting bacterial cell wall synthesis. This they do probably by binding to penicillin-binding proteins (enzymes as transpeptidases, carboxypeptidases, & endopeptidases which play important role in formation and maintenance of cell wall structure). More specifically they inhibit the transpeptidation stage – ie the last stage of transpeptidation in cell-wall formation, by acting as the structural analogue of the concerned enzymes. Therefore, the cell wall formed is defective in structure and can not sustain the cell which dies. Other mechanisms also are operative.

*ii) Penicillin-induced bacterial autolytic effect:* Inhibition, by penicillin, of various enzymes which normally would facilitate cell wall expansion leads to inhibition of cell-wall synthesis, resulting in autolysis of bacteria from increased osmotic pressure. This autolysis is cell-cycle dependent, and occurs mostly when the cell is actively dividing (Ed)

# Procaine benzylpenicillin

**Availability**: Injection (Powder for solution for injection), procaine benzylpenicillin 1-g vial (1 million units), 3-g vial (3 million units)

**Uses**: Syphilis; anthrax; childhood pneumonia; diphtheria carrier state; cellulitis; mouth infections; bites

**Contra-indications**:
. Hypersensitivity to penicillins; intravascular injection

**Precautions**: History of allergy; renal failure; interactions.

**Dose**:
i) *Infections due to sensitive organisms*, by deep intramuscular injection , ADULT 0.6 to 1.2 g daily
ii) *Pneumonia*, by deep intramuscular injection , CHILD 50 mg/kg daily for 10 days

iii) *Syphilis*, by deep intramuscular injection , ADULT 1.2 g daily for 10 to 15 days, or up to 3 weeks in late syphilis
iv) *Congenital syphilis*, by deep intramuscular injection , CHILD up to 2 years, 50 mg/kg daily for 10 days

(Reconstitution & administration are done according to manufacturer's directions)

**Adverse-effects**:

. Hypersensitivity reactions including urticaria, fever, joint pains, rashes, angioedema, anaphylaxis, serum sickness-like reaction, haemolytic anaemia, interstitial nephritis; . Neutropenia, thrombocytopenia, coagulation disorders and central nervous system toxicity (associated with high doses and severe renal failure);

. Jarisch-Herxheimer reaction (during treatment for syphilis and other spirochaete infections, probably due to release of endotoxins);

. Rarely, non-allergic (embolic-toxic) reactions;

. Pain and inflammation at injection site

# Phenoxymethylpenicillin

**Availability**: Tablets, phenoxy-methylpenicillin (as potassium salt) 250 mg.

Oral suspension (Powder for oral suspension), phenoxy-methylpenicillin (as potassium salt) 250 mg/5 ml

**Uses:** Streptococcal pharyngitis; otitis media; erysipelas; mouth infections; secondary prophylaxis of rheumatic fever; post-splenectomy prophylaxis.

**Contra-indications**: Hypersensitivity to penicillins; serious infections.

**Precautions**: History of allergy; pregnancy and breastfeeding; interactions.

**Dose**:
i) *Infections due to sensitive organisms*, by mouth , ADULT 500-750 mg every 6 hours; CHILD up to 1 year, 62.5 mg every 6 hours; CHILD 1-5 years, 125 mg every 6 hours; CHILD 6-12 years, 250 mg every 6 hours
ii) Secondary *prophylaxis of rheumatic fever*, by mouth , ADULT 500 mg twice daily; CHILD 1-5 years, 125 mg twice daily; CHILD 6-12 years, 250 mg twice daily

Patient Advice: Phenoxymethylpenicillin should be taken at least 30 minutes before or 2 hours after food

**Adverse-effects:**
Hypersensitivity reactions including urticaria, joint pain, rash, angioedema, anaphylaxis; nausea and diarrhoea.

# Down's Syndrome

*Bashir Gaash*

Trisomy 21 is seen in approximately 1 of every 800 live births, making it the most common aneuploid condition compatible with survival to term. Although this condition was first described by Hohn Langdon Down in 1866, and it took another hundred years to find out that it was caused by the presence of an extra copy of chromosome 21.

**Prevalence:** General population: 1 in 1000 conceptions

Maternal age 35 years: 1 in 250

Maternal age 48: 1 in 11

Advanced maternal & paternal age, both, are risk factors. Increasing maternal age is associated with higher disjunction rate during meiosis I. However, this does not mean that mothers below 35 years will not deliver a Downs baby. In fact, most babies (70-80%) with Downs are born to mothers under 35 years of age. This is because non-disjunction occurs sporadically at any age.

**Trisomies, nondisjunction, & maternal age.**

The prevalence of Downs syndrome among offsprings varies with maternal age. Among mothers younger than 30 of age, the risk is less than 1/1000. It increases to approximately 1/400 at age 35 years, 1/100 at age 40, and approximately 1/25 after age 45. Most other trisomies, including those in which the fetus does not survive to term, also increase in prevalence as maternal age increases. This risk is one of the primary indications for prenatal diagnosis among women older than 35 years of age.

Several hypothesis have been advanced to account for this increase, including the idea that older women are less likely to spontaneously abort a trisome pregnancy. Direct studies of the frequency of chromosomal abnormalities in sperm & egg cells indicate that the pattern is in fact due to an increase in non-disjunction among older mothers. Since all of a female's oocytes are formed during her embryonic development, an ovum of a 45 year old woman is also 45 years old. This long period of suspension in prophase I (before being shed in ovulation) may impair disjunction. Despite studies on the effect of various environmental factors on chromosome, maternal age has emerged as the only known consistently correlated factor.

In spite of the strong correlation of maternal age with nondisjunction of chromosome almost 3/4$^{th}$ of Downs children are born to mothers younger than 35 years. This is because 90% of children are borne bt women of that age group.

The effect of paternal age is minor; this is because spermatocytes, unlike oocytes, are generated throughout the life of the male.

## Clinical features

There is considerable variation in the appearance of patients, however, there is a constellation of features that make the diagnosis easier.

***Facial features***:

A low nasal root,
Upslanting palpebral fissures,
Small ears (which are sometimes over-folded),
Flattened maxillary and malar region,
Round cheeks,
Corners of the mouth sometimes down-turned.

***Neck***: Short neck with the skin redundant at the nape of the neck, especially in newborns.

***Occiput***: Flat

***Hands & feet***: Broad & short;

About 50% have a deep flexion crease across their palms (simian crease)

Decreased muscle tone (hypotonia) is consistently present, and helps in diagnosis.

**Prognosis & Complications**

1) About 3% develop *obstruction / atresia* of duodenum, esophagus or anus.
2) *Respiratory infections* are quite common.
3) Risk of developing *leukemia* is 15-20 times higher than in the general population.
4) Approximately 40% are born with structural heart defects:

Most common is an *atrio-ventricular canal* (because inter-arterial and inter-ventricular septa fail to fuse normally during fetal development). This leads to blood flow from left to right side of heart which results in pulmonary hypertension.

Another common cardiac defect is ventricular septal defect.

5) *Mental retardation* is moderate to severe (IQ between 25 to 60 in most). Downs syndrome is the most common genetic disorder causing mental retardation. In the USA, Down's accounts for 10% of mental retardation.
6) *Conductive hearing loss* (sometimes neural)
7) Hypothyroidism is common, especially during adolescence.
8) Various *eye abnormalities*

**Prognosis*:***

***1) Survival:*** Survival rates are significantly decreased because of so many medical problems. As recently as early 1960s, only a half of them would survive their 5th birthday. Congenital heart defects are the most important single cause of death. Because of modern treatment (including corrective surgery, antibiotic treatment, & treatment of leukemia), now approximately 80% of the children with Down's syndrome will survive till their 10th birthday and about half the patients would survive till 50 years.

***2) Intellect:*** Enriched environments have been shown to significantly improve their intellectual function.

3) **Sterility**: Male patients are almost always sterile; 40% of females patients fail to ovulate. A female with Downs has a 50% risk of producing a gamete with two copies of chromosome 21 (which would then produce a trisomic zygote). However, approximately 3/4ths of trisomy 21 conceptions are spontaneously aborted.

Because reproduction is so uncommon, nearly all cases of trisomy are regarded as new mutations. Approximately 95% of trisomy are caused by non-disjunction, with most of the remainder being caused by chromosome translocations. In 90% to 95% of trisomy 21 cases, the extra chromosome is contributed by the mother. Mosaicism, in which only some cells of the body have extra chromosome, is seen in 2-4% cases of trisomy. It results in milder clinical expression of abnormality. Mosaicism, affecting primarily the germ line of a parent can lead to multiple recurrences of the disease in offsprings. Therefore recurrence risk in mothers under 30 years of age is 1% ie 10 times the expected risk in this age group.

**Other trisomies**:

***Edwards syndrome*** (Trisomy 18; 47,XY,+18) is the 2nd most common autosomal trisomy (prevalence 1/6000 live births). However, only 5% of such pregnancies survive to term, the vast majority end in still birth with congenital anomalies.

Clinically, such babies suffer prenatal growth deficiency [low gestational age (LGA), lighter for dates], characteristic facies (small ears with unraveled helix, small mouth that is hard to open), short sternum, characteristic over-lapping fingers with clenched fists, and short big toes.

Most of them have major anomalies; congenital heart defects especially VSD are most common, followed by omphalocele, diaphragmatic hernia, and spina bifida. Mortality rate is very high, and mere 5% reach their first birthday.

***Patau syndrome*** (Trisomy 13; 47,XY,+13) leads to oro-facial clefts, microphthalmia, and polydactyly. Malformations of CNS, CVS and kidney are common.

The condition is less common than Edwards syndrome, but, again, only 5% are born alive and 95% of them die before completing their first year.

# Anticipatory Guidance:

A new approach for the care and treatment of patients with Downs syndrome (and other genetic & chromosomal disorders), *anticipatory guidance*, sets guidelines which if followed strictly by the primary care physician, would help to prevent further disability or illness and improve survival.

*1) Evaluation of heart defects***:** Atrio-ventricular canals are the most common congenital heart defects seen in the neonates with Downs. Sugical correction of this condition should be done before 1st birthday; afterwards, pulmonary hypertension has been present too long for surgery to be successful. Therefore, now it is recommended that an echocardiogram be performed during newborn period.

*2) Eye problems* especially strabismus are often present, therefore eyes should be regularly examined. In asymptomatic children, ophthalmologic examination before the 4th birthday is recommended to evaluate visual acuity.

3) *Hypothyroidism* is common especially in adolescent period. Therefore, thyroid profile should be done on annual basis.

4) *Sensori-neural & conductive hearing loss*, both, seen in children with Downs. Hearing test should be done at 6-8 months of age and as needed afterward.

5) Older patients with instability of the first & second vertebrae may get spinal cord injuries. Imaging studies are recommended in children with neurological symptoms and in those planning to participate in athletic activities.

6) Children should be referred to appropriate preschool programmes (where available) to provide for developmental disabilities.

1. A karyotype will establish whether the condition is the result of a true trisomy or a translocation. If the latter is the case, the recurrence risk in future pregnancies is greatly elevated. A karyotype will also help to establish whether the patient is a mosaic. This may help to predict and explain the severity of expression of the disorder.
2. The risk ranking varies with many factors (chances of occurrence/recurrence):
   - 25 year old female with one previous Down syndrome child (approximately 1%)
   - 25 year old male carrier of a 21/14 translocation (1% - 2%)
   - 45 year old female with no family history (approximately 3%)
   - 25 year old female carrier of a 21/14 translocation (10%-15%).

**Patient Guidance**

# Downs Syndrome

Down's Syndrome is a congenital malformation accompanied by moderate to severe mental underdevelopment. It is caused by a genetic abnormality, specifically in the 21st chromosome.

### INCIDENCE AND DIAGNOSIS

The overall incidence of Down's syndrome is approximately 1 in 800 births, but the risk increases with rising age of the mother. Prenatal tests such as amniocentesis and chorionic villus sampling can be used to detect the chromosomal abnormality causing Down's syndrome. In addition, maternal blood tests can suggest the presence of a foetus with Down's syndrome when levels of a protein, *alpha-foetoprotein*, are lower than usual, or when levels of the female sex hormone *oestriol* (a form of oestrogen) and *human chorionic gonadotrophin* (a pituitary hormone that controls the sex hormones) are abnormal.

Individuals with Down's syndrome are often short in stature and have a small, round head with a high, flattened forehead and fissured, dry lips and tongue. A typical feature is a fold of skin, the epicanthic fold, on the inner corner of each eye. The palms show a single transverse crease and the soles have a straight crease from the heel to the space between the first and second toes.

### CAUSES

The chromosomal abnormality involved in most cases of Down's syndrome is trisomy-21, or the presence of three copies of the 21st chromosome. As a result, the affected person has 47 chromosomes in all body cells instead of the normal 46, although how this causes the condition's symptoms is not yet known. Scientists assume that the reason for the abnormal chromosomal assortment is the fertilization of an ovum with 24 chromosomes by a sperm with a normal assortment of 23, but they have also found that the sperm can carry the extra chromosome as well. The abnormal ovum or sperm is derived from a germ cell in which the pair of 21st chromosomes holds together and passes into the same sperm or ovum instead of separating. In the type of Down's syndrome called translocation, the extra chromosome-21 material is attached to one of the other chromosomes; when some, but not all, of the body's cells carry an extra chromosome 21, the condition is a type of Down's syndrome called mosaicism.

### OUTLOOK

Congenital heart disease, usually in the form of endocardial cushion defects, affects around 40 per cent of babies with Down's syndrome. Septal defects and

Fallot's tetralogy also occur. Many of these heart defects can be corrected surgically; babies should be screened by echocardiography soon after birth as the defects may well be difficult to detect. In the absence of a congenital heart defect, however, the majority of children can expect to live into their sixth decade.

Sensory problems include hearing impairments, which occur in many children with Down's syndrome. Annual audiometry and specialist consultation is recommended. Visual impairment owing to refractive errors or strabismus (squint) is also common and should be checked annually. Cataracts often develop but are usually outside the visual axis.

Although Down's syndrome itself is not yet amenable to medical treatment, medical care of the accompanying disorders and infections results in an almost normal lifespan. In the past, many children with Down's syndrome were institutionalized, but this rarely happens today. Most children with Down's syndrome take part in school activities and curricula, and most adults hold a job.

Unlike the cretins, Downs syndrome children are alert and happy, take interest in life, and love music. Because of this vivacity, in the past they have sometimes been termed 'cheerful idiots'. Given a conducive & congenial atmosphere they can be helped to pass life almost normally.

**Answers to quiz III:**

The child is suffering from typhoid fever. Repeated stool culture and widal test could help in diagnosis. Management includes antibiotics, hydration (if needed iv fluids) and personal hygiene.

S. typhi only infects humans, and causes typhoid fever when an individual eats contaminated food. S typhi can survive for a long time, even in frozen and dried foods. After an incubation period of usually 10-14 days, vague influenza like illness with fever, malise, pains and headache develops. The fever persists for a week and the child will become ill with vomiting, abdominal pain, diarrhoea and cough. Older children and adults may get constipation. The affected child looks septic and confused, and has a high temperature. There will be tachycardia and tachypnea, but later on, as the disease progresses, bradycardia may evolve and chest signs will appear. There is generalized tenderness in the abdomen, which is also distended. There may be meningeal signs and hepatosplenomegaly in many cases. Sometimes perforation of gut may occur, especially in the $2^{nd}$ or $3^{rd}$ week. This is usually associated with sudden deterioration, hypotension, tachycardia, abdominal pain and rigidity. The blood culture is positive in more than 2/3 of patients in the first week, but only in half of these patients will the stool sample be positive. The Widal test may be helpful; an O antibody of more than 4-fold will indicate infection with S. typhibut a high H-antibody will indicate previous infection or vaccination. Anaemia, hyponatremia and thrombocytopenia occur in his illness.

Supportive treatment with careful electrolyte and fluid balance is more important than trying to treat the infection with antibiotics. Chloramphenicol, co-trimoxazole and amoxicillin are very effective in treating S typhi. Ceftriaxone and ciprofloxacin are used more frequently these days as species of S. typhi become more resistant to other antibiotics. The duration of illness varies from 7-14 days with the introduction of antibiotics. (Also see page 14-20)

# Burns

With special reference to the developing world*

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Developing countries have a high incidence of burn injuries, creating a formidable health problem. High population density, illiteracy, and poverty are the main demographic factors associated with a high risk of burn injury. The exact number of burns is difficult to determine: judicious extrapolation suggests that India, with a population of over 1 billion, has 7 to 8 lakh burn admissions annually. The high incidence makes burn an endemic health hazard. A multitude of social, economic and cultural factors interact, thereby complicating the management, reporting, and prevention of burns.

## Epidemiology

The epidemiology of burn injuries is different from that in the developed world. Most burn injuries are sustained by women aged 16-35 years. Women of this age group tend to be engaged in cooking, and most work at floor level and relatively unsafe kitchens and wear loose fitting clothes such as saris, dupattas, and ghararas, etc. Children and elderly people are at relatively less risk because many house-hold still exist as joint families, and the system safe guards these age groups to some extent.

The commonest mode of burn injury is a flame burn. Most such incidents are related to malfunctioning kerosene pressure stoves. These are cheap contraptions without safety features, and burns occur when carbon deposits block the kerosene vapour outlets. Unsupervised and careless handling of fire-crackers during the festival of Diwali leads to an increased incidence of injuries during the festival period. Fire is also used in homicide and suicide.

## Problems in management

Burn management in developing countries is riddled with difficulties. Lack of government initiative and low literacy rates preclude effective prevention programmes. Many uneducated households are fraught with superstition, taboo, weird religious rituals, and faith in alternative systems of "medicine" which complicates management.

Most burn centres are situated in large cities and are inadequate for the high incidence of injuries. Resuscitation is often delayed as patients have to travel long distances and transport facilities are poor, many burn centres are also plagued with lack of resources, lack of operating time and shortage of blood. Generally there are no dedicated burn surgeons, and surgeons without formal training in burn management are involved in burn care. Burn nursing is also not a recognized concept. These conditions make excisional surgery impossible for a large percentage of patients. There is generally no coordination between district hospitals and tertiary centres.

*Burn management problems in developing countries*

- High incidence of burns
- Lack of prevention programme
- Inadequate burn care facilities
- Lack of resources
- Lack of trained staff
- Poor infrastructure and coordination
- Social problems

## Strategies for effective burn care in developing countries

The approach to burn management has to be radically different from that in the Western countries.

**Strategies for burn management in developing countries**

- Effective prevention programmes
- Burn as national health agenda
- Central registry of burns
- Create a professional burn group
- Adequate safety legislation
- Induct district Hospital and primary health centers
- Encourage patient management at home
- Cost effective treatment procedures
- Develop regional centers of excellence

## Prevention programmes

Prevention programmes should be directed at behavioural and environmental changes which can easily adopted into lifestyle. The programmes need to be executed with patience, persistence, and precision training high risk groups.

Depending on the population of the country, burns prevention could be national programmes. This can ensure sufficient funds are available and lead to proper coordination of district, regional and tertiary care centres. It could also provide for compulsory reporting of all burn admissions to a central registry and these data could be used to evaluate strategies and prevention programmes. There should be adequate provision by law to set manufacturing standards for heating and electrical equipment, fire safety standards for high rise buildings, and procedures for storage and transportation of hazardous materials, explosive chemicals, and firecrackers. A national body of burn professionals should be constituted to educate all healthcare staff involved in burn care.

## Providing treatment

To provide optimal burn care to a large population with limited resources, it is imperative to strengthen existing infrastructure. A few regional burn centres should be developed to provide tertiary management and training to burn care staff. General surgeons working in district hospitals should form the nucleus of the burn-care service and decide on referral procedures.

**Cost effective burn treatments to conserve scarce resource**

Parkland formula for fluid resuscitation - It is cost effective and ensures proper compliance

It is not possible to keep referral patients at burn centres for six to eight weeks of treatment; they can be discharged after two to three weeks of stabilization. Such patients can then be treated at district hospitals or at home with the help of primary health centres. Thus, primary health centres can act as liaison between burn patients and district hospital. The incidence of burn wound septicemia with domiciliary treatment is remarkable low. These patients can be readmitted as necessary for blood transfusion, treating septicemia and skin grafting.

**Conservative burn wound management**

This involves using closed dressing, eschar separation, and skin grafting. This takes the pressure off operating facilities and provides comparable results of surgery.

Certain well-effected and cost-effective treatment procedures need to be adopted to conserve resources; these include using Parkland formula for resuscitation pursuing conservative burn wound management and using amnion as a biological dressing.

**Amnion as a biological dressing**
This is easily available, is free of cost, and can be comfortably preserved for a week

## *Burn disaster*

A disaster is a situation that is unpredictable, massive, and poses an immediate threat to public health. A burn disaster is "an event resulting in mass burn casualties and severe loss of human lives and material from a known thermal agent".

**Characteristics of a burn disaster**
Large number of patient with extensive burn injuries
Immediate care and Assistance may not be adequate
A high incidence of serious associated injuries
Site of the disaster is not always accessible
Response time may be prolonged
Local infrastructure may

Disaster normally exceeds the resources of healthcare facilities.

Disaster management involves coordinating the activities of various health disciplines to prevent disaster, and help in rehabilitation of victims.

**Factors to be considered while developing a disaster plan**
Unpredictability
Time (day night during festivities, etc)
Area (City, non –urban, accessibility etc,)
Characteristics (explosion, building fire, toxic fumes etc)
Type of building (dwelling, hotel, office etc)
Type of trauma burn, associated injury, inhalational injury
Number of people injured
Degree of preparedness to manage disaster

**Disaster plan**

An organized disaster plan can reduce loss of property, social disruption, and suffering. A disaster plan should specially be tailored for a particular region and nature of fire disaster. Ultimately, a coordination system must be developed that includes medical and public safety organization, law and order agencies, and transport agencies.

**First aid at the site of burn disaster**
Quantitative assessment of burns
Qualitative assessment of burns
Commence intravenous resuscitation
Catheterization
Analgesia Hospital transfer

The communication lines from the central command should be fast and multilingual. It should be able to advise workers at the disaster site, direct transport agencies, and simultaneously relay the information to surrounding hospitals. All the regional and distant hospitals must be incorporated in a multi-tier system as the number of cases may overwhelm local facilities.

Hospitals play a pivotal role in providing trained staff. All doctors and nurses, irrespective of their specialties and whether they are included in the plan, should be educated about the basics of burn care. With a burn specialist at the core, the hospital disaster management team also includes a respiratory physician and an anesthetist. There should be prompt and judicious deployment of staff. Teams of psychologists should manage panic among disaster victims and their relatives both at the disaster site and at hospitals. Accurate triage by clinicians experienced in burns must guide the flow of patients from the site to the inner circle of healthcare facilities (primary and secondary care hospitals) and then to the outer circle (tertiary care hospitals and burn centres).

Transportation needs are guided by the number of victims, their condition, the nature of the fire disaster, and geographical consideration. Possible modes of transport include ambulances, local transport vehicles, military vehicles, helicopters, fixed wing aircraft, and rescue boats.

**Principles of disaster management**

Prevention
Effective multidisciplinary response
Disaster profiles
Mobilization of workforce resources
Disease patterns
Local community or national involvement
Risk assessment
phase
Reconstructive Post- emergency phase

## Managing disaster

Immediate care is provided by people present at the scene of the disaster, who may be survivors or passers- by. These first responders are later guided by trained healthcare workers who arrive at the site. On site management includes first aid, patient triage and ambulance-staging with a basic aim of maximal use of resources.

### Triage

Triage is the cornerstone of effective burn disaster management and is done at the disaster site by staff with knowledge of burn treatment. Triage takes into consideration the total number of patients, bed availability, and transportation capacity.

Triage should be prognostic, and patients should be categorized on the basis of age, extent of burn, sit of burns and presence of inhalation injury:

**Group I** – Minor burns (<10% of total surface area in children; <20% in adults ) to non-critical areas.
Assigned to – Out patient care, dressing, tetanus prophylaxis.

**Group II** – Minor burns of critical sites (face, hands genital)
Assigned to – Short hospital stay, special wound care or operation.

**Group III**- Major burns (20-60%)
Assigned to – Admission to burn unit, intravenous resuscitation.

**Group IV** – Extensive burns (>60%)
Assigned to – Lower priority to transfer.

**Group V** – Minor burns with inhalation injury or associated injury
Assigned to - Oxygen, incubation, transfer to intensive care unit.

The patients in groups III and V are evacuated first, followed by group IV. Group II cases are evacuated at the end. Group I cases are either discharged after first aid or asked to make their own way to the nearest primary care centre

## Further treatment

Initial care is in the line of ABC of resuscitation. An adequate airway and respiration must be ensured. All patients except those with minor burns must receive fluid resuscitation based on a simple formula. Wounds should be covered with a sterile sheet until they are dressed. Dressing should be simple with only antimicrobial pads and Gamgee tissue. Effort should be made to detect and treat associated injuries.

Secondary triage may also be done at this time. If necessary, seriously injured patients can be sent to centres of higher level while less serious patients who reach the tertiary centres are referred back to primary care centres. The success of such a plan lies in accurate triage at every level, so that all centres are used optimally and best possible treatment is delivered to all according to the severity of injury; with minimum delay.

(Adapted from the British Medical Journal)

World Health Organisation……

## Classification of depth of burn

**First degree (superficial) burns**: The tissue damage is restricted to the epidermis and upper dermis. Nerve endings in the dermis become hypersensitive and the burn surface is painful. Blister formation is common. If the burn remains free from contamination, healing without scarring takes place in 7 days.

**Second degree (dermal) burns**: The lowest layer of the epidermis, the germinal layer, derives support and nourishment from the dermis. Portions of the germinal layer remain viable within the dermis and are able to re-epithelialize the wound. A deeper burn penetrates into the dermis and fewer epidermal elements survive. The amount of residual scarring correlates with the density of surviving epidermal elements. Healing of deep dermal burns may take longer than 21 days and usually occurs with such severe scarring that skin grafting is recommended. Because vessels and nerve endings of the dermis are damaged, dermal burns appear paler and are less painful than superficial burns.

**Third degree (full-thickness) burns**: Full thickness burns destroy all epidermal and dermal structures. The coagulated protein gives the burn a white appearance, and neither circulation nor sensation are present. After separation of the dead eschar, healing proceeds very slowly from the wound edge. Skin grafting is always required, unless the area is very small. Severe scarring is inevitable.

**Mixed depth**: Burns are frequently of mixed depth. Estimate the average depthby the appearance and the presence of sensation. Resuscitation is based on the total of 2$^{nd}$ and 3$^{rd}$ degree burns and local treatment on the burn thickness at any specific site.

# Chronic Obstetric Pulmonary Disease

***Rohini Bhan***

Chronic Obstructive Pulmonary Disease (COPD) is a slowly progressive disease of the airways that is characterized by a gradual loss of lung function. What can be grouped under the term varies from country to country. In the U.S., the term COPD includes chronic bronchitis, chronic obstructive bronchitis, or emphysema, or combinations of these conditions. It represents the fourth leading cause of death in the U.S.

The symptoms of COPD can range from chronic cough and sputum production to severe, disabling, shortness of breath. In some individuals, chronic cough and sputum production are the first signs that they are at risk for developing the airflow obstruction and shortness of breath characteristic of COPD. In others, shortness of breath may be the first indication of the disease.

## Epidemiology:

### Distribution:

***a) Prevalence:***

- 12.1 million adults ages 25 and older reported being diagnosed with COPD in 2001.
- About 24 million adults have evidence of impaired lung function indicating that COPD is under-diagnosed.
- The prevalence of self-reported COPD is higher in females than males and in whites than blacks.

***b) Mortality***

- About 119,000 adults ages 25 and older died from COPD in 2000.
- While the COPD death rate for females more than doubled between 1980 and 2000, and the number of deaths for females surpassed the number for males in 2000, the overall age-adjusted death rate for COPD remained higher for males in 2000. The age-adjusted COPD death rate was about 46 percent higher in males than females and 63 percent higher in whites than blacks.
- COPD is the fourth leading cause of death in the U.S. and is projected to be the third leading cause of death for both males and females by the year 2020.

***c) Hospitalizations***

From 1995 to 2000, the trend in COPD hospitalization rates was about the same for males and females. However, the rates were slightly higher among blacks than whites during this same period. In 2000, the COPD hospitalization rates were 31.5 and 36.0 per 10,000 population for whites and blacks, respectively.

***d) Emergency Department Visits and Hospitalizations***

- About 1.5 million emergency department visits by adults 25 and older were made for COPD in 2000.
- More emergency department visits for COPD were made by adult females than adult males (898,000 vs. 651,000).
- About 726,000 hospitalizations for COPD occurred in 2000. More females than males were hospitalized for COPD (404,000 vs. 322,000).

***e) Costs of COPD***

The cost of COPD to the nation in 2002 was estimated to be $32.1 billion. Direct medical services accounted for $18.0 billion, and indirect cost of morbidity and premature mortality was $14.1 billion. Medicare expenses for COPD beneficiaries were nearly 2.5 times that of the expenditures for all other patients.

***Costs of COPD in the US:***

¡The total estimated cost of COPD in 2002 was $32.1 billion.

$18 billion direct costs

$14.1 billion indirect costs

***EMPHYSEMA***

In 2001, the prevalence of emphysema was appreciably higher for the 65 and older age group than the 45-64 age group for each race-sex group. The prevalence was higher in males than females and in whites than blacks. The prevalence was highest in white males and lowest in black females. Over the past two decades, prevalence of emphysema has consistently been higher for the 65 and above age group.

***CHRONIC BRONCHITIS***

In 2001, the prevalence of chronic bronchitis was lowest among the 25-44 age group. Across age groups, females had higher rates than males for both races. Among the 25-44 and 65 and older age groups, prevalence was higher for whites than blacks for each sex group. For the 45-64 age group, chronic bronchitis was higher among females, and black females in particular, had the highest prevalence for this age group.

In 1997, the survey questions used to determine the prevalence of COPD in the developed world changed. Prior to 1997, the prevalence was based on individuals who had, or knew someone in the family who had, chronic bronchitis or emphysema during the past 12 months. The new survey asks, “During the past 12 months, have you been told by a doctor or other health professional that you have chronic bronchitis?”; and “Have you ever been told by a doctor or other health professional that you have emphysema?” Based on these questions, during 2001, 12.1 million U.S. adults 25 years and older reported having COPD (figure 1). In addition, millions may be unaware that they have COPD because they have minimal or no symptoms. Therefore, COPD may be under-diagnosed.

In the developed world, the most important risk factor for COPD by far is cigarette smoking. Pipe, cigar, other types of tobacco smoking, and passive exposure to cigarette smoke are also risk factors. Other documented causes of COPD include occupational dusts and chemicals. Outdoor air pollution adds to the total burden of inhaled particles in the lungs, but its role in causing COPD is uncertain. The most important measure for preventing COPD – and for stopping disease progression – is avoidance of smoking.

The most important risk factor for COPD by far is cigarette smoking. Pipe, cigar, other types of tobacco smoking, and passive exposure to cigarette smoke are also risk factors. Thus, the most important measure for preventing COPD – and for stopping disease progression – is avoidance of smoking.

The diagnosis of COPD is confirmed by the presence of airway bstruction on testing with spirometry.

There is no known cure for COPD at the present time. Treatment is usually supportive and designed to relieve symptoms and improve quality of life. Patients with COPD require emergency treatment and sometimes ospitalizations during periods of exacerbations of their disease

With continued exposure to cigarettes or noxious particles, the disease progresses and individuals with COPD increasingly lose their ability to breathe. Acute infections or certain weather conditions may temporarily worsen symptoms (exacerbations), occasionally where hospitalization may be required.

# Immunity: An Introduction

*Ayaz Amin*

Over the last decades, body of knowledge on immunology has grown by leaps and bounds. The newer jargon is quite unfamiliar to some who had qualified decades back and could not keep in touch. The purpose of this series is also to acquaint those with a limited background in immunology with the current understanding of our immune system. Medical students also will find the section beneficial.

The immune system is a remarkable defense mechanism of the bosy. It provides the means to make rapid, specific, and protective responses against the myriad potentially pathogenic microorganisms that inhabit the world in which we live. The tragic example of severe immunodeficiencies, as seen in both genetically determined diseases and in acquired immunodeficiency syndrome (AIDS), graphically illustrates the central role the immune response plays in protection against microbial infection. The immune system also has a role in the rejection of tumors and may exert important effects in regulating other bodily systems.

**Innate Immunity**

Most pathogenic microorganisms attempting to infect an individual have to face powerful nonspecific defenses.

i) The epithelium provides both a physical barrier to the entry of microbes and produces a variety of antimicrobial factors.

ii) Microbes that penetrate the epithelium are met with macrophages and related cells that have receptors for cell-surface molecules found on many microbial agents. These interactions may lead to phagocytosis of the pathogen, activation of the macrophage so that it can destroy the agent and to the induction of an inflammatory response that recruits other cell types, including neutrophils, to the site.

iii) Microbial pathogens may also be recognized by components of the complement system leading to the enhanced phagocytosis of the agent and in some instances to its lysis as well as to independent activation of inflammatory responses.

iv) The innate immune system also acts to recruit antigen-specific immune responses, not only by attracting cells of the immune system to the site of the infection, but also through the uptake of antigen by dendritic cells that transport antigen to lymphoid tissue where primary immune responses are initiated. Dendritic cells also produce cytokines that can regulate the quality of the immune response so that it is most appropriate to combating the pathogen.

**Primary Responses**

Primary immune responses are initiated when a foreign antigenic substance interacts with antigen-specific lymphocytes under appropriate circumstances. The response generally consists of the production of antibody molecules specific for the antigenic determinants of the antigen (immunogen) and of the expansion and differentiation of antigen-specific helper and effector T-lymphocytes. The latter include cells that produce cytokines and killer T cells, capable of lysing infected cells. Generally, the combination of the innate immune response and the

primary response are sufficient to eradicate or to control the microbe. Indeed, the most effective function of the immune system is to mount a response that eliminates the infectious agent from the body.

**Secondary Responses and Immunologic Memory**

As a consequence of the initial encounter with antigen, the immunized individual develops a state of immunologic memory. If the same (or a closely related) microorganism is encountered again, a secondary response is made. This generally consists of an antibody response that is more rapid, greater in magnitude, and composed of antibodies that bind to the antigen with greater affinity and are more effective in clearing the microbe from the body. A more rapid and more effective T-cell response also ensues. One effect is that an initial infection with a microorganism initiates a state of immunity in which the individual is protected against a second infection. In the majority of situations, protection is provided by high-affinity antibody molecules that rapidly clear the re-introduced microbe. This is the basis of vaccination; the great power of vaccines is illustrated by the elimination of smallpox from the world and by the complete control of polio in the Western world.

**Specificity of immune response**

The immune response is highly specific. Primary immunization with a given microorganism evokes antibodies and T cells that are specific for the antigenic determinants found on that microorganism but that fail to recognize (or recognize only poorly) antigenic determinants expressed by unrelated microbes. Indeed, the range of antigenic specificities that can be discriminated by the immune system is enormous.

**Tolerance to self-antigen**

One of the most important features of the immune system is its ability to discriminate between antigenic determinants expressed on foreign substances, such as pathogenic microbes, and potential antigenic determinants expressed by the tissues of the host. The capacity of the system to ignore host antigens is an active process involving the elimination or inactivation of cells that could recognize self-antigens through a process designated immunologic tolerance.

**Autoimmune Diseases**

Failures in establishing immunologic tolerance or unusual presentations of self-antigens can give rise to tissue-damaging immune responses directed against antigenic determinants on host molecules. These can result in autoimmune diseases. It is now recognized that a range of extremely important diseases are caused by autoimmune responses or have major autoimmune components, including systemic lupus erythematosus, rheumatoid arthritis, insulin-dependent diabetes mellitus, multiple sclerosis, myasthenia gravis, and regional enteritis. Efforts to treat these diseases by modulating the autoimmune response are a major theme of contemporary medicine.

**AIDS: A virus the immune system fails to eliminate**

Immune responses against infectious agents do not always lead to elimination of the pathogen. In some instances, a chronic infection ensues in

which the immune system adopts a variety of strategies to limit damage caused by the organism or by the immune response. One of the most notable infectious diseases in which the immune response generally fails to eliminate the organism is AIDS, caused by the human immuno-deficiency virus (HIV). In this instance, the principal infected cells are those of the immune system itself, leading to an eventual state in which the individual can no longer mount protective immune responses against other microbial pathogens.

## Major Principles of Immunity

The major principles of the immune response are:

1. Elimination of many microbial agents through the nonspecific protective mechanisms of the innate immune system

2. Highly specific recognition of foreign antigens coupled with potent mechanisms for elimination of microbes bearing such antigens

3. A vast universe of distinct antigenic specificities and a comparably vast capacity for the recognition of these antigens

4. The capacity of the system to display immunologic memory

5. Tolerance of self-antigens

### CELLS OF THE IMMUNE SYSTEM AND THEIR SPECIFIC RECEPTORS AND PRODUCTS

The immune system consists of a wide range of distinct cell types, each with important roles. The lymphocytes occupy central stage because they are the cells that determine the specificity of immunity. It is their response that orchestrates the effector limbs of the immune system. Cells that interact with lymphocytes play critical parts both in the presentation of antigen and in the mediation of immunologic functions. These cells include dendritic cells, and the closely related Langerhans cells, Monocyte /macrophages, natural killer (NK) cells, neutrophils, mast cells, basophils, and eosinophils. In addition, a series of specialized epithelial and stromal cells provide the anatomic environment in which immunity occurs, often by secreting critical factors that regulate migration, growth, and/or gene activation in cells of the immune system. Such cells also play direct roles in the induction and effector phases of the response.

The cells of the immune system are found in peripheral organized tissues, such as the spleen, lymph nodes, Peyer's patches of the intestine, and tonsils, where primary immune responses generally occur. A substantial portion of the lymphocytes and macrophages comprise a re-circulating pool of cells found in the blood and lymph, as well as in the lymph nodes and spleen, providing the means to deliver immuno-competent cells to sites where they are needed and to allow immunity that is initiated locally to become generalized. Activated lymphocytes acquire the capacity to enter non-lymphoid tissues where they can express effector functions and eradicate local infections.

Some memory lymphocytes are "on patrol" in the tissues, scanning for reintroduction of their specific antigens. Lymphocytes are also found in the central lymphoid organs, thymus, and bone marrow, where they

undergo the developmental steps that equip them to mediate the responses of the mature immune system.

Individual lymphocytes are specialized in that they are committed to respond to a limited set of structurally related antigens. This commitment exists before the first contact of the immune system with a given antigen. It is expressed by the presence on the lymphocyte's surface membrane of receptors specific for determinants (epitopes) of the antigen. Each lymphocyte possesses a population of receptors, all of which have identical combining sites. One set, or clone, of lymphocytes differs from another clone in the structure of the combining region of its receptors and thus in the epitopes that it can recognize. The ability of an organism to respond to virtually any non-self antigen is achieved by the existence of a very large number of different lymphocytes, each bearing receptors specific for a distinct epitope. As a consequence, lymphocytes are an enormously heterogeneous group of cells. Based on reasonable assumptions as to the range of diversity that can be created in the genes encoding antigen-specific receptors, it seems virtually certain that the number of distinct combining sites on lymphocyte receptors of an adult human can be measured in the millions.

Lymphocytes differ from each other not only in the specificity of their receptors but also in their functions. There are two broad classes of lymphocytes: the B-lymphocytes, which are precursors of antibody-secreting cells, and the T-(thymus-derived) lymphocytes. T-lymphocytes express important helper functions, such as the ability to aid in the development of specific types of immune responses, including the production of antibody by B cells and the increase in the microbicidal activity of macrophages. Other T-lymphocytes are involved in direct effector functions, such as the lysis of virus-infected cells or certain neoplastic cells. Specialized T-lymphocytes (regulatory T cells) have the capacity to suppress specific immune responses.

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# Immunization Status of Infants in a Remote District of Kashmir

*Bashir Gaash, Rohini Bhan, Shabnam Bashir*

Immunization is a simple and cost-effective measure for preventing death and disability in infants and young children. Yet, despite the international emphasis, universal immunization has not been attained in most of the developing countries.(1) The underlying reasons for this failure have generally been non-availability of vaccine, breakdown of cold-chain, complacency of the staff, socio-economic disorder, or an unfavourable public attitude.

India, too, is according high priority to immunization, however, results remain far from satisfactory and regional imbalances are quite sharp.(2) . Jammu & Kashmir State generally, and its backward areas especially, are considered poor performers. However, no authentic data is available to substantiate or refute this belief. Kargil, being the most backward district of the State, was therefore taken up for an appraisal survey to determine the current status of immunization among the infants .

**Subjects, methodology & Setting:**

Kargil, located 203 km north of Srinagar and situated at an altitude of 7000 m above the sea-level, is very sparsely populated. The land is hilly, terrain very difficult, climate chilly, & weather inclement, and the only road linking it to rest of the world remains closed for more than 8 months a year. The adverse geo-climatic features, along with rampant illiteracy, conservatism, and frequent cross-border shelling, make the district a highly vulnerable area amenable to disruption of health services. In the current survey, which covered the 3 most populated blocks (Kargil, Sankoo & Drass), a total of 538 children between the ages of 12 and 23 months were evaluated for their immunization status.

**Results** show that only 65% of infants received full primary immunization, with rural areas fairing worse (62%) than the urban areas (72%). Coverage rates were similar in boys and girls. Antigen-wise, the highest coverage (92.5%) was seen for BCG, and the poorest (65%) for measles vaccine. The attrition from the first to third dose of DPT & OPV (from 89% to 83%) was remarkable; drop-out rates from the 3$^{rd}$ priming dose (83%) to booster (31%) at 16-24 months were far more steep. Some 7.5% of the infants remained completely un-immunized, while 28.5% were only partially primed. (Table I).

**Discussion**:

In the year 1998-99, the 2$^{nd}$ National Family Health Survey (NFHS-II) (3) was undertaken by the International Institute for Population Sciences, Mumbai, to provide information on the immunization status of infants. However, Kargil had been left out of the J & K State.

Our study showed a higher coverage in Kargil than the State-average found in the NFHS-II and other surveys (3,4,5)(Table II). The coverage for BCG, DPT $_3$ &

$OPV_3$ was far higher in Kargil than what the Rapid Household Survey (MOHFW, Government of India, 1999) found in District Baramulla. By inference, thus, performance in Kargil - *the most backward district of the State* - was higher than the districts with a better geo-demographic and socio-economic background. This suggests that, educational backwardness, poverty, and conservatism, ─ the hallmarks of Kargil ─ don't necessarily keep populations from taking the advantages of the available health care facilities. A comparative analysis of the official immunization statistics of Kargil & Leh in 1998-99, too, revealed a much poorer performance in Leh despite a better topography, more income, and higher literacy.

The fact that immunization coverage among infants from socio-economically better families and of highly educated mothers was lower than in their less privileged counterparts suggests negative attitude of educated mothers towards immunization of their infants.

Despite a higher comparative performance revealed in our study, the pattern of steadily decreasing proportion of infants from the 1st priming to 3rd dose, and a further remarkable attrition for booster dose at 16-24 months (Fig 2), was similar to that found elsewhere in the State. This indicates that the enthusiasm of the parents generated with the birth of the child is not maintained, which, in turn, suggests lack of sustained health education activity by the concerned health workers.

Comparative analysis of the evaluated figures reveals that the actual coverage for all antigens was lower than that conveyed officially. The NFHS-II also found a consistent overestimation in the official statistics of the J & K State (6). Gross exaggeration of immunization coverage in official data is found even at the national level (Table IV), as has been pointed out by the WHO-Unicef evaluation studies. This suggests that policy-makers & planners should not rely heavily on the officially-quoted figures, and that well-designed evaluation studies by independent agencies may be required annually to assess the actual coverage.

**Table I. Proportion of 12-23 month old children found to be actually covered* in various evaluation studies.**

| Name of the Survey | Total sample | Rural | Urban | Male | Female |
|---|---|---|---|---|---|
| | % | % | % | % | % |
| Current Study (Kargil) | 65.1 | 62.1 | 72.2 | 66.3 | 63.0 |
| MICS¤ (J&K) | 54.9 | 50.7 | 72.9 | 58.4 | 50.3 |
| NFHS-II€ (J&K) | 56.7 | 53.4 | 73.1 | 61.4 | 50.0 |
| RHS¥ (J&K) | 41.8 | - | - | 65.7 | 60.8 |

* Children who had received BCG, 3 doses of DPT & OPV each, & measles vaccine were considered to be fully immunized..

¤ **MICS**: *Multiple Indicator Cluster Survey, 2000. Department of Women & Child Development, Govt of India & Unicef.*

€ **NFHS-II**: *National Family Health Survey, 1998-99. International Institute for Population Sciences, Mumbai & ORC USA.*

¥ **RHS**: *Rapid Household Survey, Phase II, 1999. Ministry of Health & Family Welfare, Govt of India.*

**Table II. Immunization Coverage by Vaccine (Percent of Children Aged 12-23 months covered)**
***Comparison of State-level Evaluation Figures with Those in Kargil Study***

| Vaccine | Current Study | MICS | NFHS-II | RHS |
|---|---|---|---|---|
| Year of Survey | 2000-01 | 1999 | 1998-99 | 1998-99 |
| *Geo-demographic area represented* | *Kargil District* | *J & K* | *J&K* | *J & K* |
| BCG | 92.6 | 89.6 | 85.7 | 84.7 |
| DPT1 | 88.9 | 83.7 | 85.7 | - |
| DPT2 | 84.0 | 78.7 | 83.6 | - |
| DPT3 | 83.0 | 68.4 | 72.3 | 63.4 |
| OPV1 | 88.9 | 93.7 | 88.3 | - |
| OPV2 | 84.0 | 91.6 | 85.4 | - |
| OPV3 | 83.0 | 82.0 | 74.3 | 61.3 |
| Measles | 65.1 | 65.5 | 68.9 | 63.2 |
| All Vaccines | 65.1 | 54.9 | 56.7 | 41.8 |
| None | 7.4 | 6.3 | 10.4 | 5.0 |

**Table III: Vaccine Coverage in India (Percent Achievement of Targets):**
***Comparison of official and evaluation figures(1999 & 2000)***

| Vaccine | Official figures | Evaluation figures | Official figures | Evaluation figures |
|---|---|---|---|---|
| | *(1999)* | *MICS (1999)* | *(2000 - 01)* | *WHO-Unicef Evaluation Study (2001)* |
| BCG | 99 | 68 | 99 | 73 |
| DPT1 | - | 64 | - | - |
| DPT3 | 93 | 47 | 94 | 64 |
| Pol3 | 93 | 59 | 89 | 70 |
| Measles Vaccine | 89 | 50 | 89 | 56 |

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# Special Supplement

## *Drug Use in Renal impairment*

# Drug Use in Renal impairment

Reduced renal function may cause problems with drug therapy for the following reasons:

1. The failure to excrete a drug or its metabolites may produce toxicity.
2. The sensitivity to some drugs is increased even if the renal elimination is unimpaired.
3. The tolerance to adverse effects may be impaired.
4. The efficacy of some drugs may diminish.

The dosage of many drugs must be adjusted in patients with renal impairment to avoid adverse reactions and to ensure efficacy. The level of renal function below which the dose of a drug must be reduced depends on how toxic it is and whether it is eliminated entirely by renal excretion or is partly metabolized to inactive metabolites.

In general, all patients with renal impairment are given a loading dose which is the same as the usual dose for a patient with normal renal function. Maintenance doses are adjusted to the clinical situation. The maintenance dose of a drug can be reduced either by reducing the individual dose leaving the normal interval between doses unchanged or by increasing the interval between doses without changing the dose. The interval extension method may provide the benefits of convenience and decreased cost, while the dose reduction method provides more constant plasma concentration.

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In the following table drugs are listed in alphabetical order. The table includes only drugs for which specific information is available. Many drugs should be used

with caution in renal impairment but no specific advice on dose adjustment is available; it is therefore important to also refer to the individual drug entries. The recommendations are given for various levels of renal function as estimated by the glomerular filtration rate (GFR), usually measured by the creatinine clearance. The serum-creatinine concentration can be used instead as a measure of renal function but it is only a rough guide unless corrected for age, sex and weight by special nomograms.

***Renal impairment is usually divided into three grades***:

**mild** - GFR 20-50 ml/minute or approximate serum creatinine 150-300 micromol/litre

**moderate** - GFR 10-20 ml/minute or serum creatinine 300-700 micromol/litre

**severe** - GFR <10 ml/minute or serum creatinine >700 micromol/litre

When using the dosage guidelines the following must be considered:

- Drug prescribing should be kept to a minimum.
- Nephrotoxic drugs should, if possible, be avoided in all patients with renal disease because the nephrotoxicity is more likely to be serious.
- It is advisable to determine renal function not only before but also during the period of treatment and adjust the maintenance dose as necessary.
- Renal function (GFR, creatinine clearance) declines with age so that by the age of 80, it is half that in healthy young subjects. When prescribing for the elderly, assume at least a mild degree of renal impairment.
- Uraemic patients should be observed carefully for unexpected drug toxicity. In these patients the complexity of clinical status as well as other variables for example altered absorption, protein binding or metabolism, or liver function, and other drug therapy precludes use of fixed drug dosage and an individualized approach is required.

**Table of drugs to be avoided or used with caution in renal impairment**

| Drug | Degree of impairment | Comment |
|---|---|---|
| Abacavir | Severe | Avoid |
| Acetazolamide | Mild | Avoid; metabolic acidosis |
| Acetylsalicylic acid | Severe | Avoid; sodium and water retention; deterioration in renal function; increased risk of gastrointestinal bleeding |
| Aciclovir | Mild<br>Moderate to severe | Reduce intravenous dose<br>Reduce dose |
| Alcuronium | Severe | Prolonged duration of block |
| Alcuronium | Severe | Prolonged duration of block |
| Allopurinol | Moderate<br><br>Severe | 100-200 mg daily; increased toxicity; rashes<br><br>100 mg on alternate days (maximum 100 mg daily) |
| Aluminium hydroxide | Severe | Aluminium is absorbed and may accumulate.<br>NOTE. Absorption of aluminium from aluminium salts is increased by citrates which are contained in many effervescent<br>preparations (such as effervescent analgesics) |
| Amiloride | Mild<br><br><br><br>Moderate | Monitor plasma potassium;<br>high risk of hyperkalaemia in renal impairment;<br>amiloride excreted by kidney unchanged<br>Avoid |
| Amoxicillin | Severe | Reduce dose; rashes more common |

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| Amoxicillin + Clavulanic acid | Moderate to severe | Reduce dose |
| Amphotericin | Mild | Use only if no alternative;<br>nephrotoxicity may be reduced with use of complexes |
| Ampicillin | Severe | Reduce dose; rashes more common |
| Atenolol | Moderate<br><br>Severe | Reduce dose (excreted unchanged)<br><br>Start with small dose;<br>higher plasma concentrations after oral administration;<br>may reduce renal blood flow and dversely affect renal function |
| Azathioprine | Severe | Reduce dose |
| Benzathine benzylpenicillin | Severe | Neurotoxicity-<br>high doses may cause convulsions |
| Benzylpenicillin | Severe | Maximum 6 g daily;<br>neurotoxicity-<br>high doses may cause convulsions |
| Bleomycin | Moderate | Reduce dose |
| Captopril | Mild to moderate | Use with caution and monitor response;<br>initial dose 12.5 mg twice daily.<br>Hyperkalaemia and other adverse effects more common |
| Carbamazepine | | Manufacturer advises caution |
| Ceftazidime | Mild | Reduce dose |
| Ceftriaxone | Severe | Reduce dose;<br>also monitor plasma concentration if both severe renal and hepatic impairment |
| Chlorambucil | Moderate | Use with caution and monitor response;<br>increased risk of myelo-suppression |

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| Chloramphenicol | Severe | Avoid unless no alternative; dose-related depression of aematopoiesis |
| Chloroquine | Mild to moderate<br><br>Severe | Reduce dose<br><br>Avoid |
| Chlorphenamine | Severe | Dose reduction may be required |
| Chlorpromazine | Severe | Start with small doses; increased cerebral sensitivity |
| Ciclosporin | | Monitor kidney function- dose dependent increase in serum creatinine and urea during first few weeks may necessitate dose reduction (exclude rejection if kidney transplant) |
| Cimetidine | Mild to moderate<br><br>Severe | 600-800 mg daily; occasional risk of confusion<br><br>400 mg daily |
| Ciprofloxacin | Moderate | Use half normal dose |
| Cisplatin | Mild | Avoid if possible; nephrotoxic and neurotoxic |
| Clindamycin | | Plasma half-life prolonged- may need dose reduction |
| Clonazepam | Severe | Start with small doses; increased cerebral |
| Cloxacillin | Severe | Reduce dose |
| Codeine | Moderate to severe | Reduce dose or avoid; increased and prolonged effect; increased cerebral sensitivity |
| Colchicine | Moderate | Reduce dose |

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| | Severe | Avoid or reduce dose if no alternative |
| Cyclophosphamide | | Reduce dose |
| Dacarbazine | Mild to moderate<br><br>Severe | Dose reduction may be required<br><br>Avoid |
| Daunorubicin | Mild to moderate | Reduce Dose |
| Deferoxamine | | Metal complexes excreted by kidneys (in severe renal impairment dialysis increases rate of elimination) |
| Desmopressin | | Antidiuretic effect may be reduced |
| Dextromethorphan | Moderate to severe | Reduce dose or avoid; increased and prolonged effect; increased cerebral sensitivity |
| Diatrizoates | Mild | Reduce dose and avoid dehydration; nephrotoxic |
| Diazepam | Severe | Start with small doses; increased cerebral sensitivity literature |
| Didanosine | Mild | Reduce dose; consult manufacturer's |
| Diethylcarbamazine | Moderate to severe | Reduce dose; plasma half life prolonged and urinary excretion considerably reduced |
| Digoxin | Mild | Reduce dose; toxicity increased by electrolyte disturbances |
| Dimercaprol | | Discontinue or use with extreme caution if impairment develops during treatment |

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| Eflornithine | | Reduce dose |
| Ephedrine | Severe | Avoid;<br>increased CNS toxicity |
| Ergometrine | Severe | Manufacturer advises avoid |
| Ergotamine | Moderate | Avoid;<br>nausea and vomiting;<br>risk of renal vasoconstriction |
| Erythromycin | Severe | Maximum 1.5 g daily (ototoxicity) |
| Ethambutol | Mild | Reduce dose;<br>if creatinine clearance less than 30 ml / minute monitor plasma-ethambutol concentration;<br>optic nerve damage |
| Fluconazole | Mild to moderate | Usual initial dose then halve subsequent doses |
| Flucytosine | | Reduce dose and monitor plasma-flucytosine concentration-consult manufacturer' s literature |
| Fluphenazine | Severe | Start with small doses;<br>increased cerebral sensitivity |
| Furosemide | Moderate | May need high doses;<br>deafness may follow rapid i/v injection |
| Gentamicin | Mild | Reduce dose; monitor plasma concentrations; |
| Glibenclamide | Severe | Avoid |
| Haloperidol | Severe | Start with small doses;<br>increased cerebral sensitivity |
| Heparin | Severe | Risk of bleeding increased |

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| Hydralazine | | Reduce dose if creatinine clearance less than 30 ml/minute |
| Hydrochlorothiazide | Moderate | Avoid; ineffective |
| Ibuprofen | Mild<br><br>Moderate to severe | Use lowest effective dose and monitor renal function;<br>sodium and water retention;<br>deterioration in renal function possibly leading to renal failure<br><br>Avoid |
| Imipenem + Cilastatin<br><br>Reduce dose | Mild | Reduce dose |
| Insulin | Severe | May need dose reduction;<br>Insulin requirements fall;<br>compensatory response to hypoglycaemia is impaired |
| Iohexol | Moderate to severe | Increased risk of nephrotoxicity;<br>Avoid dehydration |
| Iopanoic acid | Mild to moderate<br>Severe | Maximum 3 g<br><br>Avoid |
| Isoniazid | Severe | Maximum 200 mg daily;<br>Peripheral neuropathy |
| Lamivudine | Mild | Reduce dose;<br>consult manufacturer's literature |
| Lithium | Mild<br><br>Moderate | Avoid if possible or reduce dose and monitor<br>plasma concentration carefully<br><br>Avoid |
| Lopinavir with Ritonavir | | Avoid oral solution due to propylene glycol<br>content;<br>use capsules with caution in severe impairment |
| Magnesium hydroxide | Moderate | Avoid or reduce dose;<br>increased risk of toxicity |

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| Magnesium sulfate | Moderate | Avoid or reduce dose; increased risk of toxicity |
| Mannitol | | Avoid unless test dose produces diuretic response |
| Meglumine iotroxate | Moderate to severe | Increased risk of nephrotoxicity; Avoid dehydration |
| Mercaptopurine | Moderate | Reduce dose |
| Metformin | Mild | Avoid; increased risk of lactic acidosis |
| Methotrexate | Mild<br><br>Moderate | Reduce dose; accumulates; nephrotoxic<br><br>Avoid |
| Methyldopa | Moderate | Start with small dose; increased sensitivity to hypotensive and sedative effect |
| Metoclopramide | Severe | Avoid or use small dose; increased risk of extrapyramidal reactions |
| Morphine | Moderate to severe | Reduce dose or avoid; increased and prolonged effect; increased cerebral sensitivity |
| Nalidixic acid | Moderate to severe | Use half normal dose; ineffective in renal failure because concentration in urine is inadequate |
| Nelfinavir | | No information available- Manufacturer advises caution |
| Neostigmine | Moderate | May need dose reduction |
| Nevirapine | | No information available- Manufacturer advises avoid |
| Nitrofurantoin | Mild | Avoid; peripheral neuropathy; ineffective because of inadequate urine concentrations |
| Ofloxacin | Mild | Usual initial dose, then use half normal dose |

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| | Moderate | Usual initial dose, then 100 mg every 24 hours |
| Penicillamine | Mild | Avoid if possible or reduce dose; nephrotoxic |
| Pentamidine isetionate | Mild | Reduce dose; consult manufacturer' s literature |
| Pentavalent antimony compounds | Moderate<br>Severe | Increased adverse effects<br>Avoid |
| Pethidine | Moderate to severe | Reduce dose or avoid; increased and prolonged effect; increased cerebral sensitivity |
| Phenobarbital | Severe | Avoid large doses |
| Polyvidone-iodine | Severe | Avoid regular application to inflamed or broken mucosa |
| Potassium chloride | Moderate | Avoid routine use; high risk of hyperkalaemia |
| Prazosin | Moderate to severe | Initially 500 micrograms daily; increased with caution |
| Procainamide | Mild | Avoid or reduce dose |
| Procaine benzylpenicillin | Severe | Neurotoxicity- high doses may cause convulsions |
| Procarbazine | Severe | Avoid |
| Proguanil > > | Mild<br>Moderate<br>Severe | 100 mg once daily<br>50 mg on alternate days<br>50 mg once weekly; increased risk of haematological toxicity |

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| Propranolol | Severe | Start with small dose;<br>higher plasma concentrations after oral administration;<br>may reduce renal blood flow and adversely affect<br>renal function in severe impairment |
| Propylthiouracil | Mild to moderate<br><br>Severe | Use three-quarters normal dose<br><br>Use half normal dose |
| Pyridostigmine | Moderate | Reduce dose; excreted by kidney |
| Quinine | | Reduce parenteral maintenance dose for malaria treatment |
| Saquinavir | Severe | Dose adjustment possibly required |
| Sodium chloride | Severe | Avoid |
| Sodium hydrogen carbonate | Severe | Avoid;<br>specialized role in some forms of renal disease |
| Sodium nitroprusside | Moderate | Avoid prolonged use |
| Spironolactone | Mild<br><br>Moderate | Monitor plasma K+ ;<br>high risk of hyperkalaemia in renal impairment<br><br>Avoid |
| Stavudine | Mild<br><br>Moderate to severe | 20 mg twice daily (15 mg if body weight less than 60 kg)<br><br>20 mg once daily (15 mg if body weight less than 60 kg) |
| Streptomycin | Mild | Reduce dose; monitor plasma concentrations |
| Sulfadiazine | Severe | Avoid; high risk of crystalluria |
| Sulfamethoxazole + | Mild | Use half normal dose if creatinine |

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| Trimethoprim | | clearance 15-30 ml/minute;<br>avoid if creatinine clearance less than 15 ml/minute and plasma-sulfamethoxazole concentration cannot be monitored |
| Sulfasalazine | Moderate<br><br>Severe | Risk of toxicity including crystalluria<br>- ensure high fluid intake<br><br>Avoid |
| Trimethoprim | Moderate | Reduce dose |
| Valproic acid | Mild to moderate<br>Severe | Reduce dose<br><br>Alter dosage according to free serum valproic acid concentration |
| Vancomycin | Mild | Reduce dose-<br>monitor plasma-vancomycin concentration and renal function regularly |
| Vecuronium | Severe | Reduce dose;<br>duration of block possibly prolonged |
| Warfarin | Severe | Avoid |
| Zidovudine | Severe | Reduce dose;<br>manufacturer advises oral dose of 300-400 mg daily |