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PRESIDENT WRITES

Dear Fellows and Members,

Audit is a necessary inconvenience for evaluating performance and planning. Medical audit is therefore most essential in the delivery of quality health care. Despite the above medical audits are often given a quite go by amongst our midst. We need to halt this trend and make it an essential activity of all our institutions. Earlier medical audits were often post mortem affairs, however we can extend the concept onto all activities of health care. Audits sometimes get bogged down in the trivial, it is in such circumstances that the maturity of the chairperson helps to maintain the focus so that the obtained findings can be translated into reliable and quality patient care. Surely, the medico legal angle is to be kept in mind; but this should never stand in the way of assuring better treatment for our patients.



Let me extend all fellows and member's a prosperous and healthy 2005.

Dr. K. Jagadeesan,
President, IMSA

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All fellows and members of IMSA can have **access** to the site and get information about its objectives, benefits to the fellows/members, chapters and their activities including seminars, refresher courses, rural CME's etc. and also IMSACON - a regular annual event of international standard; *application form for enrollment as fellow/member can also be downloaded.* Fellows - members and even non fellows - members can have access to full text in the quarterly journal - JIMSA from July-Sept. 2003 onwards by putting their E-mail address under '**user name**' and using the **password 'UserJimsa'**.



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FROM EDITOR'S DESK

Dear Colleagues

The present issue of JIMSA covers wide ranging topics of day to day interest. *Editorial review* on 'skin manifestation of sexually transmitted diseases' is based on the original article published in this issue, covering various cutaneous features of HIV. Recent estimates reveal that India has the country with second largest population of HIV-infected subjects and physicians across the country are now confronting the varied manifestations of this devastating infection more frequently than ever before. This editorial is brilliantly written by Dr. J.K. Maniar; I am extremely grateful to him for this pains-taking effort. Published in this issue are two update articles on 'free radicals – a relatively new concept' in the genesis of disease and associated complications, is an exhaustive review of the latest published work by Prof. P. Nigam; another review of the 'vaccine preventable diseases' by Prof. A.P. Dubey deals with the common childhood infections-old and new; some of these have not only been successfully prevented by timely vaccination but there are others which have been eradicated or are on the verge of complete eradication; both the articles will be of immense interest to the clinicians. A series of interesting original articles and case reports, appearing in this issue come from different disciplines of Medicine; under the column *update in therapy* some of currently used drugs, in the practical treatment of a common clinical disorder 'osteoporosis', has been elaborately dealt with by Prof. Kamlesh Kohli. Also included in this issue is a **symposium** on '**Advances in neonatology**' which has been well planned by **Dr. Satish Saluja** – guest editor. The subjects selected for the symposium have been contributed by experts in the field of neonatology & pediatrics. and will surely provide useful information to the readers of JIMSA. I am extremely grateful to Dr. Satish Saluja and other contributors to the symposium.

JIMSA now has its own website www.jimsaonline.com for the last one year; fellows/members and even non fellows and non members can have free access to the full text of the articles from July-Sept. 2003 onwards by using *password* – 'userjimsa'. I request all the readers to visit the website as frequently as possible and send their suggestions for improvement. You may also spread message about the JIMSA website to your colleagues & friends.

I take this opportunity to thank the members of editorial /advisory boards and other peer reviewer, for their help at different stages of this publication. I also extend my grateful thanks to various pharmaceutical firms for financial help. **Wishing all the readers a very happy and prosperous Year 2005.**

P.D. Gulati



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Skin as a Window to Sexually Transmitted Disease

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Sexually transmitted diseases (SD) usually present with lesions affecting the external genitalia. The common presentations of sexually transmitted infections (STI) are genital ulcer disease, urethral discharge, genital growth or a swelling in the groin or the scrotum. Women can present with vaginal discharge and lower abdominal or lumbar pain. However, the extragenital skin may also be affected directly or indirectly. Therefore, a detailed cutaneous examination may give valuable clues to the diagnosis, as well as of high-risk behaviour. The cutaneous manifestations of STIs may be classified as : (i) Extragenital lesions of STIs. (ii) Surrogate markers of sexually acquired infection. (iii) Surrogate markers of high-risk behaviour and human immunodeficiency virus (HIV) infection.

Extragenital lesions of STIs :

Nearly all the bacterial and viral pathogens that cause STIs can have extragenital manifestations. The important presentations of each will be dealt with briefly -

Syphilis^{1,2} : The natural history of syphilis can be divided into primary, secondary and tertiary stages. Each stage can involve the extragenital skin and a high index of suspicion is required to arrive at the diagnosis.

Primary syphilis¹ : After an incubation period of 9-90 days, the primary lesion or the chancre develops at the site of inoculation of *Treponema pallidum*. The extragenital sites of occurrence of chancre are the lips, buccal cavity, tongue, tonsil, pharynx and rarely, the finger. The typical chancre is a single, painless, well-defined, indurated ulcer with a smooth, flat, dull-red surface which may be covered with a thin yellow or brown crust. On pressure, serous fluid may ooze. Within a few days, there is discrete and rubbery regional lymph node enlargement. The primary lesion heals within 3-8 weeks leaving a thin, atrophic scar, even without treatment.

Secondary syphilis³ : Skin lesion (syphilides) are seen in over 80% of patients with secondary syphilis. Mucocutaneous lesions are very infectious. The skin eruptions are polymorphic and several types may appear simultaneously during the course. Although secondary syphilides are considered to be asymptomatic, over 40% of patients complain of pruritus². There are various clinical subtypes-

Macular syphilide (roseola) : Rose-pink, faint, about 1cm evanescent macules are the earliest manifestations. However, because of their faint colour, indistinct margins and the dark skin color of our race, they are easily overlooked. The lesions last for a few days only.

Papular and papulosquamous syphilide : These are commonest lesions appearing as firm, symmetrical, dull-red lesions, variable

in size, present especially over the flexor aspects of the body. Occasionally, a larger papule may be surrounded by smaller lesions. This is called the 'corymbose' syphilide. As the lesion ages, scaling may appear. The sites affected may be -

Face : The chin, nasolabial folds and the margins of the scalp may be affected. The lesions on the forehead parallel to the hairline are called the 'corona veneris'.

Scalp : Scalp involvement presents as alopecia. This may be the classic 'moth-eaten' type, or the nonspecific reactional 'telogen effluvium'.

Palms and soles : These sites show the classic 'copper macules'. The papular lesions on these sites do not project above the surface of the skin, probably because of its thickness. They appear as firm, dull-red lesions with a collarette of scale.

Condylomata lata - Hypertrophied, moist, flat-topped plaques with the surface often eroded are the classical lesions seen in moist and angulated areas like the groin, vulva and perianal region. However, the axillae, nasolabial folds, and the angles of the mouth may be similarly affected (split papules). The exudate in such lesions is teeming with spirochaetes.

Pustular syphilide⁴ : Rarely, necrosis of the upper dermis and epidermis, as a result of the endarteritis cause pustulation. This variant is seen in immunocompromised patients and heals with scarring.

Malignant or ulcerative syphilide⁵ : This severe form of syphilide presents with well-defined ulcerations. The patient presents with fever, malaise, joint pains and a papulo-pustular eruption that soon becomes necrotic, resulting in the sharply marginated ulcers with a thick, rupioid crust. This is also called 'lues maligna'.

Mucosal lesions : These are found in about 30% of patients. The characteristic lesion is the 'mucous patch'. These are round or oval, grey areas surrounded by a narrow zone of erythema. Shedding of the grey, necrotic membrane reveals superficial ulceration. If many such lesions coalesce, a 'snail-track ulcer' may result.

Pigmentary changes : the syphilides heal without any residual inflammatory signs. However, areas of mild pigmentation may persist for months. In dark-haired women, depigmentation of the neck that lasts for life can be observed. This is called 'leukoderma colli'.

Tertiary Syphilis^{1,2} : This stage is characterized by 'gumma' formation. Gummata are superficial or deep destructive granulomatous lesions which can involve the skin, the subcutaneous tissue and bone. They tend to occur on the face, neck and distal extremities at the sites of trauma. They begin as asymptomatic cutaneous or subcutaneous nodules that ulcerate and coalesce to form large irregular plaques with 'punched-out' edges and arcuate, irregular borders. The floor of the ulcer shows the typical 'wash-leather' appearance. Healing occurs with atrophy leaving behind hyperpigmented scars.

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Diagnosis : This is made by demonstration of the treponemes by dark-field microscopy, and more commonly by serologic tests, namely the VDRL and the TPHA.

Treatment : Penicillin is the treatment of choice. The dosage differs according to the stage of the disease.

Chancroid^{6,7} : This is caused by *Haemophilus ducreyi*. The incubation period varies from 24 hours to 5 days. The lesion begins as a papule, which pustulates and ulcerates to form a painful, tender, shallow ulcer with ragged, undermined edges. It bleeds readily on touch. Auto-inoculation is common and multiple lesions may be present in a small area. Painful and tender local lymph nodes that may form a fluctuant 'bubo' are characteristic. Extragenital disease is rare, as is dissemination. Diagnosis is confirmed by microscopy, which shows Gram-negative bacilli with a typical 'rail-road' or 'school of fish' arrangement. Azithromycin, ceftriaxone and ciprofloxacin are the drugs of choice.

Donovanosis^{6,8} : This is caused by *Calymatobacterium granulomatis*. The incubation period is unknown. It may vary from 3 days to 6 months. Extragenital disease has been described, usually secondary to chronic genital disease. The earliest lesion is variable. It may begin as a papule, a pruritic nodule or most commonly, an ulcer. The ulcer is painless, of variable size, soft, velvety, with bright red granulation tissue and a serpiginous edge. It bleeds readily when abraded. The disease is slowly progressive and the mean duration is 18 months. Fibrosis is seen in chronic cases, especially in females. The diagnosis is confirmed by demonstration of the bipolar staining "closed safety pin" organism in tissue smears by Giemsa, Leishman or Wright's stain. Doxycycline, azithromycin, fluoroquinolones, erythromycin, cotrimoxazole or ceftriaxone are recommended for treatment.

Lymphogranuloma venereum (LGV)⁹ : This is caused by *Chlamydia trachomatis*, serovars L1, L2 and L3. The incubation period is 3-12 days and the primary lesion is an evanescent herpetiform papule that is self-limiting. This is followed by the 'inguinal syndrome' and the 'genito-ano-rectal syndrome'. Regional lymphadenopathy, painful, tender and matted due to periadenitis leading to the formation of fluctuant 'pseudobuboes', is seen after 1-6 weeks. Untreated the disease lasts for 6-8 weeks and may resolve completely. Approximately 70% affected individuals show lymphatic obstruction and intermittent recurrences. Extragenital disease is rare, although oral lesions are known to occur. There are a number of uncommon associated skin lesions. Erythema nodosum (EN) is seen in 10% of women and 2% of men affected by the disease. Erythema multiforme (EM) has also been described. Rarely, a photosensitive eruption has also been described in affected individuals. Diagnosis is confirmed by demonstration of the organism in culture on cycloheximide-treated McCoy cell lines, and by serologic tests such as the complement fixation test (LGVCF) and the micro-immunofluorescence test (MIF). Doxycycline, erythromycin and aminoglycosides form the mainstay of treatment.

Gonorrhoea^{10,11} : This is caused by the Gram-negative intracellular diplococcus (GNID), *Neisseria gonorrhoeae*. The incubation period varies from 24-72 hours, and the commonest presentation is a painful urethral or genital discharge. Dissemination is an uncommon complication occurring in less than 1% cases, especially in women with asymptomatic anogenital infection. The clinical manifestations are fever, rash and arthralgia/arthritis. Skin involvement is seen in 90% patients. The lesions begin as erythematous macules and may take two forms¹¹-hemorrhagic

infarcts, or vesiculopapular lesions on an erythematous base. The lesions appear in crops, and are asymmetrically distributed mainly on the extremities around the affected joints. The organism may be detected by Gram stain or direct immunofluorescence from the skin lesion. Blood culture is usually negative, but synovial fluid gives positive results in 50%. EM and EN have also been described in these patients. Treatment consists of intravenous cephalosporins, quinolones or spectinomycin in the initial stage, after which oral agents may be continued.

Herpes simplex virus (HSV) infection¹²: This is caused by the herpes simplex viruses, 1 and 2 (HSV-1 & -2). The incubation period varies from 3-9 days. HSV-1 usually causes orolabial disease, while HSV-2 can be sexually transmitted and manifests as a genital ulcer disease (GUD). However, orogenital intercourse may cause primary HSV-2 pharyngitis. The virus has been isolated from the pharynx in 11% individuals with primary HSV-2 genital herpes. Primary herpetic pharyngitis presents as a painful sore throat with mild erythema of the pharynx, small vesicles or erosions with red areolae, or diffuse ulceration covered with a white exudates. Dissemination is rare and seen in immunocompromised hosts. The skin lesions are either well-defined vesicles or pustules. Diagnosis is confirmed by Giemsa or Wright-stained Tzanck smear which shows multinucleate giant cells, and by culture on human fibroblast cell lines. Nowadays, ELISA and PCR have simplified the diagnosis. Treatment consists of acyclovir, valaciclovir and famciclovir.

Human papilloma virus (HPV) infection¹³: This manifests as warts, which are cutaneous neoplasms caused by the human papilloma virus. The incubation period may last from weeks to years. There are certain HPV types that are sexually transmitted and cause genital warts; the common being types 6,11,16,18 and 33. Extragenital lesions due to these types are rare. However, orogenital intercourse may result in oral papillomas, which usually affect the soft palate and the frenulum, dorsum or the lateral borders of the tongue, and rarely the lips. The lesion is usually solitary, pink, sessile or pedunculated verrucous swelling. Biopsy is diagnostic and treatment consists of surgery, electrical or chemical.

Scabies¹⁴ : *Sarcoptes scabiei* var *hominis* is the arthropod responsible for this extremely pruritic, primarily cutaneous eruption. The mite can be transmitted from an infested person to another by prolonged physical and sexual contact, or by sharing clothes or bed linen. The incubation period i.e. the time to onset of symptoms is about 4-5 weeks. The patient presents with an intensely itchy eruption affecting classically the web spaces, the wrist, the axillary folds, the waist and the genitalia. Sexually acquired scabies presents with excoriated papules or nodules on the shaft of the penis and the scrotum in males, and on the labia in females. The classical lesion of scabies is the 'burrow', from which the mite can be isolated by scraping the overlying skin. In immunocompromised patients, a severe variant of scabies with a mite load of millions is seen. It is called 'crusted' or 'Norwegian' scabies. Treatment consists of topical miticides such as 25% benzyl benzoate, 1% gamma benzene hexachloride, 0.5% malathion, 6-10% sulfur or 5% permethrin creme. A contact period of 12-36 hours is required depending on the agent used and a repeat application is required after 2 weeks, except if permethrin has been used. Oral ivermectin, as a single dose of 200 microgram/kg, is also recommended.

Phthiriasis^{15,16} : This condition is caused by infestation by the crab louse, *Phthirus pubis*. The arthropod inhabits the pubic, perianal or the axillary region by attachment to the hair by its

claws. Rarely, the eyelashes, the eyebrows and the scalp margins may also be affected. Intense pruritus is the only symptom. Blue spots, called 'maculae coeruleae' produced as a result of an enzyme secreted by the louse during its bite, are the characteristic features. Topical malathion (0.5%), 1% lindane are 1% permethrin creme rinse are the treatments of choice.

Surrogate markers of sexually acquired infection :

Apart from the viruses mentioned above, Hepatitis B Virus (HBV) and Hepatitis C virus (HCV) can also be acquired as a result of sexual transmission. These viruses do not affect the skin directly. There are a number of conditions associated with both infections that have well-defined cutaneous manifestations. Thus, these conditions can be regarded as surrogate markers of STDs.

Hepatitis B virus : HBV infection in humans may be associated with the following conditions :

i. *Polyarteritis nodosa (PAN)*¹⁷ - This is a systemic vasculitis characterized by necrotizing inflammatory lesions and involvement of the skin, the kidneys, the joints and musculoskeletal system, the gut and peripheral nerves. HBV-associated PAN shows features of immune-complex induced disease. Cutaneous involvement is observed in 25-60% of cases. The spectrum of lesions includes palpable purpura, infarctions, ulcerations, livedo reticularis, and ischemic changes of the distal digits. Subcutaneous nodules are infrequent. Limited cutaneous forms of PAN, sometimes associated with myalgias, arthralgias, and peripheral neuropathy, may occur. Only 1% or less of the total population of patients who are HBV positive develop PAN. Clinical symptoms of non-HBV-related and HBV-related PAN are the same except for orchitis, which appears to be more frequent in groups with HBsAg⁺. Diagnosis is confirmed by histopathology which reveals necrotizing arteritis involving arterioles, venules, capillaries, small and medium-sized arteries; and by evidence of p-ANCA in serum. Presence of hepatitis B surface antigen is noted in 7-36%. Corticosteroids and cytotoxic drugs form the mainstay of treatment. In addition, ribavirin and interferon alpha-2b is advocated to enhance clearance of virions.

ii. *Porphyria cutanea tarda (PCT)*¹⁸: Porphyria cutanea tarda is an autosomal dominant disorder caused by the deficiency of the hepatic enzyme Uroporphyrinogen decarboxylase (UROD) and characterized by onset of light-sensitive dermatitis in later adult life, associated with the excretion of large amounts of uroporphyrin in urine. It was so named by Waldenstrom (1937). On areas of skin exposed to sunlight, especially the face, ears and backs of the hands, chronic ulcerating lesions commence as blisters, and the skin may also be mechanically fragile (Grossman et al., 1979). HBV/HCV and HIV infection may precipitate this condition as a consequence of the hepatic inflammation, which further reduces the enzyme levels. Hyperpigmentation and hypertrichosis also occur. Diagnosis is confirmed by examination of urine for uroporphyrins, and skin biopsy which reveals a subepidermal blister with minimal inflammation. Treatment of the viral infection, photoprotection, chloroquine and phlebotomy form the mainstays of treatment.

iii. *Gianotti-Crosti syndrome (Papular Acrodermatitis of Childhood)*¹⁹: Gianotti-crosti syndrome is a benign, self-limited childhood exanthem that occurs in a characteristic distribution. It is rarely associated with systemic findings. The original cases,

described in Italy by Gianotti in 1955, were associated with hepatitis B virus infection. Adult cases are rare. A prodromal upper respiratory infection is reported in 31% of patients. Pruritus accompanies the eruption in 23% of patients. Patients may also have lymphadenopathy and mild constitutional symptoms, such as low grade fever and malaise. The cutaneous eruption is characterized by pale, pink-to-flesh-colored papules localized symmetrically over the extremities, the buttocks, and the face. Over days to weeks, the papules may acquire a smooth-topped, polished, or lichenoid appearance. The eruption lasts longer than 6 weeks in more than 50% of patients, and complete resolution typically takes more than 2 months. In cases caused by hepatitis B virus, anicteric hepatitis is evident by elevations in the levels of hepatic transaminases and antiviral antibodies. Diagnosis and reassurance are usually sufficient. Soothing, anti-itch topical preparations with pramoxine or oral antihistamines may be useful for relief of pruritus.

iv. *Miscellaneous findings* : These include palmar erythema, spider nevi, thin (paper-money) skin and 'caput medusae' on the abdomen.

Hepatitis C virus (HCV)²⁰: Cutaneous symptoms or findings relevant to HCV infection manifest in 20-40% of patients presenting to dermatologists and in a significant percentage (15-20%) of general patients. HCV is suggested and must appear in the differential diagnosis of these patients to avoid missing this important but occult factor in clinical disease in the appropriate setting. Primary causation results from direct infection of HCV in the skin, lymphocytes, dendritic antigen-presenting cells, and blood vessels. An example of this type of disorder is the recent finding of epidermal cells with HCV-RNA particles. Secondary causation occurs when HCV infection manifests in the skin due to epiphenomena resulting from the disruption of immune responses. Leukocytoclastic vasculitis due to cryoglobulinemia is a good example. Tertiary causation of dermatologic manifestations results when the disruption of another organ infected or affected by HCV causes skin manifestations that are nonspecific and typical of skin responses to that organ. Thus the various cutaneous manifestations of HCV infection may be classified as :

Primary manifestation:

These include : a) *Lichen planus* : Intracellular HCV infection of epithelial cells is proven for LP²¹. Lesions are similar to those seen in uninfected individuals. Often, the popular lesions of LP suddenly appear on the volar acral surfaces of the wrists and arms and are pruritic. Oral symptoms are less common. Hair loss in lichen planopilaris, exquisite pruritus of markedly hypertrophic plaques on the lower legs in hypertrophic LP, and painful genital erosions and be presenting findings.

b) *Acral necrolytic erythema*²²: The symptomatology of acral necrolytic erythema includes pruritus associated with recurrent, erythematous, papular eruptions with blisters and erosions on the dorsal aspects of the feet and ankles. Pain is common with variable-sized erosions. Chronic lesions are hyperkeratotic plaques with erosions and peripheral erythema preferring the acral parts of the legs. These lesions provide unusually specific markers for HCV infection.

c) *Leukocytoclastic reactions* (some): This tends to appear as an eruption of palpable purpura on the lower extremities. It may represent an HCV immune complex disease.

Secondary manifestations :

a) *Cryoglobulinemia* : Leukocytoclastic vasculitis occurs with type II mixed cryoglobulinemia in the skin and mucous membranes. These disorders display palpable purpura of the legs (which is worse distally and inferiorly), livedo reticularis, ulcerations, urticaria, symmetric polyarthritis, myalgias, cutis marmorata, and fatigue.

b) *Sialadenitis*: Dry mouth without dry eyes is the most prominent symptom of sialadenitis associated with HCV infection. Sialadenitis is an inflammatory disorder of the salivary, parotid, sublingual, and minor glands. Findings include xerostomia resulting from a chronic lymphocytic infiltrate and destruction of the salivary glands. Sjogren disease and its markers ssRo and ssLa are not found.

c) *Antiphospholipid syndrome* is a serious multisystemic illness resulting from pathologic production of the antiphospholipids anticardiolipin and lupus anticoagulant. Severe coagulopathies in the eye, the brain, the kidney, and large vessels in symptomatology refrable to vascular destruction or bleeding in these organs.

Tertiary manifestations :

Symptoms are those of disease in the specific organs, as follows-

a) *Liver failure in CHC infection* results from cirrhosis, autoimmune hepatitis, cholangitis, and HCC. Symptoms of liver failure are identical to symptoms caused by other conditions, such as ascites, jaundice and liver failure.

b) *Thyroid failure* : Thyroid destruction leading to failure occurs; symptoms of hypothyroidism are noted.

c) *Miscellaneous conditions* : These include Behcet syndrome, canities, prurigo nodularis, polyarteritis nodosa, pruritus, erythema nodosum (EN), erythema multiforme (EM), porphyria cutanea tarda (PCT), erythema dyschromicum perstans, disseminated superficial porokeratosis, generalized granuloma annulare and progressive pigmented purpura (Gougerot-Blum disease).

Surrogate markers of high-risk behaviour and human immunodeficiency virus (HIV) infection :

Certain skin conditions are consistently associated with HIV infection and thereby, high-risk behaviour. These include -

1. *Molluscum contagiosum (MC)*²³: In HIV infection, MC may be widespread and atypical. The lesions may be observed on extragenital sites, such as the face, the neck, and the scalp; or they may show altered morphology and size. Such unusual forms include solitary endophytic, aggregated, inflamed, and giant MCs. MCs mimicking sebaceous nevus of Jadassohn, ecthyma, and giant condylomata acuminata have been reported. Imiquimoid is curative. Topical aciclovir, ablation and curettage may be useful.

2. *Candidiasis*²⁴: Recurrent and persistent mucocutaneous candidiasis is common in HIV-infected patients. Clinically, it manifests as whitish, curd-like exudates on the dorsal or buccal mucosa than can be easily scraped away with a cotton swab, leaving behind a reddish friable surface that may be associated with a burning sensation - the so-called pseudomembranous candidiasis or thrush. Sometimes, only a beefy red, eroded surface can be seen (erosive candidiasis). Chronic atrophic candidiasis, presenting as angular cheilitis and candidal leukoplakia are also noted. The symptoms include burning pain, altered taste sensation and dysphagia, which is more prominent with oesophageal candidiasis.

3. *Oral hairy leukoplakia (OHL)*²⁵: Epstein-Barr (EBV) has been implicated in the pathogenesis of oral hairy leukoplakia (OHL). OHL is characterized by white, filiform, corrugated and feathery plaques on the sides of the tongue and sometimes on the oropharyngeal mucosa, which may be mistaken for candidiasis. It has no malignant potential, but it may be the initial sign of progressive immunosuppression. Treatment is usually not necessary. If symptomatic, the patient may be prescribed systemic aciclovir (3200 mg/d), topical application of 25% podophyllum resin, ganciclovir, or foscarnet.

4. *Varicella zoster virus (VZV) infections*²⁶: Primary varicella infection with visceral dissemination may be seen in HIV-infected adults, but is rare. It may progress to chronic skin involvement. Disseminated and severe varicella infections are observed in advanced AIDS. Atypical manifestations, including hyperkeratotic papules, folliculitis, verrucous lesions, chronic ulcerations, disseminated ecthymatous lesions, and chronic VZV infection mimicking basal cell carcinoma, have also been described. Herpes zoster ophthalmicus may involve the conjunctiva, cornea, anterior chamber, or the retina. Blindness is a complication of zoster retinitis. Recurrent, multidermatomal or disseminated herpes zoster is an AIDS-defining illness. Aciclovir is the treatment of choice for HSV/VZV diseases in these patients. This class of antivirals is activated by viral thymidine kinase. In some disseminated cases, the virus may develop resistance to aciclovir as a result of defective enzyme activity and prolonged/suboptimal dosage. In this scenario, use of other drugs, including cidofovir, foscarnet, and vidarabine, may be necessary.

5. *Kaposi's sarcoma (KS)*²⁷: KS was the first neoplasm reported in HIV disease. It is usually seen in gay and bisexual men, and in women in Africa. The worldwide incidence of KS in patients with AIDS may approach 34%. KS occurs at all stages of HIV disease, and its severity is not strictly correlated with the degree of immunosuppression. KS is believed to be a proliferation of endothelial cells induced by human herpes virus-type 8 (HHV-8), acquired through sexual transmission.

6. *Cytomegalovirus (CMV) infection*²⁴: CMV is also associated with nonspecific cutaneous lesions: generalized bullous toxic epidermal necrolysis-like eruption, purpuric or petechial rash as a result of thrombocytopenia, hyperpigmented indurated cutaneous plaques and bluish-red cutaneous nodules in pediatric patients (blueberry muffin lesions), which indicate extramedullary erythropoiesis.

7. *Seborrhoeic dermatitis (SD)*²⁸: It may be the initial cutaneous manifestation of HIV disease. The prevalence ranges from 7% to 80%. Its presence correlates inversely with decreasing CD4+T cell counts and thus, the incidence and severity in HIV-infected persons is closely related to the stage of HIV infection. Most cases have an ordinary clinical presentation. However, atypical features such as thick greasy scales on the face and the scalp, and involvement of axillae, groins and perianal areas have been described. It may progress to erythroderma. Histologically, distinct features such as parakeratosis, keratinocyte necrosis, lymphoid clusters at the dermoepidermal junction and a perivascular plasma cell infiltrate have been reported. SD occurs with increased frequency in patients with AIDS-associated dementia. A neurohormonal regulatory dysfunction leads to increased sebum production and consequent overgrowth of the yeast, *Malassezia furfur*.

Treatment is difficult. Application of antifungal/

corticosteroid creams separately or in combination, is the treatment of choice. Treatment with coal tar, sulfur, and salicylic acid shampoos and topical tacrolimus may be effective.

9. Pruritic papular eruption (PPE)²⁹: Various descriptions have been proposed for this entity. The etiology is obscure and no definite cause has been detected. PPE may present with different types of rashes. These include -

- *Transient*, maculopapular eruptions occur most frequently on the face and trunk. They usually heal within 4 to 6 weeks. Histologically, a lymphoplasmacytic angitis is repeatedly observed in many cases.

- A more *chronic eruption* has also been described in individuals with AIDS and ARC. It consists of multiple discrete, 2 to 5mm skin-colored papules distributed over the head, neck and upper trunk. Histology is nonspecific. No correlation has been found between disease severity and stage of HIV infection.

- A chronic, *follicular eruption* on the limbs and trunk, which is characterized histologically by a perifollicular neutrophilic infiltrate.

No pathogen has been detected in any of these conditions. The treatment is also empirical. Topical corticosteroids, phototherapy with PUVA and UVB, dapsone, topical 4% cromolyn sodium and pentoxifylline⁷⁸ have been reported to be effective.

Miscellaneous conditions²²: These include psoriasis, Reiter's disease, aphthosis, pigmentary changes, drug eruptions and certain bacterial and subcutaneous/deep fungal infections such as cryptococcosis and histoplasmosis.

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Spectrum of Cutaneous Disorders in HIV Infected Patients: A Hospital Based Study

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Abstract: Cutaneous disorders occur more frequently as HIV infection advances and immune function deteriorates. The present study was to find the prevalence and pattern of cutaneous disorders in HIV infected patients, and associated sexually transmitted diseases and systemic manifestations. One hundred and eighty five (185) HIV seropositive patients who were attending the Dermatology and STD Out Patient Department or admitted in Infectious Disease ward at JIPMER, Pondicherry from September 1998 to June 2000 were screened for mucocutaneous disorders. Ninety (48.6%) cases were found to have mucocutaneous disorders. There were 64 (71.1%) males and 26(28.9%) females. Male to female ratio was 2.5:1. Forty-five (50%) of our patients were in the age group of 21-30 years. The mean age of our patients was 28 years (range 2 months to 60 years).

Heterosexual route was the most common mode of acquisition of HIV infection and was observed in 71 (81.6%) cases. Out of 90 cases recruited into our study, 58 (64.4%) cases were in the HIV Group IV (AIDS) followed by 18 (20%) cases in HIV Group II and 14 (15.6%) cases in Group III. Mucocutaneous fungal infections were common and consisted of candidial infections in 74 (82.2%) cases, dermatophytic infections in 41 (45.6%) and pityrosporum infections in 25(27.8%) cases. Other dermatological disorders included xerosis in 12(13.3%) cases followed by pyoderma in 11 (12.2%) cases. Amongst STD's, human papilloma virus infections were noted in 17 (18.9%) cases followed by herpes simplex infections in 13(14.4%) cases. amongst the systemic disorders, pulmonary tuberculosis was observed in 30 (33.3%) patients. The discussion in this article is mainly focussed on mucocutaneous fungal disorders which are common in HIV infected patients.

Key Words : *HIV infection; Cutaneous Disorders; Fungal Infections*

Introduction

Cutaneous disorders occur more frequently as HIV infection advances and immune function deteriorates. They affect between 80% and 95% of HIV infected patients according to the literature¹⁻³, occurring at any time in the course of infection. Skin is often the first and only organ affected during the course of HIV disease. Cutaneous disorders during HIV infection are numerous.⁴⁻¹⁰ Some have drawn attention because of their onset, indicate some of the Centre for Disease Control and Prevention (CDC) acquired immunodeficiency syndrome (AIDS) clinical categories, e.g. oral candidiasis, zoster, herpes simplex, oral hairy leukoplakia and Kaposi's sarcoma¹¹, but most have been documented solely in case reports. In the context of HIV infection, cutaneous disorders can present with particular clinical manifestations: unusual anatomical sites, increased severity, treatment failure and unusual clinical appearance.¹² Moreover, it is argued that some cutaneous disorders reflect the progression of HIV disease^{4,6}, but this relationship is still controversial.^{2,10}

The present study was to find the prevalence and pattern of cutaneous disorders in HIV infected patients, and associated sexually transmitted diseases and systemic manifestations.

Material and Methods

In this study, all HIV seropositive patients (by double ELISA method) who were attending the Dermatology and STD Out Patient Department or admitted in infectious disease ward at JIPMER, Pondicherry from September 1998 to June 2000 were screened for

cutaneous disorders. Those found to have cutaneous disorders were recruited for this study. A detailed history including marital and sexual history was taken and these patients were subjected to a thorough physical examination, with particular reference to duration of the disease, site of involvement and morphology of the lesions. The clinical diagnosis was made and supplemented with laboratory procedures like microscopic examination (KOH preparation) and Gram staining in the side lab. Routine haematological, biochemical and radiological investigations were performed to rule out systemic involvement wherever felt necessary. The patients were staged according to the Center for Disease Control (CDC) classification system for HIV infection (1986)¹³. The mucocutaneous changes were recorded and correlated with various clinical parameters. Results were tabulated and analysed.

Result

In this study, a total number of 185 HIV seropositive patients were screened for mucocutaneous disorders, of them 97 (52.4%) were admitted in the Infectious Disease Ward and 88(47.6%) were seen in the Dermatology and STD Out Patient Department, JIPMER, Pondicherry. Out of 185 patients, 90 (48.6%) cases were found to have mucocutaneous disorders. There were 64(71.1%) males and 26(28.9%) females. Male to female ratio was 2.5:1. Forty-five (50%) of our patients were in the age group of 21-30 years. The mean age of our patients was 28 years (range 2 months to 60 years). Three of our patients were in the age group of 2 months - 10 years. Sixty-six (73.4%) patients were married, 13(14.4%) were single and 11(12.2%) were widows. There occupations of our patients in decreasing order of frequency were laborers 43(47.8%), drivers 21(23.3%), housewives

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17(18.9%), commercial sex workers 5(5.6%) and miscellaneous 4(4.4%). All the drivers were promiscuous; nine (42.9%) of them gave histories of present and past sexually transmitted diseases. Heterosexual route was the most common mode of acquisition of HIV infection and was observed in 71(81.6%) cases. There were 3 children who acquired HIV infection through transplacental route. Seventy-four (85.1%) patients had multiple sexual partners and 13(14.9%) had single partner (most often their spouse). None of our patients in the study group gave the history of condom use.

Of the eighty-seven sexually active patients, 50(57.5%) had contact with commercial sex workers, extra-marital contacts in 20(22.9%), premarital contacts in 4(4.6%) and seventy-six (87.4%) of them were not aware of the HIV status of their partners. Out of 90 cases recruited into our study, 58(64.4%) cases were in the HIV Group IV (AIDS) followed by 18(20%) cases in HIV Group II and 14 (15.6%) cases in Group III (Table 1).

Table 1. HIV staging and distribution of patients with dermatoses

HIV Groups	No. (%)
Group I	0
Group II	18 (20)
Group III	14 (15.6)
Group IV	58 (64.4)
Total	90 (100)

Out of ninety patients, 68(75.6%) were *symptomatic*, the usual symptoms were, fever, loss of weight, loss appetite, cough with expectoration, soreness, burning sensation of mouth, loss of taste, dysphagia, odynophagia, retrosternal burning sensation, and diarrhoea. The usual signs were pallor, emaciation, generalized lymphadenopathy, oral thrush, and white discharge per vagina and genital ulcer. *Fungal infections* were the commonest and consisted of candidial infections in 74(82.2%) cases, dermatophytic infections in 41(45.6%) and pityrosporum infections in 25(27.8%) cases (Table 2). Cutaneous cryptococcosis was seen in one patient.

A total number of 235 disorders other than fungal infections were observed (Table 2). Of these, dermatological disorders were common (109) followed by systemic disorders (82). Forty-four (18.7%) cases were associated with STD's. Other dermatological disorders included xerosis in 12(13.3%) cases followed by pyoderma in 11(12.2%) cases. Amongst STD's, human papilloma virus infections were noted in 17(18.9%) cases followed by herpes simplex infections in 13(14.4%) cases. Among the systemic disorders, pulmonary tuberculosis was observed in 30(33.3%) patients. Ten (10) patients had meningitis of these 5 had tuberculous meningitis 2 cryptococcal meningitis; 5 died during the study period.

Discussion

HIV infected patients present with various cutaneous dermatoses, fungal dermatoses being the most common.¹⁴ Many a times, cutaneous and mucosal fungal infections may give a clue to the underlying HIV infections. Moreover, they are more extensive, often atypical and aggressive, sometimes life threatening.

Majority of our patients were in the age group of 21-30 years. The mean age of the patients in our study group was 28 years. Similar findings were observed by Singh et al¹⁴ and Rosatelli et al¹⁵. Three of our patients were in the pediatric age group and presented with oral candidiasis, two of them had diaper rash, frequently relapsing after treatment. The present study had 64 males and 26 females, male to female ratio was 2.5:1 which was

Table 2. Cutaneous disorders in HIV infected patients.

Dermatological disorders	Disorders associated with HIV infection				No.
	No.	STD's	No.	Systemic disorders	
Candidiasis	74				
Dermatophytosis	41				
Pityrosporum infections	25				
Xerosis	24	HPV-anogenital	17	Pulmonary Tuberculosis	30
Pyoderma	19	Herpesgenitalis	9	Pneumocystis carinii pneumonia	5
Molluscum contagiosum	12	Scabies	7	Bronchopneumonia	5
Herpes zoster	9			Neurological insufficiency	7
Papular dermatitis of HIV	7	Syphilis	4	Meningitis	10
Insect bite reaction	6	Chancroid	1	Nephrotic syndrome	1
Drug reactions	6			Amoebic liver abscess	1
Psoriasis vulgaris	5				
Verrucae vulgaris (extensive)	4				
Herpes labialis	4				
Hidradenitis suppurativa	1				
Scleroderma	1				
Reiter's disease	1				
Others	10	Others	6	Others	23
Total	109	Total	44	Total	82

similar to that of Singh et al¹⁴ (2.9:1) but lower than that of Rosatelli et al¹⁵ (5.2:1).

The most common mode of spread of HIV infection in our study group was heterosexual contact (81.6%), as recorded in earlier study done from here.¹⁴ This study showed a preponderance of laborers (47.7%) over drivers (23.3%), which is in contrast with that of Singh et al¹⁴; where more number of drivers (26.6%) than the laborers (18.6%) were recorded. This probably reflects a changing spectrum of the disease with more people from working class of society being affected.

The majority of our HIV positive patients presented during the advanced stage of HIV disease because they become symptomatic by this stage, 64% were in the HIV Group IV; 36% were in the early stages of HIV infection. This may be due to the relatively nonspecific nature of manifestations of acute HIV syndrome, particularly in India where other endemic diseases with similar complaints are more common.^{14,16}

The prevalence of fungal dermatoses in HIV seropositive patients was found to be 48.6% which is higher than that of Hira et al¹⁷ (23.7%). Rosatelli et al¹⁵ (1997) in their study, observed fungal dermatoses in 22.6% of asymptomatic HIV infected patients and 32.4% of AIDS cases. The present study showed that 58(64.4%) cases were in HIV Group IV and 32(35.6%) in early stages, which is in contrast to that of Singh et al¹⁴ where 40.3% of cases with mucocutaneous lesions were in Group IV and 32.1% in early stages of HIV infection. According to Rosatelli et al¹⁵, fungal diseases are more frequent in the AIDS group, this is consistent with our finding.

Oropharyngeal candidiasis is the most common opportunistic infection in patients with HIV infection; occurring in as many as 90% of HIV patients at some point during the course of HIV disease.¹⁸ Oral candidiasis probably precedes other opportunistic infections. It may be a sign of transition to AIDS.¹⁴ Kumarasamy et al¹⁹ observed oral candidiasis in 46.7% of HIV infected patients. In our study, 34.05% (63 cases out of 185 HIV seropositive

patients) had oral candidiasis.

Dermatophytic infections are common in HIV infected patients. However, these skin diseases may not occur any more frequently in HIV positive patients than in comparable group.¹⁴ Studies have been few and their results are contrary. In one survey for example, the prevalence of dermatophytosis was not significantly higher in a group of HIV infected patients (37%) than in a paired population of HIV homosexual males (32%). These investigators noted that superficial infections were more common in both groups of homosexual males than in the general population.²⁰ In another study, however, the prevalence of dermatophytosis was four times higher among HIV infected persons.¹⁰ Kumarasamy et al¹⁹ in their study from south India, found 8.0 percent of HIV infected patients having dermatophytosis. Its frequency was 22.2% in the present study, which is much higher than that of Rosatelli et al¹⁵ (17.5%). This could be partially explained by the fact that the cases were also selected from Infectious Disease ward where mostly Group IV patients are admitted.

An increased colonization of *pityrosporum orbiculare* organisms have been reported in patients with HIV infection.¹⁹ The occurrence of seborrheic dermatitis in-patients with AIDS may have some unique features. The presentation is often more explosive in onset, intensely erythematous and clinically more severe than that observed in patients without AIDS. In the present study, the prevalence of pityrosporum infection was 13.5% (25 cases). Of these, seborrheic dermatitis was seen in 14 of cases, tinea versicolor in 10 of cases and pityrosporum folliculitis in 4 of cases, which was less than that of Groisser et al²¹ (80%) but more than that of Singh et al¹⁴ (3.8%).

In HIV infection, 10%-20% of disseminated cryptococcosis patients present with cutaneous involvement.⁹ In our study, cutaneous cryptococcosis was seen, in one patient. Previous study by Singh et al¹⁴ from the same institute did not encounter any case of cutaneous cryptococcosis. In contrast, Moore et al²² (10%-15%) and Murakawa et al²³ (6%) reported higher incidence of cutaneous cryptococcosis.

To conclude, a careful examination of skin and mucosae especially for mucocutaneous fungal infections may be highly rewarding in evaluating the stage of HIV disease.

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BOOK REVIEW

ICU Manual, Dr. AP Jain, Dr. Rajnish Joshi, Dr. Ashish Goel, *Paras Medical Publisher, India, 2004, pages. Rs.225.00*

In this manual the authors provide a ready reference to the ICU staff at all levels. The details of etiology and pathophysiology are intentionally excluded leaving the content to focus on management issues. The authors have provided only the standard care and some of the senior readers may have reservations about some of the management priorities listed in the manual. A potential limitation is the manual's emphasis on medical emergencies. Problems that may develop in postoperative patients or in-patients admitted to the surgical intensive care unit (ICU) are not covered. The manual also does not include pediatric and obstetric issues.

The manual is organized into three sections that cover the Protocols in ICU, Management of emergencies, and Procedures in ICU. Its four appendixes contain important information on laboratory values, formulas, and infusion rates. The first section contains many important and common protocols, which are often needed in any ICU. The Protocols are brief, clear, and easy to read and apply. The next section on management of emergencies provides a brief and concise overview of the many diverse emergencies encountered

in the intensive care unit (ICU). There are chapters on organ systems like cardiac, respiratory, hepatic and renal systems. There are also chapters on metabolic, infective and poisoning emergencies. Each chapter is set up in an efficient and logical outline form with key points accented in boldface text to facilitate ease and speed of use. Algorithmic diagrams are included which give a clear and easily followed management plan. A bibliography of key references accompanies each chapter. Lastly there is a section on common bedside ICU procedures. All chapters in this section have an effective description of the methods and illustrations of the techniques. Resident intensivists will find these chapters invaluable when learning these procedures. There is much to recommend about this manual. The format is excellent for clarity of reading and a methodical approach is preserved throughout the manual. Despite some minor reservations about the limited topics, it is recommended as an excellent resource for its intended audience of medical students and intensivists.

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Meconium Aspiration Syndrome in Meconium Stained Amniotic Fluid

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Abstract: To know the incidence and risk factors of meconium aspiration syndrome (MAS) at various gestational ages in babies born through meconium stained amniotic fluid using guidelines 2000 for neonatal resuscitation. From all deliveries conducted during November 2000 to July 2001, babies born through meconium stained amniotic fluid (MSAF) were taken up for study. Detailed maternal data especially parity, period of gestation, any history of eclampsia, pre-eclampsia or hypertension were recorded. Mode of delivery and presentation were recorded. Detailed data of infant like apgar score, gestational assessment, development of respiratory distress within 72 hours of birth were recorded. Roentgenographic examination of chest on day 3 of life was done in all infants born through MSAF. One hundred (100) babies out of 792 deliveries were born through MSAF. In 16% cases both respiratory distress and radiological opacities were present bringing the incidence of MAS to 2.02% of all live births. Anaemia and pregnancy induced hypertension were commonest risk factor. No baby was below 34 weeks of gestation. 75% babies with MAS were term and 25% preterm. Birth weight was >2000gm in 93% of babies. 43.75% of babies with MAS had severe birth asphyxia. MSAF and MAS did not develop in babies below 34 weeks of gestation. Moderate to severe birth asphyxia is a significant risk factor of MAS.

Introduction

Meconium staining of amniotic fluid (MSAF) occurs in 10.3%-22% of the live births with rising frequency along with the increase in gestational age of the fetus¹. Passage of meconium in utero is a serious neonatal disorder carrying high mortality and morbidity. MSAF is considered to be a bad predictor of fetal outcome because of its direct correlation to fetal distress and increased likelihood of inhalation of meconium with resultant deleterious effects on the neonatal lungs¹. Meconium aspiration syndrome (MAS) is defined as development of respiratory distress along with radiological evidence in a baby born with MSAF².

Previously the approach to prevent MAS was oropharyngeal suctioning on delivery of the head followed by immediate postnatal endotracheal suctioning³. Whether all babies born through thin meconium should undergo immediate postnatal suctioning is controversial. According to latest guidelines vigorous tracheal suctioning of the infant with MSAF does not improve outcome and may cause complications⁴. This study was planned to know the incidence and risk factors of MAS at various gestational ages in babies born through MSAF using guidelines 2000 for neonatal resuscitation.^{4,5}

Material and Methods

This prospective study was carried out during period from November 2000 to July 2001. In Neonatology section of department of Pediatrics of our hospital; 792 deliveries were conducted during the study period. 100 babies were born with meconium stained amniotic fluid. Detailed maternal data was recorded on a predesigned proforma. Mother's age, parity, period of gestation, any complications of pregnancy like preeclampsia, eclampsia, hypertension were recorded. The mode of delivery, presentation and indications for any interference were recorded. Mothers having meconium stained amniotic fluid detected during labour were included in the study. Intrapartum suctioning after delivery of head from mouth, pharynx and nose was performed in all deliveries born through MSAF. Direct laryngoscopy was performed for suctioning of meconium from the hypopharynx and intubation/suction of trachea done, if the infant had depressed or absent respiration, decreased muscle tone or heart rate <100bpm; none was subjected to vigorous infant tracheal suctioning.

Details of resuscitation method used, Apgar score at 1, 5min. and if needed at 10min. and subsequently were recorded. Assessment

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of gestation was done by Ballard's scoring system⁶. All infants were observed for development of any respiratory distress for 72 hrs. after birth. The infant was said to have respiratory distress if the respiratory rate was more than 60 per minute and/or chest indrawing if the infant had and/or expiratory grunt or moaning. All infants underwent roentgenographic examination of chest on day 3 of life. The cases having septicemia on clinical or on investigative basis were excluded from the study group. The meconium aspiration syndrome was labelled on the basis of development of respiratory distress along with radiological evidence of meconium aspiration developing in babies born through MSAF. The data obtained was analysed statistically.

Results

There were 792 live births during the study period. 100 babies out of 792 were born through meconium stained amniotic fluid bringing the incidence of MSAF to 12.62% of all live births. Respiratory distress was present in 27% of the babies born through MSAF. Radiological opacities were present in 73% of babies born through MSAF. However in 16% of cases both respiratory distress and radiological opacities were present which brings the incidence of MAS to 2.02% of all live births. Chest indrawing and expiratory grunt were the commonest features of respiratory distress in these babies (Table 1).

Table 1. Babies with MAS with 2 or > 2 signs of respiratory distress

Signs of Respiratory Distress	Number (n=16)	Percentage
Tachypnoea + Expiratory Grunt	11	68.75
Tachpnoea + Chest Indrawing	12	75
Chest indrawing + Expiratory Grunt	14	87.5
Chest indrawing + Expiratory Grunt + Tachypnoea	11	68.75

Out of 16 cases of MAS, 31.25%, 37.5% and 6.25% were having parity 1, 2 and 3 respectively while 25% babies were born to >para 3 mothers (p>0.05). Anaemia and pregnancy induced hypertension were the commonest risk factor in 68.75% and 31.25% of patients with MAS. In 62% cases of MSAF and MAS mode of delivery was LSCS while in 38% mode of delivery was by normal vaginal route (p<0.01). 69% of MSAF babies were males and 31% of females. No baby born through MSAF or having MAS was below 34 weeks of gestational age (Table 2). 75% of babies with

Table 2. Distribution of babbies according to period of gestation.

Period of Gestation (Completed weeks)	Babies born through MSAF (n=100)	Babies who developed MAS (n=16)
<37	14	4 (25)
37-41	82	12(75)
>42	4	0

* Figures in parentheses indicate percentages

Table 3. Distribution of babbies according to birth weight.

Birth Weight (Grams)	Babies born through MSAF (n=100)	Babies who developed MAS (n=16)
<1500	-	-
1501-1999	7	1(6.25)
2000-2499	23	6(37.5)
2500-2999	32	3(18.75)
>3000	38	6(37.5)

* Figures in parentheses indicate percentages

Table 4. Distribution of babbies according to grade of birth asphyxia by APGAR score

Apgar Score	Babies born through MSAF (n=100)	Babies who developed MAS (n=16)
No Asphyxia (8-10)	63	4(25)
Mild (5-7)	19	2(12.5)
Moderate (3-4)	4	3(18.75)
Severe (0-2)	14	7(43.75)

* Figures in parentheses indicate percentages

MAS were term babies and 25% preterm ($p<0.05$). Weight distribution of babies is shown in Table 3. It was seen that 63% babies born through MSAF had no asphyxia and 37% had asphyxia at birth (Table 4).

Discussion

Meconium staining of amniotic fluid is found in 7-21% of births^{2,7-11}. The incidence in our study was 12.6%. It usually occurs in term or post term infants. 82% babies born through MSAF were term, 14% preterm and 4% were post term. Usually but not invariably, fetal distress and hypoxia occur with passage of meconium into the amniotic fluid. These infants are meconium stained and may be depressed and require resuscitation at birth.

Meconium aspiration syndrome is defined as presence of respiratory distress and radiological opacities developing in a baby born through meconium stained amniotic fluid. MAS was present in 16% of our babies while Narang et al² have found the incidence of MAS in 10.5% babies. In thick meconium, incidence of 18.7% to 42.7% have been reported^{2,8,12}.

Anemia and pregnancy induced hypertension were the predominant risk factors in 45% and 28% babies which is consistent with earlier reports^{13,14}. Toxemia as the predominant causative factor of MSAF was observed by Miller and Nayak & Dalal^{15,16}. In 62% cases of MSAF and MAS mode of delivery was LSCS while in 38% it was normal vaginal route.

Either in utero or more often with the first breath, meconium is aspirated into the lungs. The resulting small airway obstruction

may produce respiratory distress within the first hours, with tachypnoea, retraction, grunting and cyanosis. In the present study retraction and grunting were the commonest signs of respiratory distress seen in 87.5% of babies while tachypnoea was present in 75% babbies.

Of the babies who developed MAS, 75% were term and 25% preterm; none of 4 post term babies developed MAS. The birth weight of 93% of MSAF born babies was >2000 grams and 38% babies had birth weight \geq 3000grams. Miller recorded mean birth weight 3400 ± 516 gm in babies born with MSAF¹⁶.

Of the babies born with MSAF 63% had no asphyxia at birth (Apgar score >7 at 1 minute) and did not require treatment. Depressed infants should undergo endotracheal intubation and suction should be applied directly to endotracheal tube to remove meconium from the airway. The risks of endotracheal intubation are less than the risks of meconium aspiration syndrome; 43.75% babies who developed MAS had severe asphyxia at birth which is almost similar to the earlier reports².

It can be concluded that MSAF and MAS did not occur below 34 weeks of gestation. Moderate to severe birth asphyxia is a significant risk factor for development of MAS in neonates, born through MSAF.

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“Effects of Isoflavones on Lipid Profiles and Lipid Peroxidation of Hypercholesterolemic Post Menopausal Women”

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Abstract: The study has been conducted to evaluate the effects of isoflavone, a non-steroidal phytoestrogen, on lipid and lipid peroxidation in hypercholesterolemic postmenopausal woman hypercholesterolemic postmenopausal women (n=22) showed significant reduction of lipid levels and lipid peroxidation product formation on oral administration of forty milligram of isoflavone daily for three months. Total cholesterol and LDL-cholesterol were reduced significantly ($p<0.001$) with an increase in HDL-cholesterol. Our study observed reduction of triglyceride in 50% cases while the rest showed a little elevation. Interestingly, isoflavone intake group with hyperlipidemia showed less lipid peroxidation (malonaldehyde formation) than the isoflavone untreated groups with hyperlipidemia (n=30) or without hyperlipidemia (n=25) confirming the antioxidant activity of isoflavone. Thus it provides a similar action like ‘statin’ group of lipid lowering agents (HMG coA reductase inhibitor). Such results indicate that isoflavone has immense beneficial effect on human health.

Key Words : *Isoflavone, hyperlipidemic postmenopausal woman, lipid profile, lipid peroxidation, antioxidant action, lipid lowering agent.*

Introduction

Isoflavones are ‘flavonoid’ class of compounds derived from plant sources having weak estrogenic activities. They are nonsteroidal phytoestrogen and act as partial agonist or antagonist for mammalian estrogen and also possess the property of natural selective estrogen receptor modulator (SERM). They also have many other beneficial effects on human health. Genstein, Daidzein, Glycetin are the main isoflavones present in legumes like soyabeans, lentils, beans, chickpeas etc. Postmenopausal women, lacking in estrogen, usually have a hypercholesterolemic state and imbibe the danger of vascular damages leading to heart disease, hypertension etc. Epidemiological studies on hormone replacement therapy in post menopausal women show the favourable effects of estrogen on reduction of the risk of coronary heart diseases with a cardioprotective role.^{1,2,3}

The present study emphasizes the role of isoflavones in the management of lipid profile and oxidative stress, as monitored by lipid peroxide formation in hypercholesterolemic postmenopausal women stressing the fact that isoflavones provide a similar action like ‘Statins’ group of drug (HMG CoA reductase inhibitor), which are used as a lipid lowering agent.

Materials and Methods

Fifty two (52) hypercholesterolemic post menopausal women were selected from the menopausal clinic of the department of Obstetric & Gynecology of IPGME & R and SSKM hospital, Kolkata, of them were taken as *controls* receives only vitamins and minerals for three months while remaining (22) received 40mgs of isoflavone daily for three months and constituted the ‘*study group*’.

Twenty five (25) postmenopausal women with normal lipid profile were also selected as basal group. Isoflavones were supplied by British Biologicals for clinical trial and also as Soy-Estro Capsule of Gland Chemical Pvt Ltd. Chemicals used were of analytical

grade material of Glaxo and Sigma Chemicals.

Assay of lipid profiles : Serum triglycerides were assayed following the principle of Fossati et al and Mc. Gown et al in a digital spectrophotometer^{5,6}. Total cholesterol was assayed by Ferric percholate reaction and the lavender colour complex was measured at 560nm in a spectrophotometer⁷. HDL-cholesterol was assayed with the supernatant after precipitation of VLDL and LDL in serum by magnesium chloride and phosphotungstic acid reagent. LDL-cholesterol was determined by using Friedewalds formula.

Assay of lipid Peroxidation product : Malonaldehyde, a lipid peroxidation product, was assayed in serum by thiobarbituric acid reaction. The colour complex was measured at 532nm in a digital spectrophotometer⁸. Results of different assays were statistically evaluated by student ‘t’ test and significant ‘p’ values were given in the table.

Results

Table 1 shows the changes in lipid profile in hypercholesterolemic postmenopausal women after intake of isoflavone (40mg daily) for three months. A significant reduction in total cholesterol and LDL-cholesterol in peripheral blood ($p<0.001$) is observed. Triglyceride level is little bit higher in the treated group than that

Table 1. Lipid Profile in Hypercholesterolemic Postmenopausal women at baseline and changes after 3 months of Isoflavone intake.

Treatment status	Total cholesterol (mmol/L) Mean+SD	HDL-C (mmol/L) Mean+SD	LDL-C (mmol/L) Mean+SD	Triglyceride (mmol/L) Mean+SD
which isoflavone (n=52)	8.5+0.30	2.73+0.15	4.8+0.20	1.82+0.25
with isoflavone (n=22)	5.4+0.50*	2.34+0.12	1.9+0.20*	2.27+0.18

P values = $p<0.001$, * - Significant

of the postmenopausal hyperlipidemic women without isoflavone intake.

Table 2 shows the maximum and minimum levels of lipid profiles at base as well after three months intake of isoflavones. The treated group shows eighty percent reduction in total cholesterol and ninety per cent reduction in LDL-cholesterol among the total cases in a significant way ($p < .001$) and there is increase HDL-cholesterol in thirty per cent cases. As regard to triglyceride content fifty per cent of total cases shows decrease from the base line value and the rest fifty per cent shows increase from the base line value.

Table 2. Maximum and minimum levels of Lipid Profile in hypercholesterolemic Postmenopausal women at baseline and changes after 3 months of Isoflavone intake

	Total cholesterol (mmol/L)	HDL-C (mmol/L) Range:	LDL-C (mmol/L) Range:	Triglyceride (mmol/L) Range:
Baseline (n=52)	5-15	1.30-4.48	1.52-9.59	0.56-5.6
Change after 3 months of Isoflavone intake (n=22)	4.54-7.5 (% reduction-80% cases)	1.52-3.60 (% increase 30% cases)	2.0-3.92 (% reduction 90% cases)	0.55-5.40 (% increase/decrease 50% each case)

Table 3 shows the result of lipid peroxidation formation, malonaldehyde in hypercholesterolemic postmenopausal women treated with isoflavone. Interestingly, malonaldehyde formation, (an index of oxidative stress- for peroxidation of poly-unsaturated fatty acids) in hypercholesterolemic post menopausal women, show less lipid peroxidation formation when they are treated with isoflavone showing the antioxidant activities of isoflavone.

Table 3. Lipid peroxidation product formation in hyperlipidemic postmenopausal women with or without Isoflavone intake (Anti-Oxidant action of Isoflavone)

Groups	Malonaldehyde formed (nmol/ml) Mean + SD
1. Postmenopausal women with normal lipid profile (age 45-55 yrs) without Isoflavone (n=25)	1.47 + 0.25
2. Postmenopausal women with hyperlipidemia without Isoflavone (age 45-60 yrs.) (n=52)	2.07 + 0.38
3. Postmenopausal women with hyperlipidemia + 40mg. Isoflavone intake daily for 3 months (age = 45-60 yrs.) (n=22)	0.63 + 0.20

* - p value : $p < 0.001$, significant

Discussion

Hypercholesterolemia increases the degradation of nitric oxide, an important modulator of endothelial function. Improvement in endothelial function is demonstrated in hypercholesterolemic patients, treated with the statin group of drugs (lipid lowering agent, HMG-reductase inhibitor)^{9,10}. The present study shows that isoflavone intake for three months by hypercholesterolemic postmenopausal

women has a significant ($p < .001$) reduction in total cholesterol and LDL-cholesterol concentration in peripheral blood. Furthermore, 50% of the study group showed decrease in triglyceride level while the rest shows a little elevation. Similar observations have made by earlier workers; the latter also observed been that they also up regulate LDL-receptors in liver and increase bile acid synthesis and reduce lipoprotein-a (Lp (a)) levels.^{11,12,13}

The present study reveals that malonaldehyde formation (an index of oxidative stress) is also counteracted by isoflavone because structural similarities with estradiol. It prevents lipid peroxidation product formation responsible for causing atherosclerosis in hypercholesterolemic postmenopausal women. Isoflavone derived from *dietary soya is* less expensive as compared to statin group of drugs and is of immense help in prevention of hyperlipidemia in postmenopausal women as well as in slowing down the process of atherosclerosis due to less oxidative stress phenomenon. Moreover, when hormone replacement therapy is contraindicated, isoflavone may find a place for its substitute.

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Sagittally Split Middle Turbinate : Morphology and Clinical Application

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Abstract: The nasal cavity is host to a number of variations, both normal and pathological. Sagittally split middle turbinates are rare and sparsely known among clinicians. We observed sagittally running whole thickness linear splits (clefts) bilaterally in the intermediate two-thirds of middle turbinates in two adult male cadavers. In the first case, the right split turbinate was associated with non-pneumatized bulla ethmoidalis and an accessory maxillary ostia, while the left side presented pneumatization of the upper segment. The second case presented non-pneumatized bulla ethmoidalis on both sides and a twin accessory maxillary ostia on the right side. A need was felt to study and record this entity due to its clinical importance and a lack of awareness of this condition among rhinologists and anatomists. On anterior rhinoscopy this can be mistaken for a polyp or tumor and could be responsible for causing ostiomeatal unit obstruction, thus making it imperative for endoscopic sinus surgeon to recognize this entity during surgery to prevent recurrent sinusitis.

Key words : *middle turbinate, splitting, pneumatization, bulla ethmoidalis, ostiomeatal unit, endoscopic.*

Introduction

The middle turbinate, a vital landmark in endoscopic sinus surgery, is a scroll-like integral part of ethmoid bone covered with thick mucoperiosteum, soft tissue and pseudostratified ciliated columnar epithelium. Ventrally it is attached to the cribriform plate which forms the roof of the nasal cavity and dorsally to the lamina papyracea of the lateral nasal wall which forms the medial wall of the orbit. Its attachment traverses the entire ethmoidal labyrinth dividing the ethmoidal sinuses into anterior and posterior groups^{1,2}. Middle turbinate hides various ostia of the anterior group of paranasal sinuses. For an endoscopic sinus surgeon it is important to be aware of the normal and pathological variants of this turbinate and understand their intranasal anatomy for successful performance of endoscopic procedures. Sagittally clefted middle turbinate is a rare anatomic variant among the better-known variations such as concha bullosa (pneumatized middle turbinate), triangular, L-shaped middle turbinate and paradoxically curved middle turbinate³. Surprisingly no reference of this condition was cited in anatomy or otorhinolaryngology textbooks, but for a couple of citations in ENT journals^{3,4}.

Case Report

Forty-eight formalin fixed adult cadavers (96 half-heads) were dissected of which two cadavers (4 half-heads, 4.2%) had bilaterally split middle turbinates.

Case No. 1

A bilateral whole thickness linear sagittal split in the middle turbinates was seen in a male cadaver; each split was approximately in the middle two-third with the anterior and posterior parts unsplit. The split portion therefore had an upper segment and a lower segment. The upper was attached above and free below at the split while the lower segment was free both above and below forming the free margin of this turbinate.

The maximum lengths of right and left turbinates were 42 mm and 44 mm respectively, measured along their long axis and the maximum height of each was 12mm. Upon reflecting the turbinate on the right side, non-pneumatized bulla ethmoidalis and an accessory maxillary ostia were found (Fig.) The left one was associated with pneumatization (concha bullosa) of upper segment.

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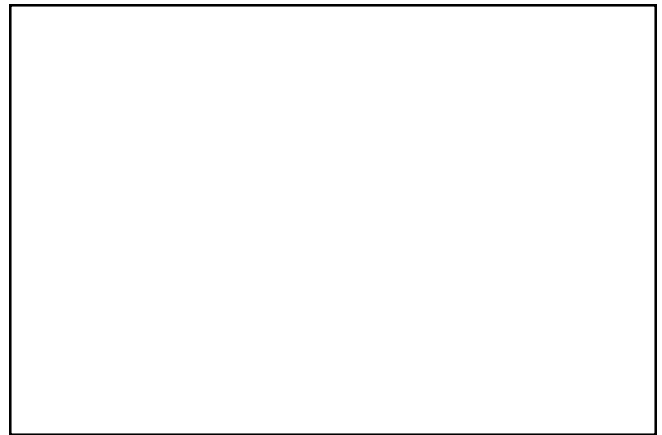


Fig. : sagittally split of right half-head middle turbinate show ... non-pneumatized bulla ethmoidalis (arrow head) and an accessory maxillary ostia (arrow).

Case No. 2

A similar split in the middle two-thirds was seen bilaterally in another male cadaver. The maximum lengths and heights of right and left middle turbinates were 40mm and 11mm and 42mm and 12mm respectively. On reflecting the turbinates, non-pneumatized bulla ethmoidalis was seen on both sides. The right side presented with a twin accessory maxillary ostia. The upper or lower split segment did not show any pneumatization on either side.

Discussion

With the turn of the twentieth century came a consensus among rhinologists that the morphology of the sinuses could be best understood by studying their embryogenesis and drainage patterns. This formed the basis of modern sinus surgery⁵. A sagittally clefted middle turbinate is seen in about 50% of five-month-old fetuses, 36% of neonates, 13% of children and 6% of adults⁶. We found splitting in 4.2% of adult cadavers. Zuckerkandl⁶ demonstrated that the middle, superior and supreme turbinate, the uncinata and bulla ethmoidalis begin to develop by about 9th to 10th week of fetal life from six prominent ridges (ethmoturbinals) separated by furrows. Subsequently some of these ridges and furrows coalesce while others disappear partly or entirely to attain the normal adult morphology of the lateral nasal wall. The middle turbinate is formed from the third ridge, preceded by the formation of inferior turbinate and followed by uncinata process, bulla ethmoidalis and superior turbinate. The exact mechanism of its

formation is unclear; it perhaps results from an arrest in the maturation process of middle turbinate⁴. It is our conjecture that this present anomaly results because, besides the normal third ridge, part of the second one (which forms bulla ethmoidalis) may also have contributed to its formation; it is the non-fusion of the second and third ridge which has resulted in the splitting. This assumption is supported by the fact that the bulla ethmoidalis was inconspicuous and non-pneumatized in both cases.

Yanagisawa and Weaver³ found on endoscopy longitudinally clefted clinically asymptomatic middle turbinate. Rossiter⁴ found a sagittally clefted anteriorly fused middle turbinate on endoscopy in an adult male patient with recurrent sinusitis. This was associated with concha bullosa of the larger medial segment. Interestingly in the two cadavers, we observed a bilateral linear sagittal split in the middle two thirds of the middle turbinates. Similar to the above mentioned endoscopic finding we observed concha bullosa of upper segment of the left middle turbinate.

Clinically the middle turbinate can present with an abnormal shape, pneumatization, polypoid mucosa or, rarely a split. Such turbinates can disrupt mucus flow, block sinus ostia or can even restrict endoscopy. A split turbinate may remain silent or be a cause of sinusitis. It can easily be missed during standard anterior rhinoscopy, or mistaken for a polyp, a tumor or enlargement of normal structures such as superior turbinate, bulla ethmoidalis or uncinate process, and may prove to be a potential factor for ostiomeatal unit obstruction⁴. Diagnosis is made by endoscopy,

CT scan or MRI and operative intervention alleviates suffering.

Knowledge of a split middle turbinate enables the endoscopic sinus surgeon to anticipate and treat such condition in an effective way and avoid to recurrence of sinusitis. Association of clefted middle turbinates with concha bullosa and infundibular blockade leading to the formation of accessory maxillary ostia needs further study.

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Literature Review

Compiled by Dr. SNA Rizvi

Effect of blood pressure on early decline in kidney function among hypertensive men. Hypertension. 2003 Dec;42(6):1144-9. Epub 2003 Nov. 03.

Few Cohort studies have examined the longitudinal association between change in blood pressure and decline in kidney function among treated hypertensive patients without chronic kidney disease. We conducted a nonconcurrent cohort study to examine the effects of blood pressure on estimated glomerular filtration rate and early kidney function decline (rise in serum creatinine > or = 0.6mg/dL during follow-up) among 504 African-American and 218 white hypertensive patients. Our results showed that each standard deviation higher treated systolic (18mm Hg) and diastolic (10mm Hg) blood pressure was associated with an average annual decline (95% confidence interval [CI] in estimated glomerular filtration rate of -0.92 ([-1.49 to -0.36] P<0.001) and -0.83 ([-1.38 to -0.28] P=0.003) mL/min (-1) x 1.73 m (-2), respectively, after adjustment for race, age, education, income, use of anti-hypertensive drugs, body mass index, and history of diabetes and dyslipidemia. Likewise, each standard deviation higher systolic and diastolic blood pressure was associated with relative risks (95% CIs) of 1.81 ([1.29 to 2.55] P<0.001) and 1.55 ([1.08 to 2.22] P=0.046), respectively, for early kidney function decline. Compared with patients with a blood pressure level <140/90mmHg, those with a blood pressure level >or = 160/95mmHg had a -2.67 ([-4.01 to -1.32] P<0.001) mL x min (-1) x 1.73m (-2) greater annual decline in estimated glomerular filtration rate and a 5.21 - fold ([2.06 to 13.21] P<0.001) greater risk of early kidney function decline. Our study found that higher levels of treated blood pressure were positively and significantly related to early decline in kidney function among hypertensive men. These results

indicate that better blood pressure control might prevent the onset of chronic kidney disease among hypertensives.

Characteristics of treated hypertension in incident hemodialysis and peritoneal dialysis patients. Am J Kidney Dis. 2003 Dec;42(6):1260-9.

The US Renal Data System (USRDS) Dialysis Morbidity and Mortality Study Wave II cohort was analyzed. A total of 2,877 patients initiating hemodialysis or peritoneal dialysis in 1996 or 1997 and treated with antihypertensives were included in this analysis. Vital status was followed until November 2000. RESULTS: Calcium channel blockers were prescribed to 70.3% of patients. Only 31.5% and 27.0% of patients with cardiovascular disease were prescribed angiotensin-converting enzyme inhibitors and beta-blockers, respectively. Mono-double-triple and more than triple therapy were reported in 48.0%, 36.1%, 13.2% and 2.7% of the cohort, respectively. In multivariable, fully adjusted models, no individual class of antihypertensives was associated with changes in all-cause mortality. In all patients, nondihydropyridine CCBs (non-DHP CCBs) were associated with a reduced risk of cardiovascular death (hazard ratio, 0.78; 95% confidence interval, 0.62 to 0.97) and among end-stage renal disease patients with preexisting cardiovascular disease, dihydropyridine CCBs (DHP CCBs) and non-DHP CCBs were associated with reduced risk of all-cause and cardiovascular mortality. CONCLUSION : Calcium channel blocker use is widespread among hypertensive dialysis patients. Antihypertensive prescription patterns suggest a lack of consensus regarding treatment of hypertension. Multivariable analysis of associations between antihypertensive class and mortality reveals results of uncertain clinical significance. Hypertension treatment trials in dialysis patients should be performed to appropriately inform treatment decisions.

Bilateral Accessory Extensor Digitorum Muscle in Hand: A Case Report

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Abstract: During dissection, presence of bilateral accessory extensor muscle in the hand was observed in one cadaver. It showed differences in its origin, division into digital slips and additional features in relation to extensor digiti minimi muscle on both the sides. Its origin from the forearm (on both sides) was more extensive on the right side. It was seen to be dividing into three slips on the right side and four on the left. Interestingly, on both sides, no slip was observed for the ring finger. Extensor digiti minimi muscle was present on the right side but absent on the left, Extensor indicis-muscle was absent on both sides.

Key words : *Accessory extensor digitorum in hand.*

Introduction

Many an instance of supernumerary muscle on the dorsum of the hand have come to light since the entity was first described by Albinus in 1734¹. This extensor digitorum brevis manus was a controversial entity for a long time because it exhibited an infrequent clinical expression^{9,10,11}. It has appeared as a painful mass with repeated exercise, being misdiagnosed as a dorsal wrist ganglion, tendon sheath cyst, tenosynovitis of extensor tendons, hemangioma, and so on usually deleted on surgery^{4,5,7,9,10,11,12}. A chance encounter of this muscle during routine dissection is being presented here.

Case Report

Bilateral accessory extensor digitorum muscle in the hand was observed in one formaldehyde fixed male cadaver during routine dissection. It showed a number of differences on the two sides.

Right hand (Figure) the muscle originated from the lower end of dorsal surface of shaft of ulna, the adjoining interosseous membrane and intermuscular septa between it and adjoining extensor muscles. It divided immediately into three bellies, the tendons of which passed under cover of extensor digitorum tendons in the fourth osteogascial compartment beneath the extensor retinaculum. Each of the three slips (all of equal thickness) crossed the dorsum of the hand to pass to the thumb, index and middle fingers. At the level of the heads of metacarpals of these digits, the tendons merged with the extensor expansion. The extensor indicis_muscle was absent. The right and little fingers received no contribution from this muscle and the extensor digiti minimi muscle was present, as normally seen. The nerve supply to the muscle was through the posterior interosseous nerve.

Left hand The muscle was observed to be originating from the dorsal aspect of lower one third of the interosseous membrane and few fibers from adjoining shaft of ulna. Just after its origin the muscle was seen to divide into four small bellies, the tendons of which passed through the fourth osteofascial compartment under cover of extensor retinaculum deep to tendons of extensor digitorum.

The four slips crossed the dorsum of the hand to reach the thumb, index, middle and little fingers. The ring finger received no contribution. Of the tendons, one to the thumb was the thickest,

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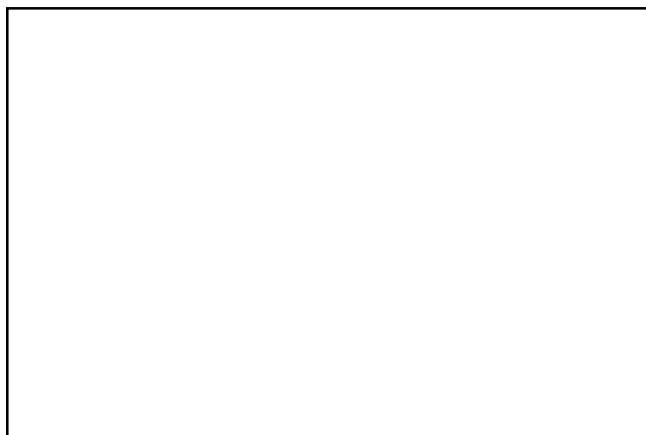


Fig.: The accessory extensor digitorum muscle in left hand.

followed by the index, little and middle fingers in decreasing order of thickness. The tendons were merging with the extensor expansion at the level of heads of metacarpals. The muscle was receiving its nerve supply from the posterior interosseous nerve.

The slip to the little finger divided into two, one inserting in the middle of the fifth metacarpal head like the others whereas the other passed laterally to merge with the extensor expansion. This probably replaced extensor digiti minimi, which was absent here. The extensor indicis was also absent.

Discussion

The extensor digitorum brevis manus is a rare muscle found on dorsum of the hand. This muscle has been described in terms of its anatomy, incidence, ontogeny, phylogeny and clinical significance by various authors. Its clinical expression on the dorsum of the hand is in the form of pain or swelling thereby leading to a misdiagnosis of a ganglion. However, in most cases it may be clinically asymptomatic and hence of minor importance and is therefore more of phylogenetic interest. During development, the extensors of the forearm are seen to differentiate from three parts: superficial, radial and deep⁴. The superficial layer gives rise to Extensor digitorum, Extensor carpi ulnaris and Extensor digiti minimi. The radial part forms Brachioradialis and Extensor carpi radialis longus and brevis whereas the deep part gives rise to Abductor pollicis longus, Extensor pollicis brevis and longus and Extensor indicis. The superficial and radial parts are phylogenetically stale whereas the deep part is not.

In early developmental stages, forearm muscles are derived from three groups: the brachioantebrachial acting on the elbow joint, the antebrachiomanual acting on the wrist joint and the manual group acting on joints of hand⁴. IN graduation to mammals, the brachioantebrachial group has undergone distal migration to lie superficial to antebrachiomanual group and the latter in turn has migrated distally to become continuous with brevis muscles of the hand. These later lose thier attachments to the carpus and become totally incorporated in the tendinous portions of long forearm extensors.

On comparing ontogenetic and phylogenetic development of individual muscles, it maybe deduced that brachioantebrachial group may have given rise to both superficial and radial layers and the antebrachiomanual to the deep layer. The manual group had disappeared completely.

Another theory put forward by Peeling⁸ suggests that the extensor digitorum brevis manus is derived from dorsal interossei but since the posterior interosseous nerve in the present study was supplying the muscle, this theory is questionable. Bingold², Boyes³ and Kaplan⁶ regard this muscle as homologous to the extensor digitorum brevis muscle of the foot. Since in the present study one of the muscle tendons was extending to the thumb (as in the foot) a conjecture of homology with the corresponding muscle in the foot may be made.

Since the Extensor indicis muscle was absent on the both sides, it may be considered that the Extensor digitorum brevis fmanus in the present study may be its representative, dividing into three and four slips in right and left hand respectively. It is interesting to observe that no contribution from this muscle extend to athe ring finger on both sides. Does it indicate an intermediate phase in evolution from a complete form (as in the foot) to its total

absence? The question is debatable.

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Free Radicals - A New Concept in Medicine

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Introduction

The recognition of organic free radicals by Gomberg in 1900 led inevitably to speculation that free radical species might be involved in living system and some enzymatic reactions involve free radical intermediates (Michaelis). However, it was not until the proposal by Slater in 1966 that the hepatotoxicity of carbontetrachloride was consequence of a free radical reaction that the idea of free radical-mediated processes forming a significant class of reactions in the generation of tissue injury gained a place in the purview of bio chemical pathology.

Free radicals are chemical species possessing an unpaired electron that can be considered as fragments of molecules and which are generally very reactive. They are produced continuously in cells either as accidental product of metabolism or deliverately (e.g. during phagocytosis). In aerobic cells the most important reactants in free radical are oxygen and its radical derivatives (super oxide and hydroxyl radical), hydrogen peroxide and transition metals. Reactive free radicals formed within cells an oxidise bio molecules and lead to cells death and tissue injury. Involvement of free radicals in the pathogenesis of a disease in difficult because of short life span of these species. But the clinical significance of this has been recognized only for the last few years.

Biochemistry of free radicals

Free radicals can be formed in three ways -

- By homolytic cleavage of a covalent bond of a normal molecule, with each fragment retaining on of the paired electron.
- By addition of a single electron to a normal molecule.
- By the loss of a single electron from a normal molecule.

Electron transfer mechanisms are more important and common in biological system than homolytic cleavages. Free radicals can be positively charged, negatively charged or electrically neutral.

Oxygen Free Radicals and Reactive Oxygen Species (ROS)

The most important free radicals in biological systems are radical derivatives of oxygen. Some of the important reactive oxygen species which are involved in pathogenesis of various diseases are listed in (Table-1).

Table 1. Reactive Oxygen Species

Species	Molecule	Species	Molecule
Superoxide ion	O ₂ ⁻	Nitricoxide	NO
Hydroxyl ion	OH	Ferryl ion	FeO ²⁺
Perferryl ion	FeO ₂ ²⁺	Allyl	R
Alkoxy	RO	Peroxy	ROO

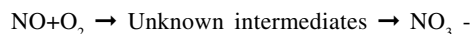
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Generation of Free Radicals in Cells

Respiratory burst : the host defence system against harmful organisms includes neutrophils, monocytes, eosinophils and macrophages which play their protective role by a metabolic event known as respiratory burst, in which a group of powerful oxidising agents like hypochlorous acid, hydrogen peroxide (H₂O₂) and number of oxygen radicals are injected in to phagocytic vacuole. Radical production is thus important for phagocytosis of internalized bacteria. This can be illustrated on patients with chronic granulomatous disease which suffer infections with certain organisms like staphylococcus aureus due to defective NADPH Oxidase system.

Eicosanoid metabolism : During the formation of endoperoxide 9,11- endo peroxy- 15- hydroperoxy prostaglandin (PGG₂) from arachidonic acid, a trace of hydroperoxide is required to react with the Fe(III) haem at the active site of cyclo-oxygenase enzyme to form a peroxy radical. This ROS can stereospecifically abstract a hydrogen atom from arachidonic acid to commence the process of PGG₂ formation. Excess of lipid peroxides can inactivate cyclo-oxygenase activity.

Endothelium-derived relaxing factor (EDRF) : EDRF is produced from vascular endothelium and is an important mediator of vasodilation. EDRF is now been identified as nitricoxide. The endothelium seems to continuously produce small amounts of superoxide which can react with nitricoxide to form nitrate ions, a non-radical product.



It is possible that the impaired endothelium- mediated vasodilation in diabetic patients could be related to increased free radical formation in vivo. NO is also produced by macrophages. In brain, nitric oxide synthetase (NoS) has been localized within neuronal cells with highest activity in neurons of the cerebellum and olfactory bulb.

Controlled leakage in enzymatic reactions : Sources of free radicals within the cells can be derived from inevitable leakage of superoxide anions from the mitochondrial electron transport chain. In addition, many compounds will react with molecular oxygen to form superoxide. Radicals may be generated during metabolism of various drugs by cyt P 450 microsomal oxidation systems, e.g. paracetamol, alcohol. Lastly, some enzymes are known to catalyse the formation of free radicals; for e.g., xanthine oxidase catalyses the conversion of hypoxanthine to xanthine and also oxidizes to uric acid. In both reactions superoxide and hydrogen peroxide are formed.

Other sources : Apart from these, free radicals can also be generated from toxic environmental pollutant; ionizing radiations; gases like Ozone, nitrogenoxide; heavy metals like Hg, Pb; cigarette smoking; alcohol; emotional stress and many more.

Damaging Reactions of Free Radicals

All classes of biomolecules may be attacked by free radicals but lipids are the most susceptible. Cell membranes are rich source of polyunsaturated fatty acids (PUFAs), which are readily attacked by oxidising radicals. The oxidative destruction of PUFAs known

as lipid peroxidation is damaging because it proceeds as a self-perpetuating chain reaction. Lipid peroxidation is of particular significance as a damaging reaction consequent to free radical production in cells because : (i) it is a very likely occurrence, given the availability and susceptibility of PUFA in membrane; and (ii) is very destructive chain reaction that can directly damage the structure of membrane and indirectly damage other cell components by reactive aldehyde production. Proteins, nucleic acids and carbohydrates are less susceptible. Random attack of radicals on proteins is unlikely to be very damaging unless very extensive. On proteins, it causes inactivation of enzymes. It damages nucleic acid by causing break in DNA strands leading to abnormal cell multiplication.

Assessment of Free Radicals

Direct detection of free radicals within biological systems is difficult because of their low concentrations and their extremely short life-span. Currently, **three principal approaches** are used to ascertain whether oxidative stress has occurred : (a) **by exogenous spin traps and free radical indicators**; (b) **by detection of free radical products**; (c) **by antioxidant status**

Exogenous spin traps and free radical indicators : The spin trap phenyl-Nt-butyl nitron reacts rapidly with free radicals to form a relatively stable spin adduct which can then be analysed by electron spin resonance. Hydroxyl radicals generated within biological fluids can be trapped by salicylate to form a 2, 3-dihydroxybenzoate, which can then be quantiated by high-performance liquid chromatography (HPLC).

Detection of free radical products - Numerous methods for detection of reaction products have been published but unfortunately they are nonspecific.

Protein oxidation : Schiff's bases are produced when an aldehyde reacts with amino groups. This can be detectable by Fluorescence spectroscopy and is considered to be a highly significant marker of free radical generation.

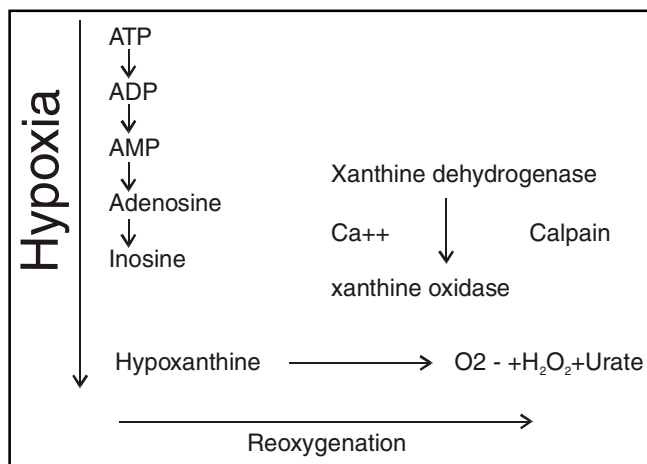
Lipid peroxidation : The detection of products of lipid peroxidation in biological materials has provided the basis for several popular assays for reactive oxygen species. Different methods used are Diene conjugates, Thiobarbituric acid test and Volatile hydrocarbons measurement.

Antioxidant status : Recently, biological fluids have been investigated for their antioxidant status either by direct measurement of the cytoprotective enzyme activities and antioxidant content or by the capacity of the sample to quench an *in vivo* generating system.

Role of Free Radicals in Disease Pathogenesis

In Ischaemic reperfusion damage : one of the more recent advances in free radical research has been the realization that reactive oxygen species may be generated during the reperfusion of ischaemic tissue. This is important in organ transplantation. There is considerable evidence that injury to ischaemic tissue occurs exclusively during reperfusion phase. Such a process is reliant on two important constituents, xanthine oxidase and a trace amount of catalytic iron such damage is also clearly relevant in patients of acute myocardial infarction and cerebrovascular accidents. Reperfusion injury may even play a role in the exacerbation of damage in patients with rheumatoid arthritis (Box).

In Carcinogenesis : Exposure to active oxygen species in aerobic organisms is continuous and unavoidable. Cancer in humans and animals is a multistep process. The complex series of cellular and molecular changes that occur through the development of cancer can be mediated by diversity of exogenous and endogenous stimuli.



Mechanism for free radical injury induced by anoxia-reoxygenation

Active oxygen species and other free radicals have long been known to be mutagenic; further, these agents have more recently emerged as mediators of the other phenotypic and genotypic changes that lead from mutation to neoplasia.

In Shock related cell injury : Shock related organ failure evolves from a variety of starting points - ischaemia, reperfusion, nonbacterial or bacterial inflammation - several mechanisms are involved. In addition to the effects of xanthine oxidase after ischaemia/reperfusion, toxic oxygen species from phagocytes that accumulate in both intra and extravascular tissue spaces are of central importance. Damage of membranes by lipid peroxidation and by exposure to mediators leads to increased permeability, tissue edema and organ dysfunction.

In Atherosclerosis : It is hypothesized that it is initiated by damage to the vascular endothelium. Endothelial cells are known to be sensitive to damage by ROS and lipid hydroperoxides. Macrophages play an important role in the development of atherosclerotic lesion. Activated monocytes and macrophages could injure neighbouring endothelial cells by secreting superoxide, H_2O_2 and hydrolytic enzymes, while factors released by macrophages can stimulate smooth muscle cell proliferation. Macrophages possess receptors for LDLs, but if LDL has already undergone lipid peroxidation it is recognized by a separate class of receptors known as Scavenger receptors. These modified LDL are taken up with greater efficiency, leading to rapid accumulation of cholesterol in macrophages and their conversion to foam cells, characteristic of atheromatous lesion.

In Inflammation : In man, free radicals play a role in a variety of normal regulatory systems, the deregulation of which may play an important role in inflammation. As examples, the second messenger roles of : NO in the regulation of vascular tone, O_2^- in the fibroblast proliferation and H_2O_2 in the activation of transcription factors such as NFkB. At the site of inflammation, increased free radical activity is associated with activation of the neutrophil NADPH oxidase and the uncoupling of a variety of redox system including endothelial cell xanthine dehydrogenase. Although free radicals thus produced, have the capacity to mediate tissue destruction, disturbances in the second messenger and regulatory activities of free radicals may also contribute significantly to inflammatory process.

Free radicals primarily attacks on PUFAs. The overall effect of peroxidation is to decrease membrane fluidity, destabilising membrane receptors. Lipid peroxidation products can inhibit protein synthesis, block macrophage action and cause changes in chemotaxis and enzymic activity.

In Neurological disorders : Reactive oxygen metabolites; namely

superoxide and hydroxyl radical and H_2O_2 , are produced as a consequence of the physiological metabolic reactions and functioning of the CNS. Evidences suggest that in several neurological diseases, for example Parkinson's disease, Huntington's disease, Alzheimer's disease and multiple sclerosis, there is iron accumulation secondary to the initial toxic lesion. The reason is uncertain but such accumulates exacerbates the initial lesion by generation of reactive oxygen species (ROS).

Diabetes mellitus (DM) : Diabetes mellitus is a syndrome initially characterized by a loss of glucose homeostasis. The disease is progressive and is associated with high risk of athero-sclerosis, renal and nerve damage as well as blindness. Abnormalities in the regulation of peroxide and transition metal metabolism are postulated to result in establishment of the disease. DM is associated with oxidative reaction, particularly those which are catalysed by decompartmentalized transition metals but their causative significance in diabetic tissue damage remains to be established.

In prematurity : In recent years increasing experimental and clinical data have provided a number of evidence for the involvement of oxygen free radicals in three main disorders of prematurity-chronic lung disease, retinopathy and intraventricular haemorrhage. Infants born prior to 30th week gestation or weighing less than 1500gm. at birth appears to be at risk. The basis for free radical involvement in these disorders is that oxygen centred radicals and related reactive oxygen metabolites are formed too rapidly to be detoxified by the antioxidant defence mechanism. In case of chronic lung disease, evidence currently favours excess oxygen as the cause of greater oxygen free radical production, whereas in retinopathy and intraventricular haemorrhage it is proposed that low oxygen tension followed by periods of reoxygenation is the more likely stimulus for excess radical formation.

In aging : Recent data available on free radical theory of aging confirm that aging is associated with an impaired control of oxygen homeostases. The presence of a system of antioxidant defence in all aerobic organisms indicates that the involvement of oxygen in the preservation of anaerobic life necessarily involves the production of activated oxygen species. The question is therefore, whether the loss of control of oxygen homeostasis acts in concert with other factors to trigger the inevitable process of aging or whether oxidative stress is an inevitable consequence of other molecular events. The failure to extend maximal life span by the attempt to maintain oxygen homeostasis appears to be inconsistent with the free radical theory of aging. If oxidative stress were to be recognized as a major factor which causes aging, the question then arises how the imbalance between pro and antioxidants is established. It can be said with certainty that oxidative stress is able to promote the process of aging and also to increase the probability of age specific diseases where free radicals are implicated.

Prospects for treatment of free radical-mediated tissue injury

Toxic metabolites of oxygen have emerged as a major final common pathway of tissue injury in a wide variety of disparate disease processes. Consequently, free radical ablation offers a substantial potential for the treatment of human diseases. This is because many constituents of the cell are potentially subject to free radical injury. The progression from free radical generation to tissue injury yields many levels for potential interventions. These can be classified into five major levels-

- (i) blockade of initial generation of toxic oxidants,
- (ii) scavenging oxidants e.g., superoxide dismutase (SOD)
- (iii) blocking the chain of toxic oxidants e.g., α -tocopherol

- (iv) enhancing endogenous antioxidant capability of the target
- (v) blocking secondary generation of toxic metabolites and/or mediators

The endogenous antioxidant system provides an important defence mechanism that allows the organism to cope with daily attacks of oxidative stress. Cellular compartmentalization is probably the most important endogenous mechanism of defence. Mitochondria, lysosomes, peroxisomes they are provide separate microenvironments in which free radicals are generated and coupled immediately to adjacent antioxidants defence system. Some of these endogenous antioxidants are summarized in Table-2. An important part of antioxidant defence system in side cells are the antioxidant enzymes, e.g., superoxide dismutase (SOD) which scavenges superoxide anion. It was recently discovered that the gene for SOD is defective in patients of Amyotrophic Lateral Sclerosis (ALS) also known as Lou Gehrig's disease. Other enzymes like catalase, glutathione peroxidase, ALA etc. have their role in antioxidant defence.

Table 2. Endogenous Antioxidants

Antioxidants	Comments
Enzymatic	
Cytochrome oxidase system	Detoxifies 95-99% of O_2 in cell
Catalase	Detoxifies H_2O_2
Peroxidase	Detoxifies H_2O_2
Superoxide dismutase (SOD)	Detoxifies superoxide anion
Glutathione peroxidase	Detoxifies H_2O_2
Non-Enzymatic	
Lipid soluble	
a-tocopherol	Vitamin E
b-carotene	Vitamin A precursor
Water Soluble	
Glutathione	---
Ascorbic acid	Vitamin C
Urate	Scavenges $O_2^{\cdot -}$, OH
Cysteine	Scavenges $O_2^{\cdot -}$, OH
Albumin	Scavenges LOOH, HOCl
Bilirubin	Scavenges $O_2^{\cdot -}$, OH
Ceruloplasmin	Detoxifies superoxide anion
Transferrin	Binds circulating iron
Lactoferrin	Binds circulating iron
Ferritin	Binds tissue iron
Haemopexin	Binds haem and prevents it from decomposing lipid peroxides

In addition to the antioxidant enzymes, there are small endogenous molecule antioxidants that play a role in defence mechanism. These molecules of antioxidants are important particularly in blood and fluids present in extracellular compartment, where antioxidant enzymes are absent or present in very minute quantities. These small molecules are lipid soluble and water soluble antioxidants summarized in Table-II. However, in many pathophysiological conditions, local endogenous antioxidants become incapable to overcome the tissue injury caused by free radicals. In such cases, the administration of exogenous antioxidants, as listed in Table-3, may be salutary.

The **beneficial effects** of various antioxidants in different clinical conditions are detailed below -

Role in Atherosclerosis and cardiovascular diseases :

- in endothelium, e.g., inhibition of lipoxigenase and thus of oxidative LDL modification, prevention of cellular transitions, reduction of monocyte adhesion.
- in smooth muscle cells, e.g., inhibition of proliferation and of the signal transducing protein kinase.
- in blood platelets, e.g. inhibition of platelet adhesion.

Table 3. Exogenous (Pharmacological) Antioxidants

Class of Agent	Specific Agent	Mechanism of action
Xanthine oxidase inhibitors	Allopurinol Oxypurinol Folic acid tungsten Pterin aldehyde	Inhibit superoxidation by Xanthine oxidase
Protease inhibitors	Soyabean trypsin inhibitor Other serine protease inhibitors	Block proteolytic activation of Xanthine oxidase from Xanthine dehydrogenase
NADPH oxidase inhibitors	Adenosine Local anaesthetics Ca++ channel blockers NSAIDs Cetiedil Diphenylene iodonium Monoclonal antibodies to NADPH oxidase	Inhibit superoxide generation by NADPH oxidase in neutrophils and macrophages
Superoxide dismutase (SOD)	Native SOD Polyethylene glycol-SOD Liposome-encapsulated SOD	Catalyse $O_2^- + 2H_+ \rightarrow H_2O_2$
Catalases	Native catalase PEG-catalase	Catalyse $O_2^- + 2H_+ \rightarrow H_2O_2$
NADPH oxidase inhibitors	Adenosine Local anaesthetics Ca++ channel blockers NSAIDs Cetiedil Diphenylene iodonium Monoclonal antibodies to NADPH oxidase	Inhibit superoxide generation by NADPH oxidase in neutrophils and macrophages
Superoxide dismutase (SOD)	Native SOD Polyethylene glycol-SOD Liposome-encapsulated SOD	Catalyse $O_2^- + 2H_+ \rightarrow H_2O_2$
Catalases	Native catalase PEG-catalase Lipase encapsulated capsule	Catalyse $O_2^- + 2H_+ \rightarrow H_2O_2$
Non-Enzymatic free radical scavengers	Mannitol Albumin Dimethyl sulfoxide Glutathione Urate Bilirubin Lazaroids	Scavenges OH Scavenges LOOH, HOCl Scavenges OH Scavenges H_2O_2 , OH Scavenges O_2^- , OH Scavenges free radicals Scavenges LOOH, O ₂ -
Inhibitors of iron redox cycling	Desferoxamine Apotransferrin Ceruleplasmin	Bind free Fe ³⁺
Substances that augment endogenous antioxidants	Ebselen Oltipraz Glutathione Acetylcysteine	Augment endogenous glutathione peroxidase activity
Antineutrophil agents	Antineutrophil serum Antiadhesion agents - Monoclonal antibodies to CD11/CD18 - Soluble GMP140 Platelet activating factor antagonists - BN52021 - WEB2086	Depletes circulating Neutrophils Inhibit neutrophil adhesion to endothelia Inhibit neutrophil adhesion and extravasation

- improves immunoresponses
- in macrophages; modulation of their migration into subintimal space, reduction of LDL-modifying 'respiratory burst' of radicals, diminishing foam cells formation by improving the catabolism of modified LDL, reduced production of cytokines like IL-1.

Glutathione, a sulphur containing naturally occurring amino acid function to decrease the formation of LDL which plays an important role in development of athero-sclerosis.

Role of antioxidants in radiation injury : Irradiation produces a cascade of free radicals. Antioxidants have been used to treat irradiation damages. These compounds also decrease the harmful effects caused by cancer chemotherapy. Submucous fibrosis, leucoplakia and photoradiation have been shown to be greatly benefited.

Role in ischemia reperfusion injury : Reperfusion of a previously ischaemic area has been shown to promote the release of free radicals. The rapid free radical activity is due to transition metal ions released by cells with subsequent damage of sarcoplasmic reticulum and membranes leading to impaired handling of calcium and other ions. SOD, catalase, tocopherol, allopurinol, desferrioxamine and glutathione improves the out come.

Role in cancer : Smokers have defective antioxidant protection. Tobacco smoke is rich in free radicals which damages the DNA causing lung cancer. Antioxidants block oxidative DNA damage resulting from carcinogen induced generation of free radical. Vit C and E inhibit nitrosamine formation and fecapentene production. N-acetyl L-cysteine reduces the occurrence of experimental tumours of lungs, colon and liver.

Antioxidants in diabetes mellitus : There is a major role of free radicals in pathophysiology of IDDM, retinopathy and nephropathy. Glucose combines with serum proteins and lipoproteins in a non-enzymatic glycation reaction and may auto-oxidise generating free radicals.

Antioxidants are shown to inhibit glucose auto-oxidation and reduce covalent linking of glucose to serum proteins and inhibit the glycation of serum proteins providing a promising future for the treatment of diabetic complications.

Role in organ transplantation : Studies show that antioxidants can decrease endothelial damage and prolong graft survival. Human recombinant SOD when given to recipients of renal transplants had reduced the rejection events and improved the graft survival.

Antioxidants and neurological disease : Brain is very vulnerable to free radical injury after any trauma and/or hypoxia because of high lipid and poor iron binding capacity. Clinical trials have shown the neuroprotective role of 'lazaroids', which are inhibitor of iron dependent lipid peroxidation. IN Parkinsonism, oxidative metabolism of dopamine is probably in-volved in production of oxidants. Increased Fe and Al and reduced glutathione has been bound thus clearing the way for antioxidants. MAO inhibitors like selegiline possibly decrease radical formation, thus slowing the disease progression. Antioxidant in brain are glutathione (in astrocytes) and vit. C (neurons).

Role in AIDS : Reports indicate that AIDS patients have less glutathione level. Thiol donating compound have been shown to inhibit viral replication and potentiate the effects of zidovudine.

Role in prematurity : Tocopherol has shown to reduce the incidence of retrolental fibroplasia, intraventricular haemorrhage and respiratory distress syndrome in neonates.

Role in cystic fibrosis (CF) : CF is associated with severe oxidative stress. Due to pancreatic involvement there is failure to absorption of fat soluble antioxidants. Supplementation of antioxidants have thus an attractive role.

Antioxidants in pregnancy and eclampsia : It has been shown that lipid peroxidation products are high and total serum antioxidants level are low in such patients, thereby implicating increased levels of fibronectin and endothelial damage. Role of antioxidants in such cases are on trial.

Role in inflammatory diseases : Antioxidants have a role in treatment of rheumatoid arthritis, Crohn's disease and ulcerative colitis.

Role in skin diseases : Human skin presents the first line of defence and the surface of skin must be equipped to deal the free radical damage. Depressed levels of antioxidants like glutathione is observed in patients with psoriasis, eczema, atopic dermatitis, vasculitis and mycosis fungoides. Therefore supplementation have shown an encouraging result.

Role in ophthalmology : Various epidemiological studies have shown that use of antioxidants reduces cataract possibly because of the role of free radical generating UV-B radiations in cataract formation. Lutein and Zeaxanthin are protective against macular degeneration.

Role in other diseases : Antioxidants defence is also seen in congestive cardiac failure, chronic renal failure, liver cirrhosis, systemic sclerosis, malaria, pancreatitis, shock etc.

Conclusion

Free radicals are constantly being generated in biological system either accidentally or deliberately. These free radicals which are highly reactive species react with biomolecules like lipids, proteins, nucleic acids etc. causing tissue injury and cell death. To limit their damage and to prevent free radical formation our body has developed a comprehensive array of antioxidant defence system. These include both enzymatic (like SOD, glutathione, peroxidase, ALA) and non-enzymatic (like ascorbic acid, tocopherol etc.) antioxidants which act by various mechanisms. Apart from this there are large number of exogenous antioxidants taken in the

form of dietary or pharmacological products which helps to contribute to natural antioxidant defence mechanism and may protect us from certain age related degenerative processes, various cancer and viral and other diseases. Although the choice of antioxidants may be important, the therapeutic time frame of the insult appears to play an even more critical role in the treatment of free radical mediated human diseases.

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Vaccine Preventable Diseases

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Abstract: Immunizations rank among the greatest public health accomplishments during the twentieth century. Childhood immunization is responsible for a substantial decrease in the morbidity and mortality from certain childhood illnesses globally. Health care providers must remain diligent and aware of the various vaccine preventable diseases and their respective vaccines in order to achieve and sustain the high vaccination levels necessary to prevent transmission of these diseases. It is imperative that no child remains unimmunized due to lack of awareness. Certain vaccines like BCG, DPT, OPV and measles are already included in the Indian National Immunization Schedule. The Indian Academy of Pediatrics has also recommended the inclusion of vaccines for mumps, rubella, hepatitis B (HB), Haemophilus influenzae type b (Hib) infection and Typhoid in the national immunization policy. Additional vaccines like those against hepatitis A and chicken Pox, vaccines have recently been introduced in India and are considered to be highly efficacious and safe. Vaccines against meningococcal infections and Japanese B encephalitis are recommended for use in epidemics. Certain high-risk groups of children need to be vaccinated against pneumococcal infection and Influenza. The anti-Rabies vaccine can be administered both pre-and post exposure. The increase in the number of effective vaccines suitable for use in infancy and early childhood has introduced substantial economic and logistical difficulties. Combination vaccines protect against many pathogens by combining all the antigens recommended for routine immunization into a single multivalent product. Those commonly being used include DT, TB, DPT, IPV, OPV, MR and MMR. The newer vaccines also incorporate conjugate Hib, acellular pertussis, or HB antigens. Advances in genetic engineering and molecular biology have led to more sophistication in vaccine production and administration. Extensive research is being done to develop futuristic vaccines for protection against dreaded diseases like HIV, malaria and tuberculosis.

Introduction

Immunizations rank among the greatest public health accomplishments during the 20th century. Childhood immunization is responsible for more lives saved worldwide, than any other medical innovation. The continued control of vaccine preventable diseases generally will require continued immunizations, at as high a coverage as possible. To make this possible it is essential that one is aware of the various diseases that can be prevented by vaccination. Health care providers must remain diligent and informed in order to achieve and sustain the high vaccination levels necessary to prevent transmission of disease.

Vaccine Preventable Diseases covered under National Immunization Schedule (Table 1)

Tuberculosis :

Tuberculosis (TB) is caused by Mycobacterium tuberculosis. Transmission is by droplet inhalation. The respiratory tract is the commonest portal of entry and the commonest form is pulmonary. Miliary and meningitis presentations are life-threatening. Although commonest in adults, the disease is usually more serious in infants, children and adolescents. TB kills more people worldwide than any other infection. There are 15-20 million cases of infectious TB, worldwide, with 4-5 million new cases and 3 million deaths, annually. In India the number of cases at any one time is estimated to be at least 1.5% of the population suffering from radiological active disease, with about 25% of these being sputum positive¹.

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Table 1. National Immunization Schedule.

Age	Vaccine
Birth	BCG, OPV 0
6 weeks	DPT1, OPV 1
10 weeks	DPT2, OPV 2
14 weeks	DPT3, OPV 3
9 months	Measles
16-18 months	DPT booster, OPV 4
5 years	DT
10 years	TT
16 years	TT
Pregnancy	TT (2 doses, 4 weeks apart)

BCG vaccine : The BCG (Bacille Calmette-Guerin) vaccine is a live, attenuated vaccine made from Mycobacterium var bovis. The original vaccine has been sub-cultured in different media in variable conditions leading to the production of many BCG vaccines, which differ in morphology, growth characteristics, sensitizing potency and animal potency. The Danish 1331 strain is recommended by the World Health Organization. Although the infection with BCG is localized, it induces cell-mediated immunity and some protection. Numerous, randomized, controlled trials have shown variable (0-80%) protection². Effectiveness rates are highest among those who get the vaccination in early childhood.

A single dose (0.1 mg in 0.1ml) should be given as soon as possible after birth, intra-dermally. The vaccine is a freeze-dried preparation, reconstituted with normal saline. It should be used within 4-6 hours of reconstitution as the organisms are temperature sensitive and bacterial contamination may occur. Bacterial multiplication leads to the development of a papule, which may ulcerate. The complete evolution of this lesion, to healing with

scar formation may take up to 6-12 weeks.

Common reactions to the TB vaccine include local reactions at the injection site. Local ulceration and regional suppurative adenitis occur in 0.1-1% while TB meningitis or disseminated TB may occur in 0.006-1.56 per million vaccinated. It may rarely cause osteitis, but this was apparently due to certain strains which are no longer widely used. Serious or long-term complications after immunization are uncommon. Contraindications are generalized eczema, infective dermatitis, hypogammaglobulinemia and severe immunosuppression³.

Diphtheria

Diphtheria is a bacterial infection caused by *Corynebacterium diphtheriae*, transmitted by droplet infection from carriers. It usually affects the respiratory tract. Diphtheria usually begins with a sore throat, slight fever, and swollen neck. Bacteria multiply in the throat, where a grayish membrane forms. A toxin is released which causes muscle paralysis, myocarditis, renal failure and death. Approximately 5% die from the disease and many more suffer permanent damage.

Diphtheria was a cyclical epidemic disease, but with increasing DPT immunization, it now occurs as sporadic cases and intermittent outbreaks of low intensity. However, in areas where the immunization rate has fallen, resurgence has been seen. Recent outbreaks have also demonstrated a shift in the age distribution to older children and adults⁴.

Pertussis

Pertussis (whooping cough) is caused by *Bordetella pertussis*. The infection is transmitted by droplet infection. Although it may occur at any age, maximum morbidity and mortality are observed in early infancy. The incidence of pertussis in older individuals varies with the frequency of exposure to *B. pertussis* and the vaccination coverage. Virulence factors include pertussis toxin, filamentous haemagglutinin, fimbriae and pertactin. Following an incubation period of 7-10 days, susceptible individuals develop catarrhal symptoms, which gradually develop into whooping paroxysms. Pneumonia is a common complication; seizures and encephalopathy occur more rarely. In its early stage pertussis is highly communicable, with a secondary attack rate of up to 90% among non-immune household contacts. Pertussis occurs endemically and epidemically. Worldwide, it causes 20-40 million cases of pertussis and 200,000-400,000 fatalities annually. Mortality rates in developing countries range from 4-15% in infants¹.

Pertussis vaccine : Pertussis results in long-lasting but not necessarily lifelong immunity. Currently, approximately 80% of the world's children are vaccinated with inactivated whole cell vaccines (wP). However due to serious adverse effects, the acellular pertussis (aP) vaccine was developed. This contains different components of *B. pertussis* and shows similar efficacies with wP vaccines (70%-90%). The duration of immunity after wP wanes over time, therefore young adults even if vaccinated in childhood can still develop pertussis. The duration of immunity after aP is still unknown. WHO endorses the use of aP vaccines in countries where wP vaccination is not widely accepted because of its reactogenicity. The main impediment to their wider use is their high cost- and concern about the duration of protection. A

number of aP vaccines are now available, either as individual vaccines or DTaP combinations, with or without the addition of hepatitis B, Hib, or inactivated polio vaccine⁵.

Immunization with wP vaccines is frequently associated with local reactions, fever and agitation. Prolonged crying and seizures are less common (<1%) whereas hypotonic-hyporesponsive episodes (HHE) are rare (<1 in 2000). Acute encephalopathy can also occur in temporal association with wP immunization, but very rarely (<1 in 10.5 million). In large multicentre studies, aP proved to be significantly less reactogenic than the wP vaccines in terms of high fever, seizures and HHE's. No causal link has been identified between either vaccine and permanent neurological damage or death³. Absolute contraindications to pertussis vaccine administration are anaphylaxis to previous vaccination and encephalopathy within 7 days of vaccination. Relative contraindications are seizures within 3 days, persistent, inconsolable crying for more than 3 hours within 48 hours, HHE occurring within 48 hours, temperature of more than 104°F, unexplained by any other cause within 48 hours and progressive neurological disorders⁶.

Tetanus

Tetanus is acquired through environmental exposure to the spores of *Clostridium tetani*. The disease is caused by the action of a potent neurotoxin. Tetanus results in severe, paroxysmal, muscle spasms. Tetanus may be post-traumatic, post-puerperal, otogenic, neonatal or idiopathic. Infection does not stimulate immunity. Tetanus is now a comparatively rare disease in the developed countries. However in developing countries neonatal tetanus is still a major health problem. Neonatal tetanus continues to be seriously underreported, since the populations at highest risk tend to live in rural areas and have the poorest access to health care and birth registration. The WHO and UNICEF have set a target of elimination of maternal and neonatal tetanus by 2005, where elimination is defined as a rate of neonatal tetanus below 1 per 1000 live births, per year, at the district level.

Tetanus toxoid : Protection is acquired through tetanus toxoid-containing vaccines (TT, DTP, DT, Td), which can be given before birth, continued during infancy, and be sustained by reinforcing doses in older individuals⁷. Doses given at the time of school entry should be Td (or TT if Td is not available). The IAP recommends TT at 10 and 16 years and then every 10 years⁸. The total number of doses is 7 by the age of 16 years. Each dose (0.5ml) is given intra-muscularly (IM). Protection against *neonatal tetanus* is determined by the maternal immunization status. Previously unimmunized women should receive two doses of TT or Td during their first pregnancy. Both doses should be at least four weeks apart, and the final dose should be given at least two weeks before delivery. Single dose, during each subsequent pregnancy up to a maximum of five doses should be continued. Supplementary immunization should be conducted in order to vaccinate at least 90% of women of childbearing age with three properly spaced doses of tetanus toxoid in high-risk areas where women have not been sufficiently immunized. This provides protection for at least five years. Women who have received a full course of 7 doses do not require immunization during pregnancy for another 10 years. Subsequently boosters should be continued as the norm. Immunization in addition to the use of clean practices during delivery, improved access to health care, and umbilical cord care should be successful in eliminating neonatal tetanus.

Elimination is maintained in former high-risk districts by strengthening routine antenatal vaccination and school-based immunization.

Diphtheria-Pertussis-Tetanus (DPT) vaccine : In the mid-1940s, the diphtheria toxoid was combined with tetanus toxoid and wP vaccine to formulate DPT. According to WHO. According to WHO, the priority for every country is to reach at least 90% coverage with three primary doses of DTP, however since 1990 the global coverage has only been around 80%. Other combinations available are DTaP, DTaP in combination with Haemophilus influenzae type b (Hib) vaccine, hepatitis B or inactivated polio vaccines⁷. DTaP is now recommended because the rate of serious reactions is lower. It is also about 95% effective in preventing diphtheria, while the protection rates are lower for pertussis and higher for tetanus. Diphtheria and tetanus toxoids do not produce lifelong immunity. Hence a booster dose of Td (tetanus-diphtheria) vaccine is needed every 10 years to maintain immunity. Each dose of DPT (0.5ml) should be given IM. The immunization schedule includes 3 primary doses during the first year of life; a booster dose in the second year and another booster at the age of 4-6 years. From seven years onwards, the adult form (Td) is used which contains approximately one-tenth of the amount of diphtheria toxoid in the paediatric form. It is used because prior subclinical infection by C. diphtheriae, or vaccination, may cause increasing sensitivity to the diphtheria component. Fifty percent of DTP vaccinees will experience no side effects. The others will experience mild reactions such as local soreness, fever, reduced appetite, tiredness, or vomiting. Some children may experience a temporary swelling at the site where DTaP was given (commoner after the fifth dose). Rarely, serious reactions (usually due to the pertussis component) may occur. Children who experience adverse reactions to DTwP or DTaP should receive DT for each of the remaining doses in the primary series.

Poliomyelitis

Polio is an intestinal viral infection caused by picornaviruses, that spread mainly via the faeco-oral route and rarely by droplet infection. There are 3 serotypes (1,2 and 3). Main is the only known reservoir of infection. Cases are most infectious 7-10 days before and after the onset of symptoms. Most people infected (approximately 95%) are asymptomatic. Abortive polio with minor symptoms (sore throat, low-grade fever, nausea, and vomiting) occurs in 4-8%. One to two percent will have non-paralytic polio while less than 1% develop paralysis. The most vulnerable age group is between 6 months to 3 years⁹.

In the pre-vaccination era, polio was found worldwide. Following the Salk (inactivated) polio vaccination from 1955 onwards, the incidence fell dramatically. It was further reduced by the advent of the Sabin (oral) polio vaccine in 1961. Currently widespread vaccination has virtually eliminated it from the developed countries. However, as long as small pockets of unimmunized persons exist, even in these areas there is a risk of sudden outbreaks. Polio still remains a major threat in developing countries. In India the last epidemic occurred in 1987.

Oral polio vaccine (OPV) and Inactivated polio vaccine (IPV): OPV is a trivalent, live attenuated vaccine while IPV is a formalin-inactivated, vaccine, containing 20, 2 and 4D antigen units of serotypes 1,2 and 3 respectively. A modified and improved IPV, which is more potent and has better antigen stabilization, is available

containing 40, 8 and 32D antigen units (1). Both OPV and IPV are highly immunogenic and protective. OPV remains the vaccine of choice for global eradication as it helps to increase herd immunity, and replaces the wild polio strains by vaccine strains (10). Multiple doses are necessary to ensure antibody response to all 3 serotypes. The IPV vaccine is 90% effective after two doses and 99% effective after three doses. Duration of immunity is unknown. IPV is also available in combination with DTaP and hepatitis B vaccines. The primary three doses of OPV (3 drops each) and booster coincide with DPT vaccination. The IAP has recommended an additional dose at birth (or as early as possible-zero dose) and 2 doses as community campaigns each year (pulse polio), till the age of 5 years¹¹. IPV is given at 2 and 4 months followed by the third dose between 8 to 18 months.

Most people have no side effects to OPV. However it may cause vaccine associated paralytic polio (VAPP) in a very small percentage (about 1 out of 6.2 million doses), due to mutation of serotype 3. This is more likely to occur in those with weakened immunity. IPV does not cause any serious side effects. Some people have local soreness. However allergic reactions to certain trace constituents of IPV (streptomycin, neomycin and polymyxin B) may occur in hypersensitive individuals. Contraindications for OPV administration are HIV infection immunosuppressive states, contact with such people or pregnancy. Contraindications to IPV are anaphylaxis to the aforementioned trace constituents are pregnancy.

Measles (Rubeola)

Measles is caused by the Morbillivirus of the paramyxoviridae family, which spreads by droplet infection. The period of greatest contagiousness is at the end of the prodromal phase. The secondary attack rate is 90% in susceptible household contacts. Measles begins with a prodromal phase followed by a typical erythematous, maculopapular rash. Otitis media, pneumonia, croup, and diarrhea are common complications. Measles encephalitis and Subacute sclerosing panencephalitis (SSPE) occurs in 1 per 1,000 and 7 out of a million cases of natural measles, respectively. Death is more common in infants, malnourished children and immunocompromised persons. Measles is endemic worldwide. Epidemics tend to occur when the proportion of susceptible children reaches 40%. In India, with an increase in vaccination, the inter-cyclical intervals of measles have increased, while the intensity of each cycle has decreased¹.

Measles vaccine : Measles vaccine is a live, attenuated virus derived from the attenuated Edmonston strain. The measles vaccine does not contain any antibacterial preservative, hence the vial should be discarded within 4-6 hours of opening. Since the vaccine became available, there has been a 99% reduction in the incidence of measles. Immunity is life long. the vaccine is available as a monovalent form or as a combination vaccine-MR (Measles-Rubella) or MMR (Measles-Mumps-Rubella). The reconstituted vaccine is given as 0.5 ml, subcutaneously, at 9 months age (270 days). Infants less than 9 months old should receive the monovalent vaccine if there is a measles outbreak. In these children, a repeat dose should be given after 3 months. A mild 'measles like' illness may occur 5-10 days after immunization in 15-29% vaccinees. Contraindications to vaccine administration include people with allergies to gelatin or any other vaccine component, immunocompromised persons and pregnancy¹².

VPDs other than those covered under UIP

Mumps : Mumps is a viral infection, caused by Myxovirus parotiditis, which spreads by droplet infection. The secondary attack rate is 86%. It is largely an endemic disease and is prevalent worldwide. It usually begins with swelling and tenderness for one or more of the salivary glands. The disease is more severe in adults. Complications include orchitis (20-50% post-pubertal males), encephalitis and aseptic meningitis (15%), pancreatitis (2-5%), ovarian inflammation (5% post-pubertal females) and deafness (1/2,000). Higher rates of fetal death have been reported in the first trimester.

Mumps vaccine : It is a live attenuated vaccine made from the Jeryl Lynn strain. Post-widespread vaccination, the incidence of mumps and reported mortality has decreased substantially. The duration of long-term immunity is not known. It is available as a monovalent or a combination vaccine (MMR). Indications for the monovalent vaccine are people who cannot receive either or both of the other component vaccines in MMR and people who are immune to either or both measles and rubella. A single dose (0.5ml) given IM produces detectable antibodies in 95% of vaccinees. It is usually given at 12-15 months of age and older. Adverse reactions are rare.

Rubella (German Measles)

An RNA virus belonging to the togavirus family, which is transmitted by droplets, causes rubella. Infectivity is greatest when the rash erupts. It mainly affects children between 3 to 10 years. A single attack results in life long immunity. Rubella is usually a mild illness. Symptoms include low-grade fever, cervical lymphadenitis and a generalized rash. Complications include joint pain, encephalitis and thrombocytopenia. Transient arthritis may occur (in adolescents and women). Rubella in pregnancy often leads to congenital rubella syndrome (CRS), which is characterized by deafness, microcephaly, mental retardation, cataracts, heart defects, thrombocytopenia and diseases of the liver and spleen. The incidence and severity of congenital defects are greater if infection occurs during the first trimester.

Rubella vaccine : It is a live, attenuated vaccine, which was developed in 1962. The current vaccine available is derived from RA 27/3 strains. The rubella vaccine is highly immunogenic, promoting an antibody response in 95% of vaccinees. It probably provides life long protection. It is available as a monovalent or as MMR. Those who cannot receive other components of MMR or those who are immune to measles or mumps or both may receive the monovalent rubella vaccine, though MMR is usually recommended. The vaccine is given as a single dose (0.5ml), subcutaneously after the age of 1 year.

The primary goal for rubella vaccination is to prevent cases of CRS¹³. It is particularly important for post-pubertal women. Susceptible people working in childcare centers and institutions should be immunized to prevent transmission to pregnant women, as well as for self-protection. Susceptible women should be vaccinated at least 28 days before conception. About 0.5% of infants and 15% of post-pubertal females vaccinees may develop acute arthritis. It usually begins 1-3 weeks after vaccination. Occasionally lymphadenopathy may also occur. Contraindications are the same as for measles vaccine.

MMR vaccine : IN 1971, measles and rubella vaccines were

combined with the live attenuated mumps vaccine as the trivalent MMR. The respective strains used are Edmonston Zagreb (measles), L-Zagreb (mumps), and Plotkins RA 27/3 (Rubella). Both measles and rubella strains are produced using human diploid cells while the mumps strain is produced from chick embryo cells. The individual harvests are then pooled and blended to yield a virus concentration of more than 1000 TCID₅₀ for measles, more than 5000 TCID₅₀ for mumps and more than 1000 TCID₅₀ for rubella. The combined vaccine yields results similar to administering individual vaccines at different sites¹⁴. MMR has high levels of immunogenicity and low levels of reactogenicity. It causes adequate seroconversion and a significant reduction in the incidence of the three target diseases. Studies in Indian children using indigenously produced vaccine have shown almost total seroconversion against measles and rubella and 90% seroconversion against mumps¹⁵. Immunity is life long.

All infants, 12 months or older should receive MMR. Susceptible adults who do not have evidence of measles immunity (diagnosed case of measles, measles antibodies or proof of receiving the vaccine) may also receive the vaccine. The reconstituted vaccine (0.5ml) is given subcutaneously. IAP recommends a single dose at 12-15 months, if measles vaccine has been given at 9 months. If measles vaccine was missed, MMR can replace it after 12 months. In 1989, the American Academy of Family Physicians, the American Academy of Pediatrics, and the Centers for Disease Control recommended administration of two doses of MMR. This was done in order to immunize the small percentage of people who had primary vaccine failure. The first dose is generally given at 12 to 15 months, and the second dose at four to six years of age³. More than 80% vaccinees will have no side effects. The side effects are mainly due to the measles component. Most children will have mild local reactions, mild rash, low-grade fever, lymphadenitis and transient arthralgia or arthritis. In about 5-15% of children, high-grade fever and rarely (0.03%) febrile seizure may occur. In extremely rare cases (<1/10,000), serious reactions like coma, anaphylaxis or shock may occur. One per 22,000 vaccinations may cause idiopathic thrombocytopenic purpura (ITP). There are allegations that MMR causes autism or inflammatory bowel disease, which have not been proved. Contraindications for administration are similar to that for measles vaccine.

Haemophilus influenzae B infection

Haemophilus influenzae type b (Hib) is an important cause of meningitis and pneumonia in children less than 2-3 years old. It is transmitted through droplet infection. The secondary attack rate in household contacts is highest in children less than 2 years (3.2%) and rare in those older than 47 months (<0.1%). Invasive disease occurs most often at three months to three years of age, peaking at six to seven months of age. Hib can cause a wide spectrum of diseases: meningitis, pneumonia, cellulitis, epiglottitis, septicemia, osteomyelitis, otitis media, arthritis and pericarditis. Complications include blindness, deafness, mental retardation, learning disabilities, and death. About 5% of children with Hib meningitis die despite antibiotic treatment. Prior to universal Hib immunization, it was the most common cause of bacterial meningitis in preschool-age children. Mortality and morbidity still remains a problem worldwide, primarily in unvaccinated children.

Haemophilus influenzae B (Hib) vaccine : The first generation unconjugated Hib vaccine licensed in 1985 was made from the Hib capsular polysaccharide (PRP). Presently available vaccines

are conjugated to protein antigens to improve immunogenicity, by promoting a T-cell immune response. These include TT (PRP-T), DT (PRP-D), meningococcal outer membrane protein (PRP-OMP), or CRM 197, a nontoxic mutant diphtheria toxin (HbOC). Hib vaccine is more effective at providing immunity than natural infection. Hib vaccine is available as a monovalent form, or in combination with DTaP, DTaP or recombinant hepatitis B vaccine.

Due to the high risk of disease, all children younger than five years should receive the Hib vaccine, beginning at two months of age. High-risk groups are unimmunized children who are daycare attendees, household contacts, belong to a low socioeconomic status, or are immunocompromised (sickle-cell disease, leukemia, HIV infected or post-splenectomy). Children over five years do not need Hib vaccine unless they have specific immunosuppressive conditions. These children may not develop protective antibodies from a single dose and may require additional doses. As Hib is age dependent, immunization involves boosting of natural infection. When initiated below 6 months of age, 3 doses should be given (1-2 months apart), 2 doses between 6-12 months and a single dose, between 12-15 months. A booster is recommended at 15 to 18 months. Beyond 18 months a single dose is recommended up to 5 years of age. Approximately 25% of children who receive the Hib vaccine experience mild side effects such as local reactions. Serious reactions are infrequent. No scientific association between diabetes and Hib vaccination has been found till now, as some authors claim¹⁶. Contra-indications to vaccine administration include children younger than six weeks and people who have had previous anaphylaxis to the vaccine.

Hepatitis B : Hepatitis B virus (HBV) is transmitted through the parenteral route, perinatal transmission, sexual contact, and rarely by surface contact. It is most commonly spread to infants by vertical transmission. Approximately 30% have no known risk factors.

HBV primarily affects the liver. Symptoms of infection include loss of appetite, fatigue, nausea, jaundice, joint pain, and skin rashes. More than 50% show no signs or symptoms, although they may become chronic carriers and develop chronic liver disease or cancer later on. Approximately 90% who are infected by vertical transmission, and 3-50% of those infected before five years, become chronic HBV carriers. People who are infected as adults have only a 6-10% risk of chronic infection. Worldwide, over 350 million people have chronic HBV infection, and approximately 1 million HBV patients die annually. Hepatitis B is a major health problem in India. About 30-40% of deaths due to viral hepatitis were due to HBV (1). In India, 3-7% of individuals are chronic carriers¹⁷. Hence, hepatitis B immunization is recommended for routine administration in countries with a high prevalence rate of HBV infection. The WHO recommends universal HB vaccination. Unfortunately the high cost has been a major deterrent for inclusion in national immunization programmes in many countries. Delhi State Government has included HB vaccination in the immunization schedule, free of cost since 1996. Govt. of India has also initiated this as a pilot project in some states/cities since 2002. However, it is yet to be included throughout the country.

Hepatitis B vaccine : HB vaccines are highly purified preparations of HbsAg. These are available as plasma derived vaccines, or recombinant vaccines (the viral genes are incorporated into yeast or mammalian cells). These vaccines are safe and immunogenic. The recombinant hepatitis B vaccines are 95% protective after a

3 dose course. Immunity is probably life long. Hepatitis B vaccine is available as a monovalent form, or in combination with Hib vaccine, DTaP, IPV or Hepatitis A vaccine¹⁸.

Everyone 18 years and younger should receive the HBV vaccine. High-risk adults (promiscuous individuals, health care workers, homosexuals, or drug addicts) should also receive the vaccine. The vaccine is given IM as a dose of 10 microgram in children. For infants the recommended schedules are 3 doses at birth, 6 and 14 weeks or at 6, 10 and 14 weeks of age. An infant whose mother is HBV infected should receive the first dose of monovalent HBV vaccine within 12 hours of birth along with hepatitis B immunoglobulin. For older children the schedule is the elected date (0), 1 and 6 months. Boosters are not routinely recommended. Infants born to HbsAg positive mothers, dialysis patients and immunocompromised patients may require additional doses if appropriate seroconversion does not occur (antibody titres less than 10 mIU/ml), 1 to 2 months after the third dose. Majority of the people (65%) do not experience any reactions. About 3% develop local reactions, low-grade fever (about 1-6%), while anaphylaxis occurs in less than 0.001%. There is substantial evidence against any causal relationship between the vaccine and Guillain-Barre Syndrome, multiple sclerosis and chronic fatigue syndrome¹⁹.

Typhoid : Typhoid fever is caused by *Salmonella typhi*. Transmission occurs via the faeco-oral route. Man is the only reservoir. Typhoid is closely associated with poor food hygiene and inadequate sanitation. The highest incidence of disease occurs in the 5-19 years age group. It is characterized by a typical, continuous fever and constitutional symptoms. Typhoid may occur sporadically, endemically or epidemically. Asymptomatic intestinal carriers are common in endemic areas. Treatment of the disease and the carrier state has become complicated by the emergence of multidrug-resistant strains of *S. typhi* (20). WHO estimates the annual global incidence of typhoid fever at 0.3% (16 million) with about 600,000 deaths. Typhoid remains a serious public health problem in several parts of Russia, SouthEast Asia, Africa and South America. It is endemic in India.

Typhoid vaccines : Vaccination of high-risk populations of recommended. The previous heat-inactivated whole-cell vaccine showed protective efficacy rates ranging between 57-75%, but was associated with frequent adverse reactions. Two newer typhoid vaccines confer comparable protective efficacy rates without significant side-effects. Both vaccines induce protective immunity for 3-5 years, after which repeat doses are required.

The first, Ty21a, is a live, attenuated, lyophilized vaccine that is administered orally. It is genetically stable. There is limited gut multiplication and a very large number of bacteria (at least 10^9) are required to induce sufficient degree of local immunity. Since the bacteria are acid labile these vaccines are available as enteric-coated capsules. The course consists of 3 separate doses on alternate days, one hour before meals. It is recommended for children above 6 years because the capsules are large and not well tolerated in younger children. The vaccine is contraindicated in acute intestinal infection, acute febrile illnesses and immunosuppressive states. The second, a parenteral vaccine is a purified and adjuvanted form of Vi polysaccharide of *S. typhi*. It is administered IM as 0.5ml dose. Since these antigens are T cell independent the vaccine is non-immunogenic below 2 years of age. Also since it induces an IgM response without an IgG response, it does not have any immunological memory.

Hepatitis A

Hepatitis A virus (HAV) is a type 72 enterovirus of the picornaviridae family. It most commonly spreads via the faecal-oral route; however rarely it can also spread through infected blood or due to sexual contact in homosexuals. Infected people are most likely to spread HAV during the two-week period before they are symptomatic.

It is a relatively benign infection in children. When infected by HAV, adults and adolescents are more likely to develop signs and symptoms than young children, and are more likely to experience severe disease. Symptoms usually last less than two months, but 10-15% will have prolonged or relapsing disease lasting up to six months. A chronic state does not occur. High risk groups are people of low socio-economic strata, people working in endemic areas, laboratory workers dealing with the virus or HAV-infected primates, homosexuals, drug addicts, chronic liver disease patients non-immune to HAV and liver transplant recipients. The exact incidence of the disease is difficult to estimate due to the large number of asymptomatic cases. However according to the WHO, 10-50 person per lakh are affected annually.

Hepatitis A vaccine : The vaccine is an inactivated form of the HM 175 strain. The vaccine efficacy is 94-100% and the duration of protection is long lasting. Immunity develops within four weeks after the initial dose. It is recommended for those who live in HAV endemic areas. Food handlers should also consider vaccination²¹. It is recommended after two years of age, when maternal antibody levels decline. A 0.5ml dose is given IM, at 0 and 6 months in children between 2-18 years. After that it is given at double the dose at 0 and 6-12 months. About 50% will have no side effects. Others may have only mild local reactions (56%), headache (14%), or temporary weakness (7%). In very rare cases a person may be allergic to some vaccine component (i.e. the preservative). The vaccine is available as a monovalent form and in combination with HBV vaccine. The hepatitis A and B combination vaccine is as safe and effective as both vaccines given separately¹⁸. Contraindications are any previous serious adverse reaction to the vaccine.

Chickenpox

Varicella (chickenpox) is caused by the varicella-zoster virus (VZV), and is characterized by a vesicular, pleomorphic, centripetal rash accompanied by fever and malaise. The virus spreads by droplet infection or drop let nuclei. It is highly communicable with a secondary attack rate of 90%. The period of communicability is 1-2 days before the onset of rash and lasts till 4-5 days after. It is generally a mild disease, but can be severe and even fatal in otherwise healthy children (<1/10,000). It can cause pneumonia and put the child at risk for invasive Group A streptococcal disease. Complications include arthritis, hepatitis, thrombocytopenia and encephalitis (1/10,000) commonly seen among adolescents, adults, and immuno-compromised persons. If infected in early pregnancy, the fetus may develop congenital abnormalities (scarring of the skin, limb deformities, eye damage, low birth weight, cerebral atrophy, and mental retardation) in 2% of cases, or it may cause spontaneous abortion or neonatal mortality. While only 5% of cases are in adults, they account for 35% of the mortality. Chickenpox is worldwide in distribution, occurring as both epidemics and endemics.

Varicella vaccine : The varicella vaccine was developed from the Oka strain. It is a live attenuated, lyophilized vaccine, containing traces of neomycin and gelatin. Both humoral and cell-mediated immunity develop in more than 95% cases after a single dose in children between 1-12 years and 99% after 2 doses in children 13 years and above. Varicella vaccine is 85% to 90% effective. The older the child when vaccinated, the better the vaccine protection²². The duration of immunity is variable. In USA, protection has been observed for 11 years, whereas in Japan it was demonstrated for at least 20 years. Breakthrough infection can occur (<1-4%) in immunized persons, as compared to annual rates of 7-8% in unvaccinated children. However the disease is milder, with fewer skin lesions, of shorter duration and there is no or low fever. It has been seen in preschoolers that even when low percentages of children were immunized, the incidence of varicella in unimmunized children decreased substantially. It has been hypothesized however, that even though this herd immunity helps protect unimmunized people during childhood, it increases the risk later on by causing infection in adulthood, when serious illness and complications are more common²³.

The vaccine is recommended for all children aged 12-18 months, and all older individuals who have not had chickenpox and are not vaccinated. However opinion is divided about the need for varicella vaccination. A mild illness in childhood, chickenpox may become more severe if it is postponed to adulthood. The chickenpox vaccine virus also may establish a latent disease and produce zoster later on, which is more severe and frequent than the natural disease. The recommended dose is 0.5ml, given subcutaneously. It is given as a single dose in children between 12 months to 12 years. In older children 2 doses are administered, 4-8 weeks apart. No booster is recommended. The majority of recipients have no side effects. Local soreness and swelling and a mild rash may occur. Very rarely (less than 0.02%), seizures caused by high fever may occur. Contraindications include a previous life-threatening allergic reaction, pregnancy, T-lymphocyte immunodeficiency states and recipients of antibody-containing products.

Meningococcal infections

The meningococcus causes septicaemia, meningitis or both. It is found in the nasopharynx of cases and carriers and spreads by droplet infection. The disease is usually caused by the serogroups, A,B,C,Y, and W-135. Most epidemics are caused by serogroup C. Death occurs in 10% to 15% and is highest in infants and adolescents. Risk factors include close living conditions and close contacts of an infected person.

Meningococcal Vaccine : The first vaccines were effective against only two groups of meningococcus. The quadrivalent vaccine is protective against groups A,C,Y and W-135. Currently available vaccines provide some protection against all groups except B. Children are not routinely vaccinated because their infection rate is low and immunity short-lived. Also if they receive the vaccine early, subsequent doses may not be protective. In older children, and adults, it is 85-100% effective and protection lasts for at least three years²⁴. Indications for vaccine administration include susceptible people during epidemics, travelers, immunosuppressed patients, people living in dormitories and laboratory personnel. A single dose (0.5ml) is given subcutaneously or by IM. Children may be revaccinated in 2-3 years if initial vaccination was before

four years. Older individuals need to be revaccinated in 3-5 years for continuous protection. The majority of vaccinees experience no adverse reactions. Local reactions are seen in 40%. Rarely (<1/10,000), an allergic response can occur. Contraindications to vaccination are people who had an allergic reaction to a previous dose, or during acute infectious diseases.

Japanese B Encephalitis

Japanese B encephalitis (JE) is a culicine mosquito-borne, flavivirus zoonotic disease. Maximum cases occur in children less than 15 years and those above 60 years. JE is endemic in parts of Eastern and South-Eastern Asia. In 2002, the WHO reported a 5-35% case fatality rate and a 75% disability rate(1).

Japanese B encephalitis vaccine : This is a formalin-inactivated vaccine, recommended for the high-risk groups and is best used in the inter-epidemic interval. However high costs, limited production, short-term protection and neurological side effects hamper its widespread use. Two doses of 1ml each should be given subcutaneously at an interval of 1-2 weeks. Revaccination can be given after 3 years. Other vaccinees currently under development are a live-attenuated vaccine, a vero cell-derived inactivated vaccine, recombinant vaccinees using pox vectors and a chimeric, live-attenuated, vaccine using the 17D yellow fever strain.

Rabies

Rabies is caused by a rhabdovirus, which is most often spread by the saliva from an infected animal. Rarely cases due to infection by airborne virus in laboratory workers and cave explorers have been reported. Virtually 100% of those infected and who do not receive the vaccine die.

Rabies vaccine : The first rabies vaccinees developed were made from nerve tissue. Currently tissue culture vaccinees are in use, which include human diploid cell (HDCV), purified chick embryo cell culture (PCEC) and Vero cell vaccinees. Indications for pre-exposure vaccination are for high-risk groups who may be exposed to the rabies virus. It is given as 3 doses of 1ml each, IM, on days 0, 7 and 28. Booster doses of vaccine are recommended every two years for those who continue to be at increased risk. Antibody levels should be tested six monthly and boosters should be given as necessary. The schedule of post-exposure vaccination depends upon the previous immunization status. Unvaccinated people should receive the vaccine at 0, 3, 7, 14 and 28 days with rabies immune globulin (RIG) with the first dose. Previously vaccinated people (within 5 years) should receive two doses of the vaccine on days 0 and 7 and RIG should not be given (25). Mild local reactions at the injection site are reported among 30-74%, while headache, nausea, abdominal pain, muscle aches, and dizziness are reported in 5-40%.

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Current Therapy of Osteoporosis

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Abstract: Osteoporosis is a systemic skeletal disease that is characterized by low bone mass with a consequent increase in bone fragility and susceptibility to fracture. Most common causes of osteoporosis include postmenopausal state in females and senility in males. It can also be secondary to a number of systemic diseases or chronic drug therapy. Treatment modalities include lifestyle modifications like performing regular exercises, cessation of smoking and alcohol intake, and consumption of food items rich in calcium and vitamin D. The drug therapy includes calcium and vitamin D supplementation, hormone replacement therapy, bisphosphonates, selective estrogen receptor modulators e.g. raloxifene, and calcitonin. Other investigational agents include phytoestrogens, tibolone, fluoride, growth hormone, anabolic steroids and thiazide diuretics.

Key words : *Osteoporosis, Hormone Replacement Therapy, Bisphosphonates, Selective estrogen receptor modulators.*

Introduction

Osteoporosis is primarily a geriatric disorder and is relatively new to medicine. Some bone loss with increasing age is normal in both men and women. Once peak bone mass has been attained, usually between the ages of 20 and 30 years, women and men lose bone at a rate of about 0.5 to 1 percent yearly, although this varies considerably from person to person. Over the past 2 decades the definition of osteoporosis has changed due to advances in the knowledge of its pathophysiology as well as technical advances in quantifying and interpreting bone mass¹. The world health organisation (WHO) has defined osteoporosis on the basis of bone mass represented by a T score that normalises bone mass relative to mean bone mass of younger adults². Indians are known to suffer from osteoporotic fractures a decade earlier than the western counterparts. Out of 6.1 crore osteoporotic patients, it is estimated that 50 lac will have fractures of spine or hip every year³.

Dual Energy X-ray Absorptiometry (DEXA) and Bone Mineral Density (BMD) are considered the best methods for assessing risk of osteoporotic fracture and for confirming the diagnosis of osteoporosis. Causes of osteoporosis may be classified as primary and secondary.

Primary : Postmenopausal (Type 1 Osteoporosis); Senile (Type 2 Osteoporosis); Senile (Type 2 Osteoporosis); Idiopathic.

Secondary : Cushing's Syndrome (including Glucocorticoid Therapy), Hyperthyroidism; Hypogonadism in men; Immobilization; Chronic heparin administration; Osteogenesis Imperfecta; primary Hyperparathyroidism; Osteomalacia; Myeloma; Mastocytosis; Renal Osteodystrophy.

Treatment modalities

Lifestyle modifications⁴ : Certain lifestyle changes should be incorporated in the daily routine like performing aerobic, weight bearing or isometric exercises on a regular basis. Walking also helps in maintaining bone mass. Outdoor exercises may increase exposure to sun and thus induce vitamin D synthesis in skin. All elderly individuals should be encouraged to stop smoking and decrease alcohol intake and should undergo regular clinical and therapeutic drug monitoring for agents that are known to enhance bone loss on chronic use (anticonvulsants like phenytoin, heparin,

glucocorticoids, lithium therapy), that can alter calcium absorption (tetracycline, loop diuretics) and for other agents like sedatives, anxiolytics, antidepressants, phenothiazines and vasodilators, that are known to increase the frequency of falls.

Calcium and Vitamin D Therapy : Low calcium intake is associated with accelerated bone loss; calcium supplementation alone has been shown to decrease occurrence of new vertebral fractures in women who have already had such fractures. The current recommended daily calcium intake is 1200-1500 mg per day in postmenopausal women. Calcium supplementation alone or in combination with hormone replacement therapy also appears to retard bone loss from the femoral neck in early postmenopausal women^{5,6}. The National Research Council Institute of Medicine recommends Vitamin D 400 IU/day for those in the age group of 51-70 years and 600 IU/day for those who are above 70 years⁷.

Hormone Replacement Therapy : The role of HRT in the prevention of osteoporosis is controversial⁸. The ability of estrogen to prevent the rapid bone loss associated with menopause is well accepted. Most of the available observational data on HRT show an association between estrogen use and reduction of fracture risk⁹. The main goal of HRT (oestrogen or oestrogen and progesterone combination) is to alleviate the symptoms of menopause. HRT can be administered orally, transdermally, topically, intranasally; or as subcutaneous implants. It reduces serum and urinary markers of bone turnover, which return to premenopausal values. Doses of 0.625mg conjugated estrogens or 1-2mg 17 beta estradiol have been found to be effective with only less than 10% of women continuing to show bone loss. Fracture data from the HERS study have recently been analyzed in an effort to provide additional clinical information on the effect of HRT on reducing bone fractures¹⁰. HERS was a large randomized study designed to evaluate the effect of HRT on cardiovascular risk; fracture data were collected as a secondary outcome¹¹. Unfortunately, the results of this study did not definitively address the role of HRT in fracture reduction in patients with osteoporosis. Recently, a meta-analysis of randomized trials of HRT was performed, including those studies in which patients were treated for at least 12 months, and data were collected on the occurrence of nonvertebral fractures¹². The most significant conclusion of this meta-analysis is that the effect of HRT on fracture risk diminishes among women initiating HRT after the age of 60.

of post-menopausal estrogen for the prevention of osteoporotic fractures is weak. However, it should be noted that the results of the HERS study and the above meta-analysis do not exclude an anti-fracture benefit of HRT; the weakness of the evidence may reflect the lack of randomized controlled trials specifically focusing on fracture endpoints, not the lack of efficacy of HRT itself.

Bisphosphonates : Bisphosphonates are analogues of pyrophosphates, which have potent inhibitory effects on bone resorption. These drugs are effective drugs in bone disorders characterized by increased bone resorption, such as paget's disease, osteoporosis, hypercalcaemia of cancer, multiple myeloma, and bony metastasis. Candidates for bisphosphonate treatment include those postmenopausal women at increased risk of osteoporosis who forego HRT, men with osteoporosis, and all individuals receiving high-dose corticosteroid therapy¹³. Bisphosphonates are characterized by poor intestinal absorption, which is further reduced if the drug is given with calcium or iron. These agents are therefore never given at meal times or with dairy products. They should be taken with a full glass of plain water in the morning at least half to one hour before breakfast, as their oral bioavailability is extremely low 10%¹⁴. The first randomized controlled trial of bisphosphonates in postmenopausal osteoporosis used cyclical etidronate (400mg/day for two weeks, then repeated every three months). Alendronate and risedronate have recently been approved for prevention and treatment of postmenopausal, glucocorticoid-induced, and male osteoporosis¹⁵. For patients who are intolerant to oral bisphosphonate, pamidronate is the only intravenous bisphosphonate that is currently available. Bisphosphonates can cause gastrointestinal upset; oesophagitis and oesophageal ulceration can be very distressing. These agents can also cause electrolyte imbalance, therefore should be used caution if renal function is impaired¹⁶.

Selective Estrogen Receptor Modulators (SERMS) : Tamoxifen, raloxifene and droloxifene are Selective Estrogen Receptor Modulators (SERMS) having differential estrogen agonistic and antagonistic activities on different tissues. It has recently been approved by FDA for prevention of osteoporosis in a dose of 60mg/day. Raloxifene causes an increase in bone mineral density (BMD) at the lumbar spine, total hip, and femoral neck, but the effect seems to be less than that of estrogen or alendronate. Raloxifene and tamoxifen spare anti-resorptive effects of estrogen on bone¹⁷. Recent data from the multiple outcomes of raloxifene evaluations showed that 60 and 120mg daily doses of raloxifene significantly decreased vertebral fracture risk during the first 36 months of treatment, compared with placebo. The most common adverse effects of raloxifene are hot flashes and leg cramps. The only serious adverse events reported with raloxifene treatment were venous thromboembolic episodes, which included deep venous thrombosis and pulmonary embolism¹⁸.

Calcitonin : This peptide, which is normally produced by the C cells of the thyroid gland, inhibits actions of osteoclasts and decreases bone resorption. Subcutaneous or intranasal calcitonin is approved for the treatment of postmenopausal osteoporosis; the effect is predominantly on lumbar spine, but is small (1-3% increases in BMD), with little effect on cortical bones¹⁹. The dosage of calcitonin is 2200 IU/day intranasally or 100 IU/day subcutaneously²⁰. It should be taken with calcium and vitamin-D, whenever required. Adverse effects with intranasal administration include transient rhinorrhoea, nasal discharge, and nasal stuffiness. Diarrhoea, nausea, vomiting, loss of appetite, stomach pain, flushing, irritation at the injection site, and increased urinary frequency may occur with subcutaneous administration.

Investigational anti-resorptive agents and bone formation agents :

Phytoestrogens : like isoflavones and lignans are plant substances that have some estrogenic effects, but are generally weaker agents. Isoflavones (genistein, daidzein) come from metabolised soybean and soy products. Lignans (enterodiol, enterolactone) are metabolised from precursors in flax seed, cereals, vegetables, fruits, and legumes. Animal data support possible decrease in bone loss with phytoestrogens²¹. There is evidence that flavonoids may play a role in preventing osteoporosis. Treatment with ipriflavone, an isoflavone derivative, for a period of one year has been shown to reduce pain and morbidity in 73% of the patients with osteoporosis. Many clinical trials are ongoing and results are awaited.

Fluoride : Sodium fluoride increases bone volume, an effect due specifically to increased osteoblastic activity. In doses of 30 to 60mg/day, fluoride increases trabecular bone mass in many but not all patients. The sustained-release product maintains lower and therapeutic fluoride levels (15-190ng/ml). On supplementation, fluoride becomes a part of bone and increases its crystallinity, thereby decreasing resorption. Bone thickness is also increased by stimulating osteoblasts, but new bone does not bridge current bone to increase lattice and strength. Role of Intermittent fluoride regimens in osteoporosis is under investigation^{22,23,24}.

Hormones : Agents such as parathormone, growth hormone, and anabolic steroids are being investigated for enhancing bone formation but generally limited by adverse reactions like glucose intolerance, hyperinsulinemia, hypertension, and edema or lower efficacy²⁵.

Thiazides : Thiazides and other calcium retaining diuretics have shown a beneficial effect on bone density in postmenopausal women. These reduce calcium excretion through increased calcium reabsorption in the distal tubule. However, these diuretics are not without risk and may aggravate hypokalemia in corticosteroid treated patients²⁶.

Miscellaneous : Oral strontium, trace elements such as copper, magnesium and zinc, non steroidal anti-inflammatory agents, proton pump inhibitors, potassium bicarbonate, ephedrine, amyler, and vitamin K are all being evaluated as potential treatment modalities for osteoporosis²⁷. Recently, the role of melatonin has also been reported in bone remodeling. Melatonin, through its free radical scavenging and antioxidant properties may impair osteoclast activity and bone resorption. Melatonin, which has shown potential in some studies as a novel mode of therapy for augmenting bone mass deserves to be studied²⁸.

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ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH

The need for uniform ethical guidelines for research on human subjects is universally recognised. It has acquired a new sense of urgency as the critical issues in the area of biogenetic research involving human subjects have become acute. Apart from the mandatory *clinical trails* on new drugs, a number of *diagnostic procedures, therapeutic interventions and prevention measures* including the use of vaccines, are being introduced which involve human subjects. Further the advent of *new medical devices and radio-active materials* and therapeutic benefits of *recombinant DNA products* have added a new dimension to the ethical issues that need to be considered before evaluating these for their efficacy, utility and safety.

Any research using the human beings as subjects shall bear in

mind the following principles of : i) **essentiality**, (ii) **voluntariness**, **informed consent**, (iii) **non exploitation**, (iv) **privacy and confidentiality**, (v) **precaution and risk minimisation**, (vi) **professional competence**, (vii) **accountability & transparency**, (viii) **maximisation of public interest and distributive justice** (ix) **institutional arrangements** (x) **public domain** (xi) **totality of responsibility** and (xii) **compliance**.

Recent advances in the field of **Assisted Reproductive technologies, organ transplantation, Human genome analysis, and gene therapy** promise unquestionable benefits to mankind. At the same time, they raise many questions of law and ethics, stimulating public interest and concern.

(Source : ICMR Publication 2000)

Drug Profile

SIROLIMUS

Sirolimus is a carbocyclic lactone-lactam macrolide-antibiotic prepared through natural fermentation from the soil actinomycete streptomyces hygroscopicus. sirolimus first demonstrated antifungal activity but, due to its structural similarity to tacrolimus, it was used for its immunosuppressive activity.

Mechanism of action : Sirolimus inhibits T. Lymphocyte activation and proliferation that occurs in response to antigenic and cytokine stimulation by a mechanism that is distinct from that of other immunosuppressants. Sirolimus also inhibits antibody production. In cells, it binds to the immunophilin, FK binding protein-12 (FKBP-12), to generate an immuno-suppressive complex. The sirolimus; FKBP-12 complex has no effect on calcineurin activity. This complex binds to and inhibits the activation of the mammalian target of Rapamycin (MTOR) a key regulatory kinase. This inhibition suppresses cytokine-driven T cell proliferation, inhibiting the progression from the G1 to the S-phase of the cell cycle.

Pharmacokinetics : It is readily but poorly absorbed after oral administration with an estimated bioavailability of 15%. Once absorbed into systemic circulation, it easily enters cells because of its high lipophilicity. 95% of drug is bound to RBG, 3% is found in plasma and 1% in lymphocytes and granulocytes. It is 100 times more potent than cyclosporine probably because of increased binding to RBG and decreased binding to lymphocytes.

Metabolism & excretion : It undergoes extensive metabolism by the CYP 3A4 system both in liver and small intestine. It is also a substrate of the efflux pump, P-glycoprotein, which is also found in the intestinal wall. The terminal half life (t_{1/2}) of drug is long ranging from 57 to 62 hours suggesting that once - daily dosing is adequate. Over 90% of the drug is removed through the faeces, and only a minor amount (2.2%) is excreted in urine. No dosage adjustment is necessary in patients with renal dysfunction. It is not removed by dialysis. It is extensively metabolized in the liver; therefore dosage modification is necessary in patients with hepatic dysfunction; 1/3rd of the

recommended dose should be given to patients with mild to moderate hepatic dysfunction. Sirolimus is metabolized by the CYP3A4 enzyme system. Any agent that alters the concentration of cyclosporine is expected to alter sirolimus concentrations. these include both enzyme inducers (eg rifampin, phenytoin) and inhibitors (azoles-antifungal, erythromycin, diltzem)

Indication : It is Indicated for the prophylaxis of organ transplant rejection. It is recommended that sirolimus should be used initially in a regimen with cyclosporine and corticosteroids.

Dosage & Administration: It is to be given orally once a day. The initial dose of sirolimus should be administered as soon as possible after transplantation. A daily maintenance dose of 2 mg is recommended for use in renal transplant patients with a loading dose of 6mg. It should be taken consistently with or without food. It must be taken 4 hours before/after cyclosporine dose.

Adverse Effects : The commonly reported adverse effects include abdominal pain, asthma, back pain, chest pain, fever, headache CVS hypertension; *digestive* Constipation, Diarrhoea, dyspepsia, nausea, vomiting; *metabolic and nutritional* : increased creatinine, oedema, hypercholesterolemia, hyperkalemia hyperlipidemia, hypokalemia, Wt gain, peripheral oedema; *musculo skeletal* - arthralgias; *nervous system* - tremor, insomnia; *respiratory system* - dyspnoea, pharyngitis, URI; *hematological* - Anaemia, leukopenia, thrombocytopenia

Drug Interaction: Drugs that may increase sirolimus blood concentration include: *calcium channel blockers* - nifedipine, verapamil; *antifungal* - clotrimazole, fluconazole, itraconazole; *macrolide antibiotic* - clarithromycin, erythromycin; *prokinetic agents* - cisapride metoclopramide;

Drugs that may decrease sirolimus concentration include *anticonvulsants* carbamazepine, phenobarbitiv, phenytoin; *antibiotics* - rifabutin, rifapentine; *vaccinations* - vaccination may be effective during Sirolimus therapy.

Compiled by Dr. Pradeep Chatterjee

Editorial

Neonatal intensive care in India is gradually improving with the emergence of many tertiary care NICU's. Respiratory distress syndrome (RDS) is the commonest neonatal emergency especially in premature babies. Hyaline membrane disease (HMD) is a condition due to lack of surfactant, predominantly seen in extremely premature infants. More than half of the babies born before 28 weeks of gestation develop HMD. Even though supportive care of these infants is of paramount importance, the aim of management is to improve alveolar gas exchange and maintain normoxemia & normocapnia.

Managing a baby with RDS still remains a challenge. Mechanical ventilation has remarkably improved the outcome in these infants. Continuous positive airway pressure (CPAP) was first used in newborns with RDS in 1971 to improve oxygenation. Over the last few decades, large number of infants with RDS have benefited with the use of CPAP. Early use of nasal CPAP significantly reduces the need for endotracheal intubation and mechanical ventilation. Recent data suggests that endotracheal delivery of surfactant followed by nasal CPAP is a useful treatment modality in infants with moderate HMD. Newer CPAP devices like Bubble CPAP and Infant Flow Device (IFD) look promising and with more experience are likely to be used more often. The main aim of mechanical ventilation is to use minimum pressures and FiO₂ to optimize gas exchange. This also helps to reduce barotrauma/volutrauma and lung toxicity. Infants needing high ventilatory pressures have a risk of developing chronic lung disease (CLD) or bronchopulmonary dysplasia (BPD). Many strategies like use of high frequency oscillation (HFO) have been tried, yet we do not have an appropriate solution that significantly reduces incidences of CLD.

Surfactant replacement therapy has been the most important discovery of this century. Numerous trials have been reported in the literature, showing beneficial use of surfactant in infants with HMD, as it reduces the need for supplemental oxygen, mechanical ventilation, risk of air leak syndromes and mortality. However, the effect on incidence of intraventricular hemorrhage

(IVH), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP) and CLD is not significant. Surfactant is slowly delivered into the lungs of infants with HMD over a period of 10-12 minutes. Natural surfactants extracted from bovine or porcine lung are more effective as compared to synthetic surfactants. With easier availability of surfactant in our NICU's its usage is increasing with promising results and better outcome in infants with RDS.

Nutritional support is of critical importance for ultimate recovery of tiny sick neonates. Often enteral feeds are not able to meet the nutritional requirements during first few weeks of life. With advances in Parenteral Nutrition and its early institution the outcome of very low birth weight babies has improved significantly. Early enteral feeding is vital, small trophic gut priming feeds should be started as soon as the infant is hemodynamically stable. Many babies who are neurologically compromised or have gastroesophageal reflux are not able to tolerate oral enteral feeds. Intra-gastric, gastrostomy feeds are some of the options. With newer advances, percutaneous endoscopic gastrostomy has become a relatively easier modality with fewer complications for establishing enteral feeds in these infants.

More than 4 million people are infected with HIV in India. It has emerged as a major global health problem. More than 3/4th cases of HIV infection in pediatric age group are due to perinatal transmission. The risk of perinatal transmission without any treatment is as high as 35-40%. Preventive strategies have been able to reduce the incidence of this mode of transmission. With availability of antiretroviral drugs this risk can be reduced by more than 50%.

I hope this issue will help our readers to update their knowledge about the advances in neonatal intensive care in developing India and will be immense benefit to those who are actively involved in newborn care.

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Respiratory support in babies with Respiratory distress syndrome

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Abstract: Respiratory distress is the commonest cause of admission in neonatal intensive care units. Respiratory support in form of oxygen therapy, CPAP, and ventilation has improved the survival in these patients. CPAP has become more popular in such cases and more emphasis is on early, nasal CPAP. Mechanical ventilation also has become less invasive with concepts of minimal handling, permissive hypercapnia, patient triggered ventilation taking edge over the old concepts. Weaning from ventilation is a difficult but most important art to learn. Careful monitoring is very important for a baby on mechanical ventilation. The survival depends on the disease entity for which baby is ventilated rather than ventilation per se.

Introduction

Respiratory distress syndrome is an acute illness usually seen in preterm infants characterized by respiratory rate > 60/min, dyspnea (intercostals, subcostal indrawing, sternal retraction) with a predominantly diaphragmatic breathing pattern and characteristic expiratory grunt or moan, all presenting within four to six hours of delivery. Pathophysiologically the condition is characterized by noncompliant (stiff) lungs, which contain less surfactant than normal and become atelectatic at end-expiration. RDS is a developmental disorder rather than disease per se and it is usually associated with premature birth. Incidence and severity of RDS generally increases with decreasing gestational age and is worse in male infants i.e. 50% infants 26-28 weeks and 20-30% of premature infants 30-31 weeks, develop RDS.

Pathophysiology

The principle mechanism of hypoxemia in HMD is venous admixture resulting from both intrapulmonary shunting and right to left shunting across the foramen ovale and PDA. *Venous admixture* (VA) an expression of the percent of this mixture made up of venous blood, can be derived from the standard shunt equation :-

$$VA(\%) = \frac{Cc'O_2 - CaO_2}{Cco_2 - CvO_2} \times 100$$

Where $Cc'O_2$ is the end pulmonary capillary blood oxygen content, CaO_2 the arterial blood oxygen content, and CvO_2 the mixed venous blood oxygen content. When the venous admixture is less than 40% an adequate arterial PO_2 can be attained by increasing FIO_2 . When venous admixture is 50% or more, increasing FiO_2 from room air to 1 changes arterial PO_2 a few mmHg, but adequate oxygenation is not achieved. There is a range of venous admixture for which oxygen therapy alone will result in adequate arterial oxygenation but with severe venous admixture arterial hypoxemia cannot be overcome even with 100% oxygen and adequate alveolar ventilation.

Intrapulmonary shunting

With in the lung some venous admixture occurs because of pulmonary blood flow through pulmonary arteriovenous anastomoses (bronchial vein-pulmonary vein communication) and

due to pulmonary capillaries perfusing areas of the immature lung where terminal airway formation is incomplete. However the contribution of these anatomic shunts to total intrapulmonary venous admixture is small.

In *hyaline membrane disease* (HMD), intrapulmonary venous admixture occurs largely as a result of the perfusion of terminal airways that are partially collapsed, collapsed, and fluid filled. For the most part, these terminal airways are either extremely under ventilated or non ventilated at all as a result of epithelial slough, exudation, and hyaline membrane formation at the junction of the respiratory bronchioles and alveolar ducts. The effect of this pathological process on terminal airway collapse is compounded by the associated surfactant deficiency, whether primary or secondary in origin. Based on this, HMD can be divided in to three compartment. First compartment is made up of terminal gas-exchange units that are intact and adequately ventilated and perfused. The *second* compartment is characterized by terminal airways that are open but markedly under ventilated. These units may be perfused, but only if local alveolar hypoxia can be relieved by breathing 100% oxygen. The *third* compartment is totally unventilated but perfused. It includes those units with terminal conducting airways that are severely affected by epithelial damage, exudates and slough. In addition, this compartment also represents any anatomic right to left shunt that is present.

Oxygenation of arterial blood in HMD depends up on proportion of terminal airways that are available for gas exchange. As long as 60% or more of the terminal airways units remains open and oxygenated and adequately perfused, acceptable arterial oxygen tension greater than 50mm Hg can be maintained by increasing the concentration of inspired gas.

Extrapulmonary shunting

During the first 12 hours after birth, predominant shunt is right to left from the inferior vena cava across the foramen ovale in to the left atrium. Even though the ducts are widely patent there is little flow through it in either direction until 12 to 24 hour of age when a left to right shunt of increasing magnitude occurs as a result of falling pulmonary vascular resistance. Significant right to left shunting at the ductus does not occur unless pulmonary vascular resistance is markedly elevated in the presence of severe hypoxemia, hypercarbia, or acidosis or systemic vascular pressure is extremely low.

Right to left shunting through persistent fetal pathways is promoted by increased pulmonary vascular resistance which in turn may be further increased by any hypoxemia resulting from shunts. A

large shunt present due to arterial hypoxemia can be diminished by increasing the inspired oxygen concentration. This sequence which is probably triggered by a reduction in pulmonary vascular resistance, helps explain why total venous admixture in HMD decreases as inspired oxygen concentration is increased. Shunting through a PDA: The ductus is patent most cases of RDS during the first 48-72 hours.

If PAP exceeds aortic pressure there will be a significant right-left shunt. Right-left shunts at ductal level are common in persistent pulmonary hypertension of the newborn, but in uncomplicated RDS these are small and constitute less than 10% of the total right to left shunt. One clinically important fact of right to left ductal shunting is the blood drawn from an umbilical artery catheter can have a much lower PaO₂ than blood passing up the carotid arteries to the eyes. Colour Doppler studies of the vascular channels in babies with RDS have demonstrated that intra vascular shunting at ductal or foramen ovale level is relatively unusual in uncomplicated RDS (as opposed to PPHN), even though both channels stay potentially patent in the early neonatal period. In fact, the shunt through the channel is predominantly bidirectional or left to right in the first few days of life. This will have little effect on blood gas values, but will increase the cardiac output and the load of the right ventricle. Obligatory shunts caused by drainage of veins of the myocardium directly in to the left side of the heart and also by anastomoses between the bronchial and pulmonary circulation are present in every individual, are of no hemodynamic or clinical significance.

Lung Function

Functional Residual Capacity (FRC) Functional residual capacity is decreased in HMD. In newborn infants without lung disease, FRC is approximately 30ml/kg. Loss of FRC occurs in HMD as a result of surfactant deficiency and displacement of gas volume by pulmonary vascular congestion, interstitial edema, and airway flooding with proteinaceous fluid. In HMD, FRC can be as low as 3ml/kg. FRC can be recovered and protected by the addition of distending airway pressure in the form of continuous positive pressure or intermittent mandatory ventilation. Change in FRC mirrors the improvement in oxygenation that occurs with the addition of distending airway pressure or without spontaneous recovery beginning on the second or third day after birth. During recovery, there is a striking correlation between improving oxygenation, increasing FRC and diuresis as excess lung water reabsorbs into the circulation and is cleared by the kidneys.

Mechanical Properties of the Lung

The marked decrease in lung compliance, one of the hallmarks of HMD, occurs as consequence of two factors, these are 1) A decrease in the number of ventilated terminal air spaces and 2) An increase in the recoil pressure of ventilated terminal air spaces. In addition, dynamic but not static, compliance is further reduced in HMD owing to change in the viscoelastic properties of lung tissue and the presence of inhomogeneity of ventilation. Like FRC, compliance also mirrors the course of pulmonary insufficiency in HMD. Intercostal and sternal retractions in the infants capable of the spontaneous ventilatory efforts provide a visual assessment of compliance at bed side. As compliance improves either as a consequence of manipulation of ventilation, or surfactant replacement therapy, or with evolution of natural course of disease, chest wall retraction diminishes, indicating that less transpulmonary

pressure is required to expand lung.

Lung resistance, which is the sum of airway resistance and lung tissue resistance, is three to six times greater in infants with HMD than in normal newborn infants. Pressure volume loops on lungs excised at post mortem from babies dying of HMD have a characteristic pattern. During inflation the volume change for a given increase in pressure is very small and during deflation the change in volume follows a tract almost similar to that seen during inflation, where as in the normal lung air is retained until low volume are reached. Furthermore, as the pressure drops to zero, very little or no air is retained within the surfactant less alveoli, corresponding to the very small FRC measured in vivo. An inevitable sequel of the abnormal lung mechanics is that the work of breathing is increased in neonates with RDS.

Effect of Alveolar Instability on Lung Volume and Compliance

Alveolar instability refers to the tendency for an alveolus to switch abruptly between the inflated state and the collapsed state. When pressure across the alveolus exceeds the critical opening pressure, an unstable alveolus inflates suddenly. During deflation, an unstable alveolus collapses abruptly when trans-alveolar pressure falls below the critical closing pressure. One compartment might remain collapsed throughout inspiration and expiration, another might be ventilated during inspiration but collapsed during expiration and yet another might be ventilated and stable to the extent that gas volume is retained at end expiration. The distribution of these compartments is affected by a variety of factors, especially treatment with surfactant replacement or with distending airway pressure with CPAP.

General Management

Minimal Handling : When hypoxic babies are disturbed and handled their respiration may become very irregular or stop altogether, their right left shunts increase and their PaO₂ falls rapidly. Even listening to the chest with a stethoscope or palpating the abdomen, may have this effect. Major disturbances such as sucking out an endotracheal tube, performing a lumbar puncture or taking a chest x-ray can cause catastrophic falls in PaO₂.

Physiotherapy : In the non-intubated baby with RDS secretions are not a problem unless infection develops, and physiotherapy is contraindicated as it opposes the principle of minimal handling.

Posture : Babies with RDS should have their position changed every 4-6 hours. In general, prone position is preferable as the blood gases tend to be better maintained with much improved lung function.

Temperature : The baby's thermal environment should be controlled if the baby is exposed during a procedure, he should be under a radiant heat source. As far as possible the baby should be kept covered to minimize heat loss.

Blood Gas Management PaO₂ : Maintain it in the range 8-12kPa (60-90mmHg) The upper limit set to avoid hyperoxaemia which may predispose the baby to ROP. PaCO₂ in normal newborn babies the normal range is 4.6-5.4kPa (35-40mmHg). If a VLBW baby in the first 6-12 hours cannot ventilate himself sufficiently well to keep his PaCO₂ below 6kPa (45mmHg), he should be ventilated. **pH:** Acidemia is common in neonates with RDS which may be of respiratory or metabolic origin. Commonest cause of

metabolic acidemia is a raised lactate from anaerobic metabolism. This may be secondary to hypoxemia, hypotension, anemia, infection, sepsis or strenuous muscle activity. Acidemia inhibits surfactant synthesis and increases pulmonary resistance. Once pH falls below 7.15 other physiological functions such as myocardial contractility and diaphragmatic activity begin to deteriorate. In all VLBW infants, pH should be kept >7.25 with a base deficit $<10\text{mmol/L}$.

Blood Pressure : In all neonates with RDS, mean BP should be maintained at around gestational age in weeks + 5mmHg and the mean BP should not be allowed to fall below their gestational age in weeks (i.e. for a 33 weeks neonate mean BP should be maintained at around 38-40 mmHg and should not be lower than 33mmHg).

Maintenance of Haemoglobin : Preterm neonate can be anemic because of an intrapartum hemorrhage, defective placental transfusion, or a twin-twin, or fetal maternal hemorrhage. Blood loss after birth is mostly iatrogenic as a consequence of sampling, but a sudden drop in the hematocrit/hemoglobin level in a baby with RDS is highly suggestive of development of an IVH. III neonates, in particular those who are premature, tolerate hemoglobin levels $<13\text{gm/dl}$ (PCV $<40\%$) badly, because of the increase in cardiac output required to meet the oxygen demands of the tissues. All hemodynamically unstable neonates with hemoglobin $<13\text{gm/dl}$ (PCV $<40\%$) should be transfused in order to maintain their hemoglobin and prevent cardiopulmonary decompensation.

Fluid and Electrolyte : Infants with RDS should be started on 40-60ml/kg/24 hour of a 10% dextrose solution. Fluid intake should subsequently be guided by the baby's weight, serum sodium, urine specific gravity and serum osmolality. The ill neonate loses 1-3% of his body weight per day. If he is losing more than desired then he may be dehydrated due to excessive insensible losses, if his weight is static or he is gaining weight, he may have difficulty handling the excess fluid which must be curtailed. Characteristically, a diuresis occurs when the baby's lung function improves concomitant with an improvement in FRC and compliance. When this occurs it is a marker of improvement and now the previous constraints on the fluid balance need to be relaxed to prevent dehydration, hemoconcentration and jaundice.

Oxygen Therapy : The primary challenge in managing the pulmonary insufficiency of HMD is achieving an adequate PO_2 . If oxygenation can be achieved, carbon dioxide removal is only a matter of increasing minute ventilation and to make up for an inadequate alveolar portion of tidal volume. Oxygen can be administered by a head box with a starting FiO_2 of 0.4 which can be increased to 0.6 as judged by the sPO_2 . The sPO_2 should be maintained between 92 ± 3 percent. If the need for FiO_2 is increasing (in an attempt to maintain SpO_2), or if the baby is developing retractions, then the baby needs to be taken up for CPAP therapy. If the neonate is accumulating CO_2 as evidenced by a blood gas then the baby needs to be taken up after mechanical ventilation. A trial of CPAP may be justified before mechanical ventilation.

CPAP : CPAP should be viewed as the vital link between oxygen therapy and positive pressure ventilation. Gregory et al used this modality in newborns with RDS in 1971 using head box, and later using endotracheal tube. It was in 1973 that Agostino et al reported the first small series of infants with RDS treated with Nasal CPAP. The superiority of nasal breathers and thus they spontaneously form a seal between the palate and the tongue. Any preterm with respiratory distress soon after birth should be put on

continuous positive airway pressure (CPAP). Numerous studies have shown the fact that early use of CPAP reduces the need for subsequent intubation and mechanical ventilation in RDS. In those who require it later, ventilation is successful at lower pressure. According to a Cochrane review, early use of CPAP (at onset of respiratory distress) was associated with decreased need for intermittent positive pressure ventilation (IPPV) by about 50% when compared to late initiation of CPAP i.e. when FIO_2 requirement of baby is more than 60%. This is clinically important, as IPPV is associated with considerable increase in complications and cost to the family. Most babies respond to oxygen therapy and CPAP. According to the Cochrane review, use of CPAP was associated with lower rates of failed treatment by about 30%, overall mortality by 50% and mortality in infants with birth weight above 1500 grams by as much as 75%. Early use of CPAP will be low-cost, simple and noninvasive option for a country like India, where most places cannot provide invasive ventilation.

Physiologic effects of CPAP

The physiologic effects of CPAP vary depending on the underlying condition of the lung. CPAP is believed to result in progressive alveolar recruitment, inflating collapsed alveoli and reducing intrapulmonary shunt. Some of the effects of CPAP like increase in gas volume in the lung and increased functional residual capacity has been measured. Initially as the FRC increases, gas exchange improves; PaO_2 increases and PaCO_2 decreases. Improved oxygenation relieves the hypoxic vasoconstriction in the pulmonary vascular bed and decreases pulmonary vascular resistance leading to increased pulmonary blood flow, decreased shunting and increased PaO_2 . In addition, CPAP has some non-specific beneficial effects on neonatal ventilation in terms of more regular breathing pattern in neonates. This is achieved by chest wall stabilization and reduction of thoracic distortion. CPAP also splints the airways and the diaphragm. It reduces obstructive apnea, increases both inspiratory and expiratory times and helps in enhanced surfactant release.

Optimal CPAP improves ventilation but excessive CPAP leads to over-distension of lung resulting in high PaO_2 along with a high PaCO_2 due to diminished tidal volume. If high CPAP continues for a considerable period of time, this can lead to serious consequences like air leaks. Excessive CPAP also leads to increased dead space ventilation leading to a rise in PaCO_2 .

Methods of applying CPAP include : (i) face mask (ii) face chamber (iii) nasal prongs (iv) nasopharyngeal tube and (v) gregory box.

Indications of CPAP : (i) oxygen concentration $>60\%$ to keep $\text{PaO}_2 > 8\text{kPa}$ (60mmHg). (ii) Recurrent apneic attacks. (iii) Weaning from IPPV.

Newer CPAP Systems : Bubble CPAP is CPAP delivered by CPAP system with underwater seal. It has been shown that CPAP delivered by underwater seal causes vibration of the chest due to gas flow under water, which is transmitted to infant's airway. These vibrations simulate waveforms produced by high frequency ventilation. Bubble CPAP has also been shown to reduce need for intubation and mechanical ventilation, as well as use of postnatal steroids and trend towards decreased incidence of chronic lung disease. Another new mode of CPAP delivery is use of dual flow CPAP, or Infant Flow Drive CPAP. Mazzella et al have shown superiority of IFD over nasal CPAP in terms of decreased oxygen requirement and respiratory rates and lesser need for mechanical ventilation. Babies who failed nasal CPAP could be rescued by

IFD and mechanical ventilation could be avoided.

There is evidence to prove that giving surfactant to the patient after brief intubation can enhance beneficial effect of early CPAP in preterms. In this approach, the preterm is started on CPAP as soon as he develops respiratory distress. When respiratory distress on CPAP progresses beyond a predetermined point (ratio of arterial to alveolar oxygen tension (a/A) of less than 0.36, the baby is intubated, given surfactant, and then extubated and put back on CPAP again. This minimizes the hazards of mechanical ventilation in the baby. Surfactant and CPAP act in conjunction in fulfilling the aim of increasing lung volume and the functional residual capacity.

Mechanical ventilation

The decision to start mechanical ventilation in a neonate should be individualized and based on clinical as well as blood gas parameters. Though there are guidelines for initiating mechanical ventilation, the best guide is the evolving clinical state of the neonate.

Indications : (1) PaCO₂ greater than 50mmHg or rapidly rising. (2) PaO₂ less than 50mmHg or oxygen saturation less than 90% with FiO₂ above 0.6 with adequate trial of CPAP. (3) pH less than 7.25. (4) Intractable apneic spells (5) Impending or existing shock. (6) RR > 70 with moderate to severe retractions or cyanosis in FiO₂>0.4. (7) CPAP failure.

Ventilator : A continuous - flow, pressure limited, timed-cycled Ventilator is useful for ventilating newborn babies with HMD. High frequency oscillatory ventilation may be useful to minimize lung injury in very small and/or sick infants and to manage infants to whom air leak syndromes complicate RDS.

Initial Steps & Setting

The basic steps of mechanical ventilation initiation include :

- 1) **Endotracheal Intubation**
- 2) **Bag & tube ventilation using a manometer to access the initial pressure requirement.**
- 3) **Start ventilator, Ensure air oxygen mixture is warmed to 37°C & humidified 70-100%.**
- 4) **Selection of appropriate ventilator settings.**
- 5) **Evaluation to check adequacy of ventilatory support.**
- 6) **Initial Settings :**

a. FiO ₂	0.5
b. Rate	40-50/min
c. PIP	18-20 cm H ₂ O
d. PEEP	4-5 cm H ₂ O
e. Ti 0.4-0.5sec	
f. Flow	5-7 lit/min

The rationale for the initial settings is primarily physiologic, which means that the rate of 40-50 is chosen so as to make the baby breathe at a rate at which he would breathe, if he was breathing on his own. Similarly the inspiratory time of 0.5 seconds is also physiologic; a baby normally breathes at a rate of 40 breaths per minute, i.e. 40 breaths in 60 seconds with a normal I:E ratio of 1:2 and thus take some breath every one and a half second with inspiration lasting for 0.5 sec and exhalation lasting for 1.0 seconds. Derivation of PIP is based on the fact that a normal breath necessitates a drop of intrapleural pressure by 6 cm of water from -1 to -7 cm of water. In addition a pressure of 6 cm water is required to drive the gases through the ventilatory circuitry. Any baby on ppV has to be provided with a PIP greater than 12cm water so as to drive the gases into his lungs. This additional pressure would depend on the size of the baby and the status of the diseased lung. Pressures required would be higher for a large baby as well as a baby with severely diseased lungs.

Normal physiologic PEEP of approximately 3cm water is maintained by closure of glottis in a normal baby, this has been abolished as a consequence of intubation in a ventilated baby and hence one need to intermediate concentration as most babies who are being ventilated have been on an FiO₂ of 0.4-0.6 on hood/CPAP. This 0.5 can be adjusted subsequently based on Spo₂ and PaO₂ to achieve optimum oxygenation.

- 7) **Observe infant for absence of cyanosis & retractions and adequate chest wall movement and breath sounds**
- 8) **If chest wall movement is subnormal increase PIP by 1cm every few minutes till chest wall movement is adequate and SpO₂ is within normal range.**
- 9) **If oxygenation is inadequate as evidenced by presence of cyanosis or a subnormal SpO₂, increase FiO₂ by 0.05 every few minutes till saturation is between 92±3 percent**
- 10) **Draw an arterial blood gas sample and review the settings based on the report.**
- 11) **Subsequent clinical monitoring includes observing for color, chest wall motion along with respiratory effort, and adequacy breath sounds**

Monitoring adequacy of Ventilatory Therapy

The adequacy of ventilatory therapy is assessed by a combination of clinical parameters along with non-invasive adjuncts like pulse oximetry and capnography and a judicious use of invasive modality like the blood gases. The clinical parameters include absence of cyanosis, absence of retractions, a prompt capillary refill time of less than 3 seconds, a normal blood pressure, adequate chest expansion (easy chest rise) and an adequate air entry.

The pulse oximetry limits are set so as to avoid hypoxia as well as hyperoxia and the safe limit is 92±3% Capnography is a noninvasive estimate of the end tidal carbon dioxide which correlates well with the PaCO₂ under most situations. The blood gases should be maintained within normal range with the PaO₂ at 60-80mmHg, PaCO₂ at 35-45 mmHg and the PH at 7.35-7.45. The capillary refill time should be assessed at the sternum or the forehead with pressure by the index finger for a period of 5 seconds followed by removal of the finger. On removal the area under the finger appears blanched, the observer assesses the time taken for the colour to return, it should take less than 3 seconds.

Adjustments

Common Problems and their solutions :

1) **Metabolic acidosis :** A neonate with RDS is likely to become acidotic during the course of the illness as a consequence of either (a) Hypovolemia &/or shock, (b) Excessive work of breathing, (c) Hypoxia and (d) Excessive PEEP. Metabolic acidosis must be avoided at all costs as the pulmonary vasculature is exquisitely sensitive to changes in PH; acidosis leads to pulmonary vasoconstriction causing hypoxia, further acidosis and right or left shunting. This vicious cycle once initiated perpetuates and thus ensuing hypoxia and acidosis affect the myocardial contractility as well as hamper many other vital cellular functions eventually leading to death. As soon as a low pH is detected, check the SpO₂, CFT and assess the work of breathing. If the baby is hypoxic improve his oxygenation, if work of breathing is increased support respiration and if PEEP is high reduce it. If non of these causes are apparent check CFT and if prolonged administer a bolus of normal saline at a dose of 10ml/kg and reassess perfusion. Metabolic acidosis may be the first indication of a poor perfusion and hence perfusion must be supported with bolus or if need be pressors.

2) *Excessive CO2 retention* : A baby with RDS may have accumulation of CO2 as a result of a. severe RDS; b. tube block; c. increased dead space; d. Impending opening of the ductus arteriosus

Whenever the blood gas reveals an accumulation of CO2, cut short the ET tube if it is more than 3-4 cms beyond the lips, suction the ET tube and check improvement on EtCO2 if available. Next increase minute ventilation by increasing RR or PIP and check by repeating a gas after 20-30 minutes of ventilator setting change. If non of these problems are there, then Check the amount of fluid being infused, (Keep track of the boluses and IV pushes) if excessive, curtail the fluid as per the daily requirement.

3. *Sudden deterioration on IPPV* : a. pneumothorax b. IVH.

4. *Gradual deterioration on IPPV* : (a) Sepsis (b) Blocked tube (c) ICH (d) PDA (e) Anemia (f) Hypotension (g) Hypoglycemia etc.

Weaning

Weaning is a very delicate process and needs to be done with utmost care and precision. The process of weaning is begun once the lung condition has shown improvement i.e. the blood gases and the baby both have remained stable at a particular set of ventilatory settings for a period of 8-12 hours. In addition, as per the natural history of the disease under consideration, the phase of resolution or improvement should generally coincide with the timing of initiation of the weaning process.

The *first setting* to be reduced is the PIP (by 1 cm decrements) to 25cm H2O. The next parameter of concern is the FiO2 and hence this must be reduced next. PIP and FiO2 (by 0.05 decrements) are reduced alternately till a comparatively safe level of 20cm H2O and 0.6 respectively is attained.

Next FiO2 and PEEP are reduced hand in hand (similar to their increments) and reduction of rate is begun (2 breaths at a time) along with successive decrements of PIP keeping a close vigil on the PaCO2 values.

Rate is the last parameter to be weaned, as the rate is reduced one must watch for increased work of breathing, metabolic acidosis and fatigue which would be bothersome if the rate is decreased prematurely or at a fast pace. As the rate is reduced the Ti is also reduced in an attempt to provide prolonged expiratory phases wherein the baby can get ample opportunity to breathe on his own and takeover most of the function of breathing.

Once *minimal settings* have been reached which are defined as : (i) *FiO2* < 0.4, (ii) *PIP* 13-14, (iii) *PEEP* 3, (iv) *Ti* 0.3 and (v) *Rate* 10.

The baby can be extubated and provided oxygen by hood at a FiO2 of 0.45. Aminophylline should be started 24 hours prior to expected extubation. A blood gas 30min after extubation must be done to assess the gas parameters. The baby should be carefully monitored clinically for signs of increased work of breathing, fatigue or exhaustion. An x-ray of the chest should be obtained about 6 hrs post extubation and at least once more thereafter to rule out post extubation collapse.

Though the newer modes of ventilation like synchronized intermittent mechanical ventilation (SIMV), patient triggered ventilation (PTV) and high frequency ventilation (HFV) are in vogue, the evidence does not show their superiority over CMV, except for shorter duration of ventilation on using SIMV. A recent multicentric trial by Johnston et al. did not reveal superiority of

Desired blood gas status and the possible changes in ventilator status

Desired status	Rate	PIP	PEEP	Ti	FiO2
Increase PaCO2	Decrease	Decrease			
Decrease PaCO2	Increase	Increase			
Increase PaO2		Increase	Increase	Increase*	Increase
Decrease PaO2		Decrease	Decrease	Decrease*	Decrease

Ventilator settings based on blood gas status

Gas status	Ventilator changes required
PaO2	PaCO2
PaO2	N PaCO2
NPaO2	PaCO2
NPaO2	PaCO2
PaO2	PaCO2
PaO2	N PaCO2
PaO2	PaCO2
PaO2	PaCO2

Increase PIP which will increase MAP and increase tidal volume
Rate, PEEP and keep MAP constant
Rate and keep MAP constant
PEEP, Ti and Rate
FiO2 and MAP
PIP, Rate & FiO2
Consider possibility of Over ventilation, Sepsis of PPHN. FiO2, or MAP or use vasodilators

HFV over conventional ventilation in preterms with RDS (23).

Complications

Complications encountered in a baby with RDS are a combination of those due to Prematurity per se, sequelae of surfactant deficient RDS and those that are caused as a result of the treatment given. These are enumerated as : (1) Airleak (2) Patent Ductus arteriosus (3) Peri-ventricular hemorrhage-PVL (4) Infections (5) Bronchopulmonary dysplasia (6) Necrotising enterocolitis and (7) Renal failure (8) ROP.

Prognosis

The prognosis of RDS has improved tremendously in the western world with almost 90% survival and in most cases a neurologically intact survival. Most deaths occur as a consequence of either infection, IVH-PVH or BPD. Survival in our country is steadily improving but varies from centre to centre. There is considerable morbidity associated with RDS, nearly 50% seek readmission in the pediatric ward during the first year of life for surgery for hydrocephalus or inguinal hernia repair, failure to thrive or sequelae of NEC surgical repair. Most admissions are related to neurologic sequelae or respiratory problems.

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Surfactant Replacement therapy in Newborns

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Abstract: Hyaline membrane disease is the most common respiratory disorder of the infants. It mainly affects the preterm babies below 35 weeks of gestation and is the major cause of mortality in this age group. Hyaline membrane disease is characterized by respiratory distress starting almost immediately after birth or maximum within first 6-8 hours of life. The basic defect in HMD is alveolar collapse secondary to surfactant deficiency. Surfactant has become the routine care in the management of preterm babies with HMD. After ventilation, surfactant has been proven to be the most important agent, which has improved the survival in preterm infants. Natural surfactant has been proven to be better than synthetic surfactant. Prophylactic surfactant usage should be restricted to babies less than 28-29 weeks of gestation, in older gestations it should be delivered early in the course of disease for optimal action. Surfactant therapy is definitely cost effective and without significant side effects. The surfactant usage is currently being extended to other neonatal respiratory disorders.

Introduction

Hyaline membrane disease is the most common respiratory disorder of the neonates. It mainly affects the preterm babies below 35 weeks of gestation and is the major cause of mortality and morbidity in this age group. It can also affect more mature babies born to diabetic mothers, suffering from birth asphyxia or having congenital deficiency of surfactant apoprotein B. Hyaline membrane disease is characterized by respiratory distress starting almost immediately after birth or maximum within first 6-8 hours of life in a preterm baby. The clinical hallmark is grunting respiration, hypoxia, increased oxygen and artificial ventilation requirement in a significant proportion of cases.

The basic defect in HMD is alveolar collapse secondary to surfactant deficiency. A very and Mead first described this association in 1959 (1). They reported that the lungs of preterm infants with HMD lacked the surface tension lowering agent characteristic of pulmonary surfactant. It took almost 20 years before Fujiwara et al, 1980(2) reported the clinical use of surfactant in preterm babies with HMD. They treated 10 neonates with surfactant prepared from solvent extract of bovine lungs and observed that it improved the oxygenation and decreased mortality and incidence of pneumothorax.

First randomized controlled trial to test its efficacy was done in 1984 and after that over 80 such trials have been done. Metanalysis of these trials show a decrease in oxygen requirement, ventilatory support, pneumothorax and mortality related to respiratory failure has drastically come down by 40%. Even larger trials involving 4000-5000 infants with weight <1500gms have shown a reduction in mortality by 30%. No consistent effect has been observed in the incidence of retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC) and bronchopulmonary dysplasia (BPD). Surfactant therapy is now the routine care in the management of preterm babies with HMD. After ventilation, surfactant has proved to be the most important agent, which has improved the survival in preterm infants.

Composition of surfactant(3) : Lipid constitute the major fraction of surfactant (nearly 90%), dipalmitoylphosphatidylcholine (DPPC) is the most active substance, which lowers surface tension. DPPC can reduce surface tension to zero but it requires surface active proteins for

its adsorption (SP-B and SP-C) and other unsaturated phospholipids for its spread. DPPC is synthesized in the endoplasmic reticulum and fetal lung accumulates large amount of DPPC in the last trimester. 90% of the total surfactant pool is recycled requiring surface-active proteins for this action. Though a term neonate's surfactant pool is 10 times more than that of adult lungs but preterm babies are deficient in surfactant pool. In addition in preterm neonates, surfactant has decreased biophysical function and is more sensitive to inactivity by inhibitors. In neonate recovering from RDS, concentration of DPPC increases over 4-5 days to normal infants. Surfactant pool in a term neonate is about 100mg/kg of phospholipids and this is the dose delivered to these babies.

Effects on lung mechanics⁴

Surfactant deficient lungs have poor compliance and low functional residual capacity. There is alveolar collapse at the end of expiration leading to low FRC and ventilation perfusion mismatch resulting in intrapulmonary right to left shunting. Surfactant helps in prevention of alveolar collapse at the end of the expiration, leading to improvement in FRC and thereby improving the compliance (5). As a result there is improvement in oxygenation and ventilation requirement goes down substantially. It is not very effective late in the course of the disease, as by that time hyaline membrane is already formed and surfactant cannot reach the alveolar air fluid interface.

Types of surfactant

It has two broad categories. (1) *Natural* (2) *Synthetic*

Natural surfactant is obtained mainly from either bovine or porcine lungs. Beractant (Survanta) and surfactant TA (surfacten) are lipid extracts of bovine lung mince with added DPPC, tripalmitoylglycerol and palmitic acid. Other natural surfactants are curosurf (porcine lung mince), Infracurf (calf lung surfactant extract). All natural surfactants contain SP-B and SP-C. The purification procedure that includes extraction with organic solvents removes the hydrophobic proteins SP-A and SP-D.

Synthetic surfactant - Exosurf consists of 85% DPPC, 9% hexadecanol, 6% tyloxapol (a spreading agent). Other is pumactant, which is a 7:3 mixture of DPPC and phosphatidylglycerol. Neither of these two synthetic surfactants contains any of the phospholipids and apoproteins.

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Two other synthetic surfactants that are likely to be available for human use soon are lucinactant and venticute, which contains genetically engineered recombinant apoproteins SP-B and SP-C respectively.

Use of surfactant

Various clinical trials have proved that surfactant therapy definitely improves the outcome in preterm babies by decreasing the incidence of pneumothorax, PIE and mortality. Various issues have been raised to find out the best use of surfactant. These issues are: whether to use natural or synthetic surfactant, what is better prophylactic or rescue treatment, what should be the timing, dose of surfactant in cases of established HMD and how effective is the combination therapy i.e. use of maternal corticosteroids and surfactant. All these issues are discussed below one by one.

Natural Vs Synthetic therapy⁶

Natural surfactant has been documented in various clinical trials to be better than the synthetic surfactant because of its rapid onset of action, sustainability of action because of apoproteins and decrease in the frequency of pneumothorax and mortality.

Prophylactic Vs Rescue treatment

Trials have been conducted to find out the best timing for giving surfactant. Prophylactic therapy means delivery of surfactant before baby develops respiratory distress. The rationale for the use of prophylactic therapy was that in animal models when surfactant was given immediately after birth there was more uniform and homogenous distribution of surfactant in fluid filled lungs leading to less acute lung injury. Systematic review by CJ Morley 1997(7) concluded that prophylactic treatment saved seven more lives than rescue treatment for every 100 babies treated. But this approach destabilizes the patient and surfactant is received by a group of preterm babies who do not require it leading to the wastage. Another issue in prophylactic therapy is, whether to deliver surfactant with the first breath even before resuscitation or delay it after baby has been resuscitated. This issue has been looked into by Kendig et al 1988(8) and he concluded that surfactant may be administered with equal or greater efficacy after initial resuscitation and confirmation of endotracheal tube.

Early Vs Late rescue therapy of HMD⁹

The rescue therapy means delivery of surfactant after baby starts having respiratory distress. The recommendation is to give surfactant therapy as soon as possible, as even minimal mechanical ventilation in a very short time can cause acute lung injury. The results of metaanalysis of various studies have shown decrease in the risk of pneumothorax, pulmonary interstitial emphysema and mortality if given within 2 hrs of birth (early) vs >3 hrs of birth (late).

Combination Therapy¹⁰

The incidence of hyaline membrane disease has been reduced after universal introduction of antenatal steroids in suspected preterm births. Surfactant therapy is definitely beneficial in babies with respiratory distress. The combination therapy i.e. the use of maternal corticosteroids with surfactant has even better outcomes. In a trial from Finland in

1994, Kari and associates (11) found that infants with RDS randomized to receive maternal corticosteroids showed better response compared to infants who did not receive prenatal corticosteroids. In another metaanalysis of randomized multicentric trials it was observed that when maternal corticosteroids and surfactant therapy were used alone results were quantitatively similar in terms of improving the respiratory outcome but when used together there was better outcome. Death decreased significantly from 19.6% in the group receiving neither surfactant nor corticosteroids to about 7% in a group receiving either treatment. No infant died of respiratory distress that received combined treatment.

Guidelines for use of surfactant

The preterm babies below or equal to 28-29 weeks of gestation with no history of maternal corticosteroids should be given surfactant immediately after birth after initial resuscitation (prophylactic therapy). Babies who are ≥ 30 weeks of gestation should be clinically assessed and if they are having respiratory distress, requiring intubation with chest x-ray picture showing feature of HMD, should be given surfactant as early as possible, i.e. within 2 hrs. In preterm babies who are more than 32 weeks surfactant therapy should be given if baby is having $FiO_2 > 0.4$ and $MAP > 7$ cm of H₂O and clinical picture is suggestive of HMD.

Dose of Surfactant

Surfactant dose is 100mg/kg of phospholipids, which is the surfactant pool of term neonate. In surfactant this is equal to 4ml/kg and in exosurf 5ml/kg.

Repeat dose of surfactant¹²

There is controversy regarding the number of doses of surfactant required for the best results. Various trials have been conducted to find out the answer. As surfactant is rapidly metabolized, only 20-30% of dose can be recovered from the air spaces after 24 hrs of ventilation, improve after a single dose is unsustained and its function can be inhibited by proteins in small airways, so multiple doses can overcome this functional inactivation. In the OSIRIS trial two dose treatment schedule was found to be equivalent to a treatment schedule of four doses.

Side effects of surfactant

Surfactant is so far a safe drug with minimal side effects. It may have transient side effects like cyanosis, bradycardia, increased oxygen requirements, hypoxemia, increased PaCO₂ during administration¹³, which can be minimized after careful monitoring. It also increases the risk of pulmonary hemorrhage, which is 5-7% with natural surfactant and 3-5% with synthetic surfactant. The pulmonary hemorrhage is nothing but hemorrhagic pulmonary edema and is so more often seen in presence of a patent ductus arteriosus. Careful monitoring and faster weaning after surfactant therapy can minimize it. There are no long-term side effects like neurodevelopmental delay, growth retardation and late allergic and respiratory disorders attributable to surfactant alone.

Method of administration of surfactant

Surfactant administration should take precedence over admission procedure, putting long lines and nursing care. The whole procedure should be carried out under aseptic precautions.

Method of delivering exogenous surfactant to the affected lungs consists of the following steps:

- (1) **Stabilize the patient hemodynamically. Never give surfactant to a baby who is desaturating or is in shock.**
- (2) **Keep the baby in supine position. Previously the baby's position used to be changed during administration but the latest recommendation is not to change the position as changing the position destabilizes the baby and does not lead to better spread.**
- (3) **Intubate the baby with dual lumen endotracheal tube and confirm the position clinically.**
- (4) **Fill the surfactant from the bottle with wide bore needle into the 10ml syringe. Don't shake the bottle as it leads to foth formation.**
- (5) **Deliver surfactant through the side port of the Endotracheal tube in 4 boluses of 1ml/kg each over a total of 10-15 minutes making a total dose of 4ml/kg.**
- (6) **During administration don't disrupt mechanical ventilation as constant PEEP help in better dispersion of the surfactant.**
- (7) **Monitor baby's saturation, blood pressure (ideally invasive), heart rate and Transcutaneous PaCO₂ throughout the procedure.**
- (8) **Constantly monitor the ventilatory settings as surfactant rapidly improves the compliance of the lung necessitating rapid decrease in the ventilatory settings.**
- (9) **In face of nonavailability of transcutaneous PaCO₂ monitor, a blood gas after 15-20 minutes is mandatory to see PaCO₂.**

Cost of surfactant

Natural imported surfactant is available at the rate of Rs. 13000-15000/vial while synthetic surfactant is available at the rate of Rs. 25000/vial. An Indian company has come up with a *synthetic* surfactant available at the cost of Rs.4500/vial. The effectiveness of this surfactant is being tried in a clinical trial at present. Surfactant replacement therapy for neonatal respiratory distress syndrome has the potential to reduce morbidity and mortality of very premature infants. A study was done¹⁴ to investigate whether surfactant replacement therapy reduces hospital charges for these infants. They compared the hospital charges incurred by a group of patients treated with surfactant with hospital charges for the control group who did not receive surfactant. Average daily charges in the surfactant treated patients were 25% less than for the control patients. Most of the savings in daily charges were due to a 52% reduction in daily charges for laboratory, X-ray, respiratory therapy and other ancillary services. This study showed reduction in neonatal mortality and morbidity from respiratory distress syndrome, and it also significantly reduced requirement of ancillary services and so their charges. In this way surfactant therapy is cost effective by improving survival without increasing overall hospital costs.

Expanded Use of surfactant

After successful use of surfactant in hyaline membrane disease, it has been used in a number of other neonatal respiratory disorders like meconium aspiration syndrome, congenital diaphragmatic hernia¹⁵, pulmonary hemorrhage¹⁶, acute lung injury¹⁷, acute respiratory disorder syndrome¹⁸, pneumonia and sepsis. There are some trials supporting its use in MAS and acute lung injury. There are only few small prospective, randomized, controlled trials supporting surfactant use in non-HMD cases. Use of surfactant Therapy for any disorder other than HMD must be considered "Off the shelf" and experimental and should be decided on case to case basis.

Conclusion

The use of surfactant has revolutionized care of preterm babies suffering

from hyaline membrane disease. It judicious use with careful monitoring has improved survival, decreased incidence of air leak syndrome but has not affected the incidence of chronic lung disease, NEC, ROP and IVH. Natural surfactant has been proved to be better than the synthetic surfactant. Prophylactic surfactant usage should be restricted to babies less than 28-29 weeks of gestation. In older gestations it should be delivered early in the course of disease for optimal action. In other neonatal disorders surfactant is being used on experimental basis only.

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Total Parental Nutrition in High-Risk Preterm Babies

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Abstract: Parental nutrition is used most commonly for preterm babies because of their gut immaturity and their inability to take total feeds directly. TPN includes providing fluids, electrolytes, carbohydrates, proteins, fats, vitamins and trace elements in adequate amounts to maintain growth. Administration of parental nutrition requires regular monitoring for biochemical and catheter related side effects. One needs to know the methodology of parental nutrition administration for its successful execution.

Introduction

Total parental nutrition is required in any baby who is not going to be on full enteral feeds by 5-7 days. Tiny sick babies are born with limited resources and have higher requirements of nutrients per kilogram of body weight often due to respiratory problems, sepsis etc. Most commonly TPN is used for the preterm babies in the nursery as they have feeding intolerance and so need intravenous support. It is also used for any baby with surgical problems, sepsis, persistent pulmonary hypertension, chronic lung disease, etc who is critically ill & whom early feeding is not an option.

TPN includes providing fluids, electrolytes, carbohydrates, proteins, fats, vitamins & trace elements in adequate amounts to maintain growth. Preterm babies have limited energy stores and need to be on IV glucose and proteins as early as possible to prevent protein catabolism.

The TPN calculations for the preterm babies are based on the fetal growth patterns and extrapolations of the requirements in more mature babies. Till 26-28 weeks of gestation fetus has minimal lipid uptake from placenta, has a glucose delivery parallel to energy requirements and amino acid uptake in excess of protein accretion requirements. In NICU the ELBW babies receive lipids in high amounts, glucose often more than in-utero requirements and amino acids in low amounts.

Fluids & Electrolytes

Fluids requirements vary with gestational age, day of life and in different disease states. Full term & preterm babies lose upto 10-15% of birth weight respectively and this is mostly in the ECF component. Weight should be monitored at least once a day (and more often in premies) and babies should be allowed to lose upto 3% of birth weight daily (keeping urine output > 2ml/kg/hr.) till they have achieved the loss of 10-15% of the birth weight as mentioned above.

When and how to start and which increments? : fluids should be started at 60ml/kg/day in full term babies and 80-100 ml/kg/day in preterm babies. Many preterm babies may require initial fluid resuscitation with normal saline 10-20ml/kg (IV albumin is not recommended) over 1-2 hours for poor cardiac output, poor peripheral circulation and accompanying acidosis. Glucose should be started in preterm babies as soon as possible and amino acid drip can be added on day one itself. Sodium Chloride (2-4 meq/kg/day), potassium (1-2meq/kg/day), calcium are usually added after 24 hours of life or after weight loss of 6% of birth weight (approximately 48 hrs).

Fluids are increased by 10-20ml/kg/day (keeping urine output >

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2ml/kg/day, weight loss at 3% day, and serum Na<150) & serum electrolytes should be monitored daily in the first week. At the end of the 1st week the skin of the premature baby gets keratinized and fluids need not be given at more than 150-160 ml/kg/day.

If hyponatremia develops (Na>150), usually due to excess water loss via skin in premies, then the fluids may have to be increased upto 200ml/kg/day or more. Hyponatremia may develop due to sodium free fluids being given (also due to hypotonic fluids given to mother during delivery & oxytocin use) and adequate sodium correction should be done over 24 hours for sodium values below 130meq/l. Late onset hyponatremia with peripheral edema is seen in growing premies, due to excessive renal Na losses & use of diuretics for chronic lung disease, so requirements of Na may be as high as 8-10 meq/kg/day.

Non oliguric hyperkalemia may be seen in ELBW babies due to increased fractional excretion of Na along with decreased K excretion, decreased GFR & relative aldosterone insensitivity 91). Insulin infusion may be required along with glucose to control K levels.

Special scenarios for fluid adjustments : If a PDA (patent ductus arteriosus) is present then the fluids should be restricted to 100ml/kg/day (and even lower if indomethacin is given) and similar strategy may be employed in hyaline membrane disease (HMD) till diuresis sets in by 48-72 hours.(2)

Babies with NEC (necrotizing enterocolitis - usually in 2nd -3rd week) lose lot of fluids in third spacing and need vigorous resuscitation with Normal Saline. They often develop hyponatremia is hypotonic maintenance fluids are increased to 1.5-2 times the normal. These babies may be given 120-130ml/kg/day of fluids (with 2-4 meq of Na/kg/day) and additional fluids given as Normal Saline infusion every couple of hours (ie Q6-Q8 hours).

Hypoxic Ischemic Encephalopathic babies may require vigorous resuscitation with N Saline 10-30ml/kg for shock/acidosis and may also require inotropic support to maintain good tissue perfusion. Restriction of IV fluids may be required (in view of risk of SIADH) but adequate intravascular volume should be maintained, as these babies are prone to PPHN (persistent pulmonary hypertension).

Infants with chronic lung disease have high calorie requirements but at the same time their fluids need to be restricted to 150ml/kg/day. Diuretics may need to be added to decrease pulmonary edema and fluid retention and oral Na-K supplements may be needed to offset the renal losses.(3)

Thus fluid & electrolyte management should be individualized for each baby after daily evaluation of Cardiovascular, Respiratory status, weight change, peripheral edema, urine output, serum Na & K and the underlying pathology.

Amino Acids :

The amino acid composition in the TPN is derived from the amino acid composition of the cord blood, from blood values of breast fed babies and still the ideal composition is unknown. Preterm babies on glucose-only fluids lose 1% of protein stores per day & thus amino acids need to be added to IV fluids from Day One of life. Usually 1-1.5gm/kg/day of parenteral protein is adequate to prevent protein catabolism and 3-4g/kg/day is sufficient to equal protein accretion rates of fetus in ELBW babies (4,5). In fetus 50% of amino acids are used for energy production and part of the amino acids in TPN are also oxidized for energy production. For 1 gm of protein accretion 10 calories/kg/day needs to be added to the RMR (resting metabolic rate = 40-50 cal/kg/day). Thus for an Amino acid intake of 2gm/kg/day (for nitrogen retention) minimum calories required are 50-60 cal/kg/day. Usually this energy can be met with glucose infusion rates of 8-10mg/kg/min.

Amino acids are usually started @ 1gm/kg/day from Day 1 and then increased incrementally upto 3-4g/kg/day in next 3-4 days, though there is no evidence to suggest increasing the proteins faster is detrimental or not tolerated well by ELBW babies.

Protein intake of >4gm/kg/day is not usually recommended and in TPN induced cholestasis & babies in stress (sepsis, surgery, NEC etc) proteins are limited to 2.5 gm/kg/day.

Acidosis, hyper-ammonemia were seen in TPNs in 1980s due to poor utilization of the Amino Acids but with improved crystalline amino acids in TPNs since 1990s these complications are not seen. In the fetus, high amino acid oxidation for energy utilization leads to high BUN, and a rising BUN in ELBW premie may not be a sign of amino acid intolerance, rather it maybe an indication of amino acid oxidation. Thus acidosis, ammonia and azotemia are poor markers to reflect amino acid intolerance.

Carbohydrates :

Glucose is the primary source of energy for brain. Premies have high glucose requirement as they have large metabolically active organs like heart, liver, kidney and brain compared to their body weight. Endogenous glucose production in premies is 4-7 mg/kg/min the endogenous production cannot be completely suppressed with insulin infusion unlike in full term babies and adults. Glucose infusion should be started at 6mg/kg/min and increased gradually to 12mg/kg/min keeping serum glucose below 180 mg/dl when glycosuria may develop leading to polyuria and dehydration. Twenty to eighty percent of ELBW babies develop hyperglycemia due to hepatic & peripheral tissue insuli resistance and this may limit the amount of glucose that can be infused(6). Maximal oxidative capacity for glucose in babies is 12-13mg/kg/min and beyond this rate the glucose is converted to fat in an energy inefficient process leading to increased CO₂ production (especially @ 16-18mg/kg/min.)⁷. For treating *hyperglycemia*

- decrease glucose infusion rates or use hypotonic solutions of as low as D 2.5% till serum glucose is below 150mg/dl (only for transient hyperglycemia)
- start IV amino acids from Day of Life One (as they enhance endogenous insulin secretion)
- start insulin infusion if the blood sugar is more than 200-250 mg/dl especially with urinary spill over and osmotic diuresis. (this may also help in weight gain in ELBW babies though development of lactic acidosis remains a concern.)

As the preterm baby has minimal glycogen stores before 28 weeks of gestation any serum glucose below 40mg/dl needs to be treated with 2ml/kg IV push of D10 W accompanied with an increase in the baseline glucose infusion rate.

Lipids :

Preterm babies have minimal fat stores and develop Essential Fatty Acid deficiency within 72 hours if not given intralipid (IL) infusions. Lipids can be started from Day 1-2 & EFA deficiency can be prevented with a IL dose as low as 0.5gm/kg/day (8). Routinely lipids are increased by 1gm/kg/day to reach a maximum of 3gm/kg/day though no evidence exists to show that lipids are tolerated better when the dose is gradually increased daily. Lipids in the blood stream are cleared via. (a) lipoprotein lipase in the endothelium, (b) hepatic lipase, (c) lecithin cholesterol acyltransferase.

The activity of all these enzymes remains low in preterm babies and activity of (a) & (b) can be induced with low dose heparin (usually running in the central line). Currently available IL are of soybean + safflower oil and a 20% solution given over 24 hours infusion is ideal (as the clearance of IL depends on rate of infusion/min). Triglyceride levels should be monitored initially 2-3 times per week and then weekly and levels below 150-200mg/dl are acceptable.

Lipids are known to increase pulmonary pressures and thus need to be used cautiously in RDS & PPHN. Infusion rates > 0.025mg/kg/hr (1.5gm/kg/day) have shown to worsen pulmonary vascular resistance in multiple studies(9). Concerns of lipid deposition in the lungs of preterm infants have been allayed in recent studies which found lipid deposition in lungs artifactual(10). In ELBW babies with bilirubin levels of 10-12mg/dl the intralipids should be restricted to 2gm/kg/day (with serum albumin of at least 2.5 gm/dl.) due to concern of bilirubin displacement by free fatty acids. In stress due to sepsis, surgery the lipid intake should be restricted to 2gm/kg/day as the ability to utilize lipids is diminished.

Medium Chain Triglyceride - Intralipid preparations are in trial presently and have the theoretical advantage of (1) improved lipid oxidation (2) carnitine independent oxidation (3) low risk of displacing bilirubin bound to albumin.

Carnitine is required for oxidation of fatty acids. Current TPNs do not have carnitine in them and at present there is no recommendation to add carnitine in IV fluids.

Calories :

Calorie requirement of preterm babies on TPN for maintaining existing weight is 50 cal/kg/day (60 cal/kg/day for enteral feeds) and 100 cal/kg/day for growth (120 cal/kg/day for enteral feeds). Protein calories (4 cal/gm) are included in the calculations through all protein calories are not available for energy expenditure. Carbohydrates and lipids are the main source of energy and provide 3.4 cal/gm and 9 cal/gm respectively. In enteral feeds the ratio of carbohydrate to fat calories should be 65/35 with EFA providing 3-5% of the total caloric intake and MCTs not providing more than 40% of the fat derived calories. By 2 weeks of age all the ELBW babies should regain their birth weight, and then grow by 15-20 gm/kg/day if receiving adequate amount TPN and enteral feeds. In babies with BPD the energy requirements are higher but giving more than 160-180 cal/kg/day is not of benefit.

Vitamins & Trace Elements :

Vitamin supplementation should start as soon as protein is added to the TPN. Water soluble vitamins act as co-enzymes in carbohydrate and protein metabolism and cannot be stored in the body (except vitamin B12). Vitamin D requirements are 160-400IU/kg/day though studies have shown even 30IU/kg/per day to be effective in preventing osteopenia of prematurity (11). Vitamin A (requirement 1670 IU/kg/day) is usually low in commercially available IV multivitamin preparations and intramuscular injections

of Vit A may be used to reduce the incidence of Chronic Lung Disease (IM x 3 per week). MVI (NBZ Pharma Ltd.) has 1000 IU of Vit.A and 100IU of Vit.D per ml along with the other fat soluble and water-soluble vitamins. A dose of 1.5ml/kg/day in IV fluids is adequate to meet the daily requirements.

Trace elements like Zn, Cu, Se, Iodine, Manganese, and Chromium should be added to the TPN as their deficiency states may aggravate the metabolic problems. Cececel (Core Healthcare Ltd.) manufactures three types of trace element solutions of which Cececel-4 has Chromium, Copper, Manganese and Zinc. Cececel-5 has Se in addition to the 4 elements and Cececel 7 has Iodine & Molybdenum in addition to the trace elements in Cececel 5. A dose of 0.05 ml/kg/day meets the daily requirements.

Minerals : The accretion rate for Calcium is 120-150mg/kg/day in the 3rd trimester and 75-85 mg/kg/day for Phosphorus. The Ca/P ratio in TPN should be 1.7/1 for accretion rates of 90%. When EBM is well tolerated HMF (Ca fortifier) should be added to oral feeds, as breast milk is inadequate in Ca for the growing premie. If preterm formula is being used exclusively then Ca supplementation is not required.

Preparation of TPN in NICU :

Commonly available amino acid solution in India is Aminoven Infant 10% (Fresenius Kabi India) which has 10gm of amino acids per 100ml. Ivelip 20% (Baxter) is the lipid solution used in NICU, which has 20 gm of lipids per 100ml. Start with glucose infusion rates (GIR) of 6mg/kg/min and the goal is to increase GIR by 1-2mg/kg/min every day to reach at least 50-60 cal/kg/day within 2-3 days to prevent protein catabolism. Add insulin for persistent hyperglycemia and add amino acids (1.5gm/kg/day and increase to 3.5 gms/kg/day over next 3-4 days) & intralipids (1gm/kg/day from Day 2 and increase by 1gm/kg/day to maximum of 3gm/kg/day).

Calculate the total volume required per day, deduct the volume for intralipids and feeds. Calculate the GIR and the total glucose required per day in 24 hours and then use a combination of D10% & D25% to make the required glucose concentration.

For a 1kg preterm baby :

Day 1 Start with: Total volume of fluids 90ml/kg/day
Protein at 1.5gm/kg/day 15ml of Aminovin
Glucose infusion rate (GIR) at 6mg/kg.min 75 ml/day

8640mg glucose per day (8.6 gm)
i.e. 7.5ml D25% (1875mg)

+
67.5ml D10% (6750mg)

This will be a D9.5% TPN when amino acids and the glucose solutions are finally mixed.

D10% solution has 10gm glucose/100ml or 100mg/ml
D25% solution has 25gm glucose/100ml or 250mg/ml
N Saline has 0.154meq/l & 3% saline has 0.514meq/l

Calories :Glucose-29cals (8.6gmsx3.4cals/gm)
Proteins-06cals (1.5gmsx4cals/gm)
Total 35 cals

Day 2 Total volume of fluids 100ml/kg/day
Increase proteins to 2.5gm/kg/day 25ml of Aminovin
Add 2meq/kg of Na & 1 meq/kg 05ml of 20% IL
of K to 24 hr fluids Start Intralipid
1gm/kg/day
Increase GIR to 8mg/kg/day (if no 70ml
hyperglycemia)

11520mg glucose per day (11.5 gm)
i.e. 25ml of D25% (7500mg)

+
40ml of D10% (4000mg)

Calories : Glucose - 39cals (11.5gm x 3.4cals/gm)
Proteins - 10cals (2.5gm x 4 cals/gm)
Intralipid - 9 cals (1gm x 9 cals/gm)

Total Calories 60 cals

This will be a D12% TPN when the amino acids and glucose solutions are finally mixed. (nitrogen retention starts if the calories are at least 60 cal/kg/day with 2gm/kg of protein intake. Volume for saline not used here to simplify the calculation).

10% Calcium gluconate can be given 150-200mg/kg/day from Day 1 via a separate IV line either as a continuous drip over 24 hours or as Q6 hr infusions. It should not be added to TPN with sodium bicarbonate as it may precipitate.

Peripheral IV lines can be used for providing TPN if the requirement is for less than a week and intralipid solutions Y-ed into the TPN line help in decreasing the complication of IV line infiltration. For TPN lasting longer than 7 days a central line must be placed in the form of PICC line for a Broviac. Heparin in TPN, whether via peripheral or central line (35-150 units per day) helps in preventing hypertriglyceridemia and decreases complication of clotting in IV lines.)

Complications of TPN

Electrolyte imbalances, hypo & hyperglycemia, hypertriglyceridemia, vitamin and trace element excess and deficiencies (management as discussed above), metabolic bone disease are some of the complications of TPN. Prolonged TPN use is associated with cholestatic jaundice with elevation of direct bilirubin and liver enzymes. The exact cause is not known but proportions of amino acids in TPN, high glucose intake and some trace elements, sepsis, hemodynamic instability have been implicated. The longer the use of TPN and the more premature and sick the baby, higher is the incidence of cholestasis (with 90% of babies on TPN for >90 days having cholestasis)

Metabolic acidosis is a complication in preterm babies on TPN as the amino acids are in the form of chloride salts & due to renal losses of bicarbonate. TPN solutions buffered to base excess of 12mmol/L with hydroxide and acetate salts of sodium & potassium help in decreasing the TPN associated acidosis and also improve calcium and phosphorus retention.

Monitoring

Electrolytes Na, K, Cl, Ca, bilirubin, BUN & creatinine should be monitored daily for the initial 3-4 days and then 2 times per week (Preterm baby will need closer bilirubin monitoring as needed clinically). Triglycerides should be monitored daily for the first 3-4 days when the lipids are being increased and then once a week. Weight should be monitored daily along with a strict intake-output chart. Serum protein, albumin, SGOT, SGPT, bilirubin & alkaline phosphatase are done on day 4-5 and then every 2 weeks.

Weaning From TPN

As the oral feeds are increased the TPN rate should be decreased proportionately and the glucose concentration brought down to D10%. This makes administration simpler as the need to recalculate TPN daily is avoided. Feeds are usually initiated as trophic feeds (5-10ml/kg/day via oro-gastric tube, EBM preferentially) by 1-2 days of life and increased by 10-20 ml/kg/day or more rapidly as

tolerated. EBM should be fortified with HMF.

(human milk fortifier) once full feeds are well tolerated and MCT oil can be added to improve the caloric content. By 32 weeks feeds can be given via spoon or directly from breast. Lactodex-HMF (Raptakos, Brett & Co Ltd) has a 2gm sachet with 730 IU Vit. A, 250 IU of Vit. D, & other water and fat-soluble vitamins. It also has 50mg of Calcium along with trace elements like copper, magnesium, manganese & zinc. It also has 0.2gm of protein, 0.1gm of fat and provides 6.5 calories per sachet. Adding 1 sachet per 50ml of EBM meets all the vitamin and calcium requirements of a growing premie.

If the preterm baby is going to be on exclusive preterm formula then calcium & vitamins need not be added, as they are adequate in the preterm formula. Iron supplementation will be required in all premies from about 8-10 weeks of age whether on EBM or on preterm formula. The maximum catch-up growth for the minerals in the preterm baby is from 40 weeks to 52 weeks of age and they therefore should be on preterm formula or EBM_HMF for at least 3-6 months to meet their energy and mineral needs.

Full term babies on formula or breast milk do not require any vitamin or iron supplementation till at least 6 months of age (may need Vit D supplementation if on breast milk exclusively).

Thus TPN is essential to maintain the protein stores and provide calories to the newborn infant. Early initiation of TPN on Day One with a smooth transition to intermittent enteral feeds helps to put the preterm baby on the road to optimal catch-up growth and improved neuro-developmental outcome.

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Gastro-Esophageal Reflux in neonates: A Challenge in Feeding New Borns and Preterms

NEELAM MOHAN, INDRAJIT MAJUMDAR, VIKAS TANEJA

Abstract: Gastro-esophageal reflux (GER) is a physiologic phenomenon in infants and usually resolves by 6-12 months of age. Symptomatic GER, that is gastro-oesophageal reflux disease (GERD) is as frequent as 1 in 300 infants and results from significant reflux producing a detrimental physical change such as poor weight gain, mucosal ulceration or chronic respiratory symptoms. Neonates with GERD can present with a wide spectrum such as frequent vomitings, feeding intolerance, hypoxia, apneic spells, recurrent episodes of pneumonia etc. Patients with significant neurological deficit suffer from serious sequelae secondary to GER. In a patient with GER who is thriving and healthy no diagnostic or therapeutic maneuvers are required. In patients with GERD, available diagnostic studies are barium swallow, endoscopy and esophageal biopsy, scintigraphy and pH monitoring (gold standard). Treatment options for pediatric GERD include lifestyle changes (small frequent feeding & thickened feeds), pharmacological (prokinetics, antacids, H₂ receptor antagonists and proton pump inhibitors) and surgery. Recently, percutaneous endoscopic gastrostomy (PEG) has been made available as an option for feeding babies with GERD.

Introduction

The term gastroesophageal reflux (GER) refers to the presence of gastric contents in the esophagus proximal to the stomach. This is physiologic occurrence that takes place more often during infancy and decreases with advancing age. The prevalence of GER peaks between 1 month to 4 months of age and usually resolves by 6 to 12 months of age. No gender predilection or definite peak age of onset beyond infancy has been established. A normal newborn infant who spits up with burps, continues to feed well grows well and thrives with no respiratory or other systemic features is considered to have physiological reflux.

Pathologic reflux or gastroesophageal reflux disease (GERD) is usually significant enough to produce a detrimental physical change, such as poor weight gain, mucosal ulceration, or chronic respiratory symptoms not due to known causes. Gastric regurgitation is seen in two-third of infants while GERD is seen 1 in 300 infants.

Physiology

Factors that contribute to GERD in neonates and infants include, but are not limited to :

- Abnormal physiology of lower esophageal sphincter; non descent of lower end of esophagus into the abdomen, poorly developed crura of diaphragm with defective angulations.
- Limited gastric volume and delayed gastric emptying time.
- Increases in gastric pressure due to abdominal breathing.
- Transient lower esophageal sphincter relaxations.
- Gravitational effects due to positioning.
- Upper or lower esophageal sphincter dysfunction/in-coordination.
- Drugs that are commonly used in newborns that decrease lower esophageal sphincter tone e.g. Xanthines.

Clinical Presentation

Most infants have some reflux in the newborn period, and spitting

or vomiting during the first year of life is common. The neonate with GERD can present with a wide spectrum of presentations such as:

- Frequent vomitings, which may be projectile.
- Effortless drooling of milk from the mouth.
- Feeding intolerance.
- Increased tracheal secretions.
- Hypoxia with desaturation.
- Cyanotic episodes secondary to upper airway obstruction by pharyngeal regurgitation.
- Apneic spell with bradycardia: Instead of a pure obstructive apnea pattern, a mixed pattern of both obstructive and central types generally predominates.
- Recurrent episodes of pneumonia.
- Stridor
- Acute life threatening event.
- Abnormal behaviour and posturing with the tilting of the head to one side and bizarre contortions of the trunk referred as Sandifer's syndrome.
- Esophagitis: Leads to mucosal ulcerations, strictures, vomiting and poor feeding.

Diagnostic Evaluation

As most infants with symptoms of GER are thriving and healthy, they require no diagnostic or therapeutic maneuvers other than a careful history and physical examination, with appropriate reassurance to the parents if anxiety is present. Infants and older children who have significant neurologic deficits or psychomotor retardation often have significant GER and may suffer from serious sequelae secondary to GER.

The diagnostic studies available are :

Upper GI Barium Swallow : This study should be readily performed if history and physical examination suggest that an anatomic obstruction in the intestinal tract is likely.

Specific anatomic intestinal abnormalities that may give rise to symptoms of GER include esophageal strictures, pyloric stenosis;

gastric outlet obstruction from a variety of conditions like gastric web and malrotation; or even more distal intestinal obstruction, such as intestinal web, stenosis or atresia. The barium swallow is a sensitive way of detecting reflux but has a very low specificity rate.

Extended pH monitoring : This is considered as the gold standard for diagnosis (1). Recent research literature cites pH monitoring as 100% sensitive and 94% specific (2). 24 hours monitoring is felt to be necessary to establish an accurate record. Definition of a reflux episode varies from a drop in pH less than or equal to 4 lasting at least 8 seconds (2). to at least 15 seconds (3). Interpretation of pH probe results need to be considered with clinical symptoms and should only be done by a certified Pediatric Gastroenterologist familiar with the infant's clinical history and symptoms.

pH probes are restricted by their ability to detect only episodes that cause a change in the esophageal pH. They are able to detect the frequency of episodes of acid reflux in the distal esophagus, the time it takes for an episode of acid reflux to be cleared and over a given period of time but are unable to determine the volume of reflux material into the distal esophagus. This has allowed standardized norms to be published, which permits one to know how often reflux occurs in a particular age group.

Endoscopy and Esophageal Biopsy : The increased use of small fiber-optic endoscopes in recent years has resulted in many infants and neonates with symptoms of GER undergo an endoscopic procedure. This technique allows direct visualization of the esophageal mucosa and biopsy to determine the severity of reflux esophagitis. It is performed in infants more than 2kg. Its usefulness in diagnosing esophagitis may prelude the need to perform a pH probe study.

Although inflammatory cells, such as lymphocytes and polymorphonuclear cells have been seen in reflux esophagitis, these cells can be observed under normal conditions, and eosinophilic infiltrates have been found to be far more specific indicators of reflux esophagitis in infants (4). However, markedly increased eosinophilic epithelium (>15 eosinophils/hepf) suggest the diagnosis of eosinophilic esophagitis. Eosinophilic esophagitis is commonly associated with milk protein allergy and may not respond well to acid suppressant therapy.

Manometry : Manometric studies are difficult to perform in the un-sedated infant and have proven to be of little clinical use to patients and remain primarily a research tool.

Technetium Scintigraphy : After ingestion of the radionuclide labeled formula/meal, the neonate/infant is placed under a gamma counter. This allows seeing the reflux of the radionuclide into the esophagus and can also detect pulmonary aspiration of radionuclide. It is also possible to calculate how much radionuclide empties from the stomach over a given period of time. This test has the advantages of being noninvasive, low in radiation, and widely available. In practice, however, the value of this test in documenting and quantitating GER is small. The sensitivity is reported to be 59-93% with differences ascribed to techniques.

Table : Advantages/disadvantages of diagnostic procedures for GERD children.

Study	Advantages	Disadvantages
1. Upper GI (Barium)	Readily available	Inadequate screening

	Evaluates upper GI structures	Results-Operator dependent
2. 24hr pH probe	Quantifies reflux Evaluates atypical symptoms monitors therapy	Requires overnight hospitalization Requires special equipment and personnel
3. Endoscopy with biopsy	Evaluates persistent GERD, H.pylori infection, allergic enteropathy	Invasive & requires sedation
4. Technetium Scan	More sensitive than pH probe Picks up pulmonary aspirations	Non physiologic settings Does not rule out anatomic obstructions Cannot quantify GER

Management

Feeding Issues : As in adults, treatment options for pediatric GERD include lifestyle changes, pharmacological and surgery. Conservative medical management refers to positioning, thickening of feeds and small volume feeds. Recent literatures question the efficacy of any of these measures, and generally are performed on infants with mild or suspected GER, who do not have any pathologic disease.

Positioning : The traditional therapy of placing a child in an infant seat to reduce the amount of GER has not been shown to be effective either by clinical observation or by pH probe studies that have quantified the amount of GER. Seated position should be minimized because it provokes reflux by increasing intra-abdominal pressure. A head-elevated prone position resulted in both fewer and briefer episodes of reflux (5) but there is a possible increased risk of sudden infant death syndrome. Therefore, soft bedding material should be avoided in this setting. Medical therapy should be initiated before diagnostic evaluation or vice-versa. The medical therapy should be initiated before diagnostic evaluation or vice-versa. The pharmacological therapy includes prokinetics and antacids.

Metoclopramide and a related agent, domperidone, mildly increase resting lower esophageal sphincter pressure and somewhat increase gastric emptying under many conditions. Domperidone has marginal benefits at best and is not widely used to treat GER during infancy. The dose recommended is 0.2 mg/kg/dose to be given every 6-8 hourly. Metoclopramide has been used much more widely in US; however, few studies have demonstrated its effectiveness in widespread use for treatment of GER during infancy. It has a high range of side effects, the occurrence rate of which ranges from 11% to 34%. Although drowsiness and restlessness are the most common side effects, the most troublesome is an extrapyramidal reaction that seems to occur with increased frequency in children.

Cisapride, a 5HT agonist, is a relatively new agent used to treat GER. The mechanism of action is thought to work primarily by enhancement of release of neurotransmitters, which seem to stimulate smooth muscle contraction throughout the intestinal tract. Most of the side effects observed with cisapride are related to the gastrointestinal tract (abdominal cramps and diarrhea) but it also known to cause fatal arrhythmias. It is of paramount importance to get an ECG before starting the patient on Cisapride and a QTc interval of more than 0.44 is a contraindication to start the drug. Clinical trials suggest that it may have some benefit in treating

GER in infants (7), although results are not dramatically impressive. We give it at a dose of 0.2 mg/kg/dose every 8 hourly. Contraindications to use of cisapride are the use of other drugs that may increase the QTC like erythromycin and antifungals etc. Most side effects reported in literature have been in those babies where very high doses have been given or in those who have underlying cardiac rhythm abnormalities.

Bethanechol, a muscarinic agonist, has been shown to increase basal lower esophageal sphincter pressure in many patients; however, researchers have had difficulty in showing whether it has any effect in reducing GER (8). It has a high frequency of undesirable side effects and it's rarely used in neonates.

Erythromycin, a macrolide antibiotic has been used as a prokinetic agent in the management of GER. Erythromycin has structural similarity to peptide hormone motilin, (9) it increases the motor activity in stomach and intestine. Various studies have shown that this drug is safe and effective in facilitating enteral feeding in newborn babies with feeding intolerance and may also shorten the course of hyper-alimentation. It has been shown to increase the gastric emptying in a dose response manner, its efficacy has been compared with metoclopramide in various clinical studies(10). In GER it has been used in the dosage of 3-5 mg/kg/day in 2-3 divided doses. There has been some anecdotal reports of association of erythromycin with occurrence of hypertrophic pyloric stenosis.(11)

Histamine-2 Receptor Antagonists : Initial H2 receptor antagonist introduced was cimetidine which has been shown to be effective in children with mild to moderate esophagitis. But this drug is associated with adverse effects like diarrhea, tachypnea, bradycardia, granulocytopenia, thrombocytopenia and gynaecomastia. Cimetidine per se as well as one of its metabolite impairs the hepatic clearance of drugs because of its inhibitory action on CYP2D6. Widely used H2 receptor antagonist-ranitidine has fewer overall central nervous system and anti-androgenic side effects. It inhibits both basal as well as stimulated gastric secretions (decreases volume, acid and pepsin content); it is 4-10 times more potent than cimetidine. Very limited data are available regarding pharmacokinetics and pharmacodynamics in newborn period. It has been used in the dosage of 1 to 2mg per kg per dose two to three times daily (2 to 6mg per kg per day). Safety of Ranitidine in children has been well proven but caution is to be exercised in neonates with renal or hepatic impairment. Famotidine has no significant role in management of GERD in childhood population.

Proton Pump Inhibitors (PPI): PPIs are used in infants with recurrent vomiting and failure to thrive, and/or irritability that have not responded to H2-RAs, child with frequent heartburn or chest pain, the child with feeding resistance or dysphagia, the child with asthma, the child with recurrent pneumonia and GERD and the infant with apparent life-threatening Event (ALTE). PPIs decrease acid secretion by inhibition of the H⁺, K⁺, -ATPase in the gastric parietal cell canaliculus and are more potent suppressors of acid secretion than H2-RAs. *Omeprazole*, Cap: 10,20 40 mg, doses 0.7-3.3mg/kg/day; *Lanzoprazole*, Cap: 15,30mg dose 0.4-4mg/kg/day. Medical therapy should be re-evaluated after 2 months

Surgical Treatment of GERD

Surgery should be used, as a last resort in the management of GER, in a baby near term or weighing 2kg. Indications include:

- Recurrent aspiration pneumonia
- Recurrent failures to remain extubated
- Poor weight gain
- Persistent vomiting
- Esophageal bleeding leading to anemia
- Esophageal stricture/ulcerations

Dalt et al¹² reports little success in medical management of GER in infants with pH probe study results of >20 episodes of reflux longer than 5 minutes or reflux time > 27%. The procedure of choice is a Nissen fundoplication. There has been a high incidence of delayed gastric emptying in infants needing fundoplication (13), therefore, a technetium gastric emptying study or milk scan may be considered prior to fundoplication in order to rule out the need for concurrent pyloroplasty.

Success rate based on symptom relief in pediatric patients ranges from 57-92%. Mortality ranges from 0.4-7% and complications range from 2.2-45%. The most common complications are breakdown of fundoplication, small bowel obstruction, gas blot syndrome, infections, atelectasis or pneumonia, perforation, persistent esophageal stricture, and esophageal obstruction.

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Perinatal HIV Infection

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Abstract: HIV infection has become a major public health problem in India. The epidemic has spread from the high risk to the general population. UNAIDS has estimated that about 4 million people were infected with HIV in India by December 2003. Though the extent of pediatric infection is less, perinatal transmission accounts for sizeable number of infections. Various studies in India estimate about 80% of infections are due to perinatal transmission. The risk of perinatal transmission can be reduced from 25% to 1-2% with effective antiretroviral therapy given during pregnancy, peripartum period and to the newborn along with the elective LSCS and no breast feeding for the newborn. More than 50% of the perinatal transmission occurs during the process of delivery, which can be reduced with antiretroviral prophylaxis. US Public Health has laid recommendations for initiation and choice of drugs to be started during pregnancy, depending on when a pregnant mother is diagnosed with HIV infection. The most important determinant of perinatal transmission is the viral load and risk of transmission is negligible if viral load is less than 5000 copies/ml, however the risk is greater than 50% if the viral load is about 750,000 copies/ml. It is advisable for early detection of HIV infection in antenatal period so that an effective antiretroviral therapy may be started in pregnancy.

Introduction

HIV infection in India has become a colossal public health problem to reckon with. The epidemic has spread in the general population and is no longer confined to high-risk individuals as commercial sex workers, truck drivers and intravenous drug abusers.

The extent of the problem can be visualized from the fact that according to UNAIDS already 4 million people are currently infected in India¹. Without proper remedial measures, the epidemic is likely to be the number one killer, surpassing deaths due to tuberculosis, diarrheal diseases and respiratory infections.

Epidemiology

Human immunodeficiency virus (HIV) infection has emerged as a global problem and has already proved devastating in large parts of sub-Saharan Africa and South-East Asia with decrease in life expectancy, lost manpower and a heavy economic and social burden. According to the estimates from UNAIDS, about 42 million people are currently living with HIV infection¹. Out of these 22.4 million (53.33%) are women and children. About 3.2 million children less than 15 years are infected. Five million new infected people have been detected in 2002, women and children accounting for 2.8 million new infected cases.

Since the first case report from Chennai in 1986, there has been an exponential rise in the number of people infected with HIV in India. The infection has penetrated in the general population because of promiscuous sexual activity, infected blood and blood products, illicit intravenous drug abuse and mother to the child transmission. The Indian scenario is very grim. Figures as reported to the National AIDS Control Organization (NACO) till 31st December 1999 show 92,312 infected cases from 3.5 million people who were screened². However, a precise estimate of HIV infection in India is difficult to ascertain. There is a lot of discrepancy in the figures of total number of infected individuals

in India, as given by National AIDS Control Organization (NACO) and UNAIDS. Various sentinel surveys done by NACO have revealed that the about 3.50, 3.70, 3.86 and 3.97 million people were infected in 1998, 1999, 2000 and 2001 respectively². The number of infected cases is likely to rise if the current rate of epidemic continues.

There are two main types of the virus, HIV-1 and HIV-2. Both subtypes of virus have been isolated from the Indian population. In studies in Maharashtra, the distribution of HIV-1 is about 80%, HIV-2 is 20% and dual infection is 4%. The major clade of HIV-1 circulating in India is type C. In the areas bordering Myanmar (Burma), type E is predominant. There are no large studies comparing the relative perinatal transmission rates for HIV-1 and HIV-2 in India. In a study from Gambia, West Africa, the risk of perinatal transmission for HIV-2 was much lower than HIV-1, 24.4% and 4%, respectively. The lower transmission rate of HIV-2 correlated with the lower HIV-2 RNA levels.

While HIV-2 produces a less aggressive course than HIV-1 in adults, there are no detailed studies of the natural history of HIV-2 in children. Similarly, there is paucity of data of treatment response to antiretroviral medications for HIV-2 infection in children. NACO has defined various regions of HIV endemicity based on the seropositivity rate in the pregnant women. High prevalence states have antenatal seropositivity of >1% (Maharashtra, Tamil Nadu, Karnataka & Andhra Pradesh). Moderate prevalence states (Gujarat, Goa & Pondicherry) have HIV seropositivity <1% but the prevalence in high risk group is 5%. The low prevalence states have HIV antenatal seropositivity as <1% and the HIV prevalence in high-risk group is <5%. (HIV sentinel surveillance round 2000, NACO).

Limited data regarding the exact number of pediatric HIV infection cases is available from tertiary care hospitals in Mumbai, Delhi and Chennai. The number of cases of pediatric HIV infection is on the rise due to increasing prevalence of HIV infection in women and ineffective measures for prevention of perinatal transmission. This is primarily due to poor access to antiretroviral medication and safe breast milk substitutes. Pediatric HIV infection

accounts for 20% of all infected cases in the developing countries as compared to 2% in the developed countries³. A study done in Mumbai (B.J. Wadia Hospital) has shown that in the pediatric population, most of the infection is due to perinatal transmission (83.3%). About 14.88% of the infections occurred in thalassemia patients and hemophiliacs who had received infected blood or blood products. The mode of transmission could not be ascertained in 1.86% of the infected children⁴. Another study done at Christian Medical College, Vellore has also reflected that perinatal transmission in 87% of the 88 infected children. Transfusion induced infection occurred in 10% of the children⁵. Similar data has been reported from AIIMS, New Delhi⁶.

Perinatal HIV Transmission

Studies from India and abroad reveal that perinatal transmission of HIV accounts for more than 80% of pediatric cases. Data from USA and some developing countries like Africa have shown that the risk of transmission can be drastically reduced with the use of antiretroviral drugs pregnancy. The risk of transmission in India is approximately 35-40% without zidovudine intervention. In the risk of transmission varies from 16% to 20% in USA and Europe⁷, while in Africa the risk is 25% to 40%⁸.

The transmission from mother to fetus can occur during all stages of gestation, however most of the transmission can occur during the process of labor. Breast-feeding has been associated with further increased risk of about 12-14%. Studies done in Malawi, Africa have shown the risk is higher during first six months of life in breast-fed infants, approximately 0.7% per month compared to 0.3% per month from 12-18 months of age.

Determinants for perinatal transmission

The risk of acquiring HIV infection from an infected mother is determined by factors like the maternal viral load, CD4 count, mode of delivery, breast feeding etc.

Viral load (quantity of the virus) in the maternal blood as determined by RNA-PCR is one of the important factors responsible for the transmission. The risk of transmission is negligible at viral load of 5000 copies/ml. However it increases with a viral load of 30,000 and there is significant risk of transmission. More than 50% of women are likely to transmit the virus of their babies, if the viral load is about 750,000 copies/ml at the time delivery. Various studies have evaluated the role of factors like concurrent maternal sexually transmitted diseases, multiple sexual partners, illicit drug use as other risk factors. The role of vitamin A in prevention of transmission has not been proved in all the studies. Administration of zidovudine during antenatal & perinatal period to the mother and the baby reduces the risk of perinatal transmission. Use of other antiretroviral agents like lamivudine and nevirapine has shown to reduce the perinatal transmission significantly in different studies. Other factors, which have been incriminated for perinatal transmission, are given in the table 1.

Various trials have been done in USA, Europe, Asia and Africa after the successful implementation of ACTG 076 results. Drugs other than zidovudine have been used to decrease the rate of perinatal transmission. Trials done in Thailand, Uganda have shown that the cost factor, can be reduced drastically with short-term therapy of zidovudine or other antiretroviral drugs like lamivudine, nevirapine. Currently it is advisable to initiate a combination of zidovudine and lamivudine in the pregnant mother

Table 1. Potential factors responsible for mother-to-child transmission of HIV.

Maternal factors

Advanced HIV disease, as measured by :

Clinical staging; low CD4 count; High viral load; p24 antigenemia; Primary HIV infection

Primary HIV infection : Viral phenotype-syncytium inducing

coinfection with other sexually transmitted diseases;

First born twins; Obstetric events - vaginal delivery, invasive procedures of fetal monitoring during labor, prolonged rupture of membranes (>4 hours);

Older maternal age;

Cigarette smoking and illicit drug use during pregnancy; Unprotected sexual intercourse with multiple partners

Fetal or placental factors:

Chorioamnionitis; Prematurity; Low birth weight

Labor or birth canal factors :

Cervico-vaginal viral-load; Local HIV specific immune response; Maternal-fetal transfusion of blood

Immune factors :

Neutralizing antibody; Antibody dependent cellular cytotoxicity; Gp 120 V3 loop antibody; MHC concordance

intravenous zidovudine, oral zidovudine may be given. A summary of various perinatal drug trials have been given in table 2.

All the trials have shown that there is an obvious reduction in the rate of perinatal transmission. A regimen based on the time of diagnosis of infection in the pregnant women, compliance, economic

Table 2. Prevention of perinatal HIV transmission - Clinical trials

Trial	Regimen	Transmission
ACTG 076	Antenatal: ZDV 100mg 5 times/day	ZDV 8%
	Peripartum: ZDV 2mg/kg stat, 1mg/kg/hr iv	Placebo 26% (68%)*
	Infant: ZDV 2mg/kg 6 hrly x 6 wk <i>No breast feeding</i>	
Thai trial	Antenatal: ZDV 300mg bid at 36 weeks	ZDV9%
	Peripartum: ZDV 300mg 3 hrly	Placebo 19% (51%)*
	Infant : None <i>No breast feeding</i>	
Ivory Coast	Antenatal: ZDV 300mg bid at 36 weeks	ZDV16%
	Peripartum: ZDV 300mg 3 hrly	Placebo 25% (37%)*
	Infant : None <i>No breast allowed</i>	
PETRA	G-1 Antenatal: ZDV/3TC at 36 weeks	G-1 9% (42%)*
	Postpartum & Infant ZDV/3TC x 1 weeks	
	G-2 Labor: ZDV/3TC	G-2 11% (37)*
	Postpartum & Infant ZDV/3TCx1 week	
HIVNET 12	G-3 Labor: ZDV/3TC	G-3 18%
	G-4 Placebo	G-4 17%
	G-1 Labor : NVP 200mg at onset	G-1 13% (47%)*
	Infant : <i>breastfed</i> , NVP 2mg single dose	
INTRAME	G-2 Labor: 600mg at onset, 300mg 3 hrly till delivery	G-2 25%
	Infant: <i>Breastfed</i> , 4mg bid x 1 week	
	Antenatal: ZDV 300mg bid, starting 36-38 weeks	ZDV 18%
	Labor : ZDV 600mg	Placebo 26%(38%)*
	Postpartum ZDV 300mg bid x 1 week	
	Infant : None, <i>Breastfeeding allowed</i>	

*Efficacy of each trial

ZDV - zidovudine, NVP-nevirapine

G-1-group 1

at 12-14 weeks of gestation. Intravenous zidovudine to be given during labor and delivery and oral zidovudine to the newborn for six weeks in the postnatal period. In case of non availability of

feasibility of sustaining a regimen throughout pregnancy need to be considered before initiation of antiretroviral therapy. The ACTG 076 regimen remains the most frequently used and recommended one.

US Public Health Services (US-PHS) have recommended **treatment guidelines** for pregnant women for prevention of perinatal transmission⁹.

US-PHS Recommendations

- Co-ordinated effort between the obstetrician, clinician, virologist and the patient is essential for reduction in perinatal transmission.
- Identify the infected pregnant women after proper antenatal counselling prior to the testing. Offer various options of treatment depending on the time of gestation.
- Clinical Scenarios and Recommendations for the Use of Antiretroviral Drugs to Reduce HIV-1 Transmission.

Scenario # 1

HIV-1 infected pregnant women who have not received prior antiretroviral therapy.

Pregnant women with HIV-1 infection must receive standard clinical, immunological and virological evaluation.

The three-part ZDV chemoprophylaxis regimen, initiated after the first trimester, should be recommended for all pregnant women with HIV-1 infection regardless of antenatal HIV-RNA copy number to reduce the risk of perinatal transmission.

The combination of ZDV chemoprophylaxis with additional antiretroviral drugs for the treatment of HIV-1 infection is recommended for infected women whose clinical, virological status requires treatment or who have HIV-1 RNA over 1000 copies/ml regardless of the clinical or immunological status.

Women in the first trimester of pregnancy may consider delaying initiation of therapy until after 10-12 weeks' of gestation.

Scenario # 2

HIV-1 infected women receiving antiretroviral therapy during current pregnancy.

HIV-1 infected women receiving antiretroviral therapy in whom pregnancy is identified should continue therapy. ZDV should be a component of the antenatal antiretroviral regimen.

Women should be counseled regarding the benefits and potential risks of antiretroviral administration during this period. If therapy is discontinued during the first trimester, all drugs should be stopped and reintroduced simultaneously to avoid the development of drug resistance.

Scenario # 3

HIV-1 infected women in labor who have no prior antiretroviral therapy.

Several regimens are available, which include :

Intrapartum ZDV followed by six weeks of ZDV for the newborn; Oral ZDV and 3 TC during labor, followed by one week of oral ZDV-3TC for the newborn; a single dose of nevirapine at the onset of labor followed by a single dose of nevirapine for the newborn at the age of 48 hours; and The two dose nevirapine regimen combined with intrapartum intravenous ZDV and six week ZDV for the newborn. In the immediate postpartum period, the women should have appropriate assessments (e.g., CD4+count and HIV-1 RNA copy number) to determine whether antiretroviral therapy is recommended for her own health.

Scenario # 4

Infants born to mothers who have received no antiretroviral therapy during pregnancy or intrapartum period. The six-week neonatal

ZDV component of the ZDV chemoprophylactic regimen may be offered for the newborn. ZDV should be initiated as soon as possible after the delivery-preferably within 6-12 hours of birth. Some clinicians may choose to use ZDV in combination with other antiretrovirals drugs, particularly if the mother is suspected to have ZDV resistant strains.

In the immediate post partum period, the women should undergo appropriate assessments (e.g., CD4+ counts, HIV-1 RNA copy number) to determine if antiretroviral therapy is required for her own health. The infant should undergo early diagnostic testing so that if HIV-infected, treatment can be initiated as soon as possible.

Diagnosis of HIV Infection

Unlike adults it is difficult to diagnose pediatric HIV infection in infants with conventional HIV ELISA or Western blot technique. This is due to the transplacental transfer of maternal IgG antibodies, which reflect in the infant and persist until 15-18 months to age. Thus to confirm a clinical diagnosis other investigations like the HIV DNA or RNA PCR, viral cultures, p24 antigen detection, immunoglobulin estimation and CD4/CD8 counts need to be done for the determination of the immunological staging of the disease.

An early diagnosis is important to see for the outcome of any perinatal intervention therapy, allay the fear and anxiety of parents and initiate antiretroviral therapy at the earliest if the child is infected. In children who are older than 15-18 months the diagnostic criteria as applicable to adults will also hold true. Three positive HIV ELISAs tests done with three different kits or a confirmation with a western blot test or presence of viral RNA or DNA PCR will confirm the diagnosis. Various criteria for diagnosis of perinatal HIV infection have been summarized in table 3.

Table 3. Diagnosis of HIV Infection in Children Younger than 13 Year*

Diagnosis: HIV Infected

Child less than 18 months who is known to HIV seopositive or born to a HIV-infected mother and has positive results on two separate determination (excluding cord blood) from one or more of the HIV detection tests: HIV culture, HIV polymerase chain reaction, HIV antigen (p24)

OR

Meets criteria for AIDS diagnosis based on 1987 AIDS surveillance case definition Child> 18months of age born to an HIV infected mother or any child infected by blood, blood products or other known modes of transmission (e.g., sexual contact) who IS HIV- antibody by repeatedly reactive EIA and confirmatory tests (e.g., Western Blot or IFA)

OR

Meets any of the critteria above

Diagnosis: Perinatally Exposed

Child who does not meet the criteria above who

is HIV seopositive by EIA and confirmatory test (e.g., Western blot or IFA) and who is less than 18 months of age at the time of test

OR

Has unknown antibody status, but was born to a mother known to be infected with HIV

Diagnosis : Seroreverter

Child who is born to an HIV infected mother and who

Has been documented as HIV-antibody negative (i.e. two or more negative EIA tests performed at 6-18 months of age or one negative EIA test after 18 months of age)

and

Has had no other laboratory evidence of infection (has not had two positive viral detection tests, if performed)

and

Has not had an AIDS defining conditon.

*Modified from CDC 1994 revised classification for children less than 13 years of age MMWR 1994;43 (RR-12): 1-19.

Management of HIV Infected Children

There has been a tremendous progress in the medical management of HIV infected children in the affluent countries. Availability of potent antiretroviral medications, and early institution of

chemoprophylaxis and treatment for opportunistic infections have decreased the mortality in HIV-infected children and adults. In resource poor countries, however, the mainstay of therapy is often the treatment of intercurrent bacterial infections, prevention and treatment of opportunistic infections, and nutritional support. Despite these supportive measures, the lack of availability of antiretroviral medications means that the long term mortality due to HIV will remain high. In India, a combination of zidovudine and lamivudine costs approximately Rs. 2000-3000 per month. Protease inhibitors like saquinavir or ritonavir cost an additional Rs.3,000-5,000 per month.

The antiretroviral medications are broadly classified into three categories based on their mechanism of action-nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (Pis). Fusion inhibitors, a newer class of drugs are currently under development and testing. These drugs block the entry of the virus in the normal T-cell. In March 2003, United States FDA approved one of the fusion inhibitors, enfuvirtide (Fuzeon®) for HIV infected adults who have tried other antiretrovirals in the past and have developed resistance or have detectable viremia, in India, not all of these drugs are available. Zidovudine, lamivudine, stavudine, didanosine, nevirapine, indinavir and nelfinavir are being manufactured and marketed by Cipla and Glaxo. Abbott and Nicholas Labs are importing protease inhibitors like saquinavir and ritonavir.

Drug trials with various combinations have been conducted in adults and children. In view of the infant's immature immune system, all infants diagnosed with HIV infection ought to be treated with effective antiretroviral medications⁶. The ideal treatment regimen consists of three antiretroviral drugs, two NRTIs, and a PI, although PI-sparing regimens are increasingly becoming

popular. A PI-sparing regimen consisting of two NRTIs and one NNRTI may be an ideal option in a developing country like India because of its lower cost.

Prior to the initiation of antiretroviral therapy, a complete blood count, T-cell subset (CD4/CD8) study, and serum chemistry need to be done. The viral load, as determined by quantitative PCR, can be used to monitor clinical progression or treatment response, although studies suggest that CD4 counts and/or p24 antigens may suffice in limited resource settings. Additional assessment includes quantitative immunoglobulins, chest roentgenogram, and tuberculin testing. The child may also be evaluated for toxoplasmosis, herpes, rubella and CMV by serologic antibody tests.

The viruses become resistant over time requiring change in therapy. Genetic and phenotypic resistance assays are helpful in selecting the proper combination of therapy. Overall, despite the tremendous advances in HIV therapy, the disease remains incurable, and the long therapies pose problems with compliance, toxicity and tremendous financial burden. Treatment, therefore, needs to be individualized.

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IMSA News

IMSA Chapter Activities (Oct. to Dec. 2004)

Delhi Chapter

- 10.10.2004 : Dr. Mukesh Ajmera, "Stress Testing in IHD".
 : Dr. G. Siripathy, "Hypothyroidism - Diagnosis & Management".
 23.10.2004 : Dr. S.J. Gupta, "A Clinical Meeting".
 16.11.2004 : Dr. A.K. Ajmani, "Diabetes Mellitus".
 14.12.2004 : Dr. Arun Gogna, "Echo Cardiography".
 : Dr. (Lt. Col.) Ashok Rajput, "Bronchial Asthma".

Tamil Naidu Chapter

- 10.10.2004 : Prof. Krishnamoorthy, "Pain and Perception".
 14.11.2004 : Dr. Srimathi, "Common Cardiac Problems Including Myocardial Ischemia and Their Management".
 12.12.2004 : Dr. Mayilvahanan Natarajan, "The Custom Mega Prosthesis - The Answer to the Management of Bone Tumours".
 14.12.2004 : Dr. Krishnamoorthy Srinivas, "Brain, Mind and Music".
 19.12.2004 : **Rural CME Programme**, Dr. R. Kndaiah, "Common Ophthalmic Problems in General Practice and Current Concepts".

Election of Fellows

Fellows elected on 10-11-2004

Dr. (Mrs. Meera (Rupta) Suhas Kulkarni
 Dr. Suhas Panditrao Kulkarni
 Dr. V.P.M. Mushafa
 Dr. Anmol K. Gupta
 Dr. N.K. Sekaran
 Dr. V. Muniappan
 Dr. Govind Chandra Sahoo
 Dr. N. Chidambaram
 Dr. P. Muralidhar
 Dr. S. Viswanathan
 Dr. Roseline Fatima William

Kolhapur
 Kolhapur
 Saudi Arabia
 Shimla
 Chidambaram
 Annamalainagar
 Chidambaram
 Annamalainagar
 Annamalainagar
 Tamil Nadu
 Annamalainagar

Dr. V.U. Shanmugam
 Dr. Satishchandra Marutrao Gaikwad
 Dr. A.K. Grover
 Dr. Sethu Rajan
 Dr. Pas Rajenthiran
 Dr. V. Namachivayam
 Dr. G. Santhanam
 Dr. P.S. Krishna Moorthy
 Dr. C. Dhana Sekaran

Chidambaram
 Mumbai
 New Delhi
 Chidambaram
 Cuddalore
 Cuddalore
 Mayiladuthurai
 Cuddalore
 Chidambaram

Members elected on 10-11-2004

Dr. K.A. Shalini Maya
 Dr. Rajul Rastogi

Chidambaram
 New Delhi

Honours Dr. (Mrs) S. Sachdev, Founder Fellow of IMSA, has been conferred the **Dr. MN Passey Award** for Distinguished Services for the year 2004 in recognition of her outstanding contribution to the advancement of Rheumatology in India. The Award was presented by the Union Minister of State for Home, S. Raghupathy.

Dr. (Mrs.) S. Sachdev, has been conferred the **Life Time Achievement Award for Her Exemplary Accomplishment in the Field of Geriatrics and Gerontology** by INDIAN AGEING CONGRESS 2004, held at All India Institute of Medical Sciences, New Delhi on 7th November, 2004.

IMSA Branch Unit (Sub Chapter) at Muthiah Medical College (Annamalai University) under the IMSA Tamil Nadu Chapter was inaugurated on December 14, 2004 by Hon'ble Member of Parliament (Rajya Sabha) Dr. M.A.M. Ramaswamy, Prochancellor, Annamalai University, under the Chairmanship of Dr. K. Jagadeesan, President, IMSA. See details on page.....

IMSA Branch Unit - Annamalai Nagar, T.N. Chapter

Inauguration

An IMSA Branch Unit (sub chapter) under the IMSA Tamil Nadu chapter was inaugurated by Dr. M.A.M. Ramaswamy, the member of Parliament, (Rajyasabha) and Prochancellor of Annamalai university; Dr. K. Jagadeesan, the President of International Medical Sciences Academy (IMSA) was in the chair Dr. M.A.M. Ramaswamy delivered the inaugural address; he appreciated the aims and objectives of this world organization IMSA and the rural CME programs of the chapters and sub chapters. He stressed the importance of health care delivery at primary health centre levels which should be properly manned and equipped.

Dr. K. Jagadeesan, the president of IMSA in his presidential address highlighted activities of IMSA world over and stressed the value of academic activities and importance of rural CME programme which aims at updating the knowledge of practitioners in rural areas for better health care delivery to the rural folks; thus fulfilling an essential objective of IMSA.

Dr. P.V. Hayavadana Rao was nominated as the chairman of the IMSA branch unit and Dr. Ramesh as the Secretary. Dr. A. Govindan. Hon. Secretary. IMSA TN chapter read the Secretary's Report.

Over 300 doctors attended the inauguration among them were the various faculty members, senate and syndicate members of the university.

The first oration of the IMSA branch unit was delivered by Dr. Krishnamoorthy Srinivas - a noted Neuro Physician on 'Brain, mind & music; Dr. MG. Muthukumarasamy, the former vice chancellor Annamalai University was in the chair.

Secretary's Report

Respected Dr. M.A.M. Ramasamy, Pro-Chancellor, Dr. L.B. Venkatragan, Vice-chancellor, Dr. K. Jagadeesan, President IMSA. Dear Fellows, Ladies and gentlemen

I am proud to be alumni of Annamalai University. Here I have studied Intermediate and BSc from the years 1954 to 58. When Annamalai University celebrated its silver jubilee I was a student. To think of that silver jubilee is joy for ever for me. It is heartening to note that Annamalai University has celebrated its platinum jubilee, recently. I was thrilled to know that this magnificent Annamalai University was established by the great philanthropist, the Raja of chettinad, Dr. Raja Sir M Annamalai Chettiar in the year 1929, i.e. 18 years before we attained independence for India, on a pattern similar to the Cambridge University in many ways.

Many wondered, what had prompted him to establish the University here. As a visionary, as a great lover of fine Arts and Science, very great lover of Tamil language & Tamil Isai and an educationist par excellence had selected this backward area to locate the University probably for the benefit of the people in this region in particular and Tamil Nadu and India at large. Lord Nataraja was always there to bless him. The blocks of big buildings for Science, fine arts, Social Science, Oriental Languages, Agriculture, Engineering, the magnificent Shastri Hall with beautiful garden and a spring pool in front of it spoke of his will and zeal. Raja Sir M Annamalai Chettiar was the custodian of the Tamil Lyal Isai and Natagam and the Isai Kaluri at Annamalai University and the Annamalai Mandrum at Chennai stand testimony to his great interest.

Raja of Chettinad Dr. Raja Sir MA Muthiah Chettiar, then Prochancellor was a fatherly figure to us. As a worthy son of a worthy father having inherited all the qualities and zeal of the great philanthropist he carried on the work left by his great father. Many blocks of buildings and several new courses have been added and converted this University into post graduate University.

it gives us great pleasure to mention that respected Dr. M.A.M. Ramasamy Member of Rajyasabha & the Prochancellor, Annamalai University is continuing the work left by his father and grand father. It is worthy to mention here, a medical college in the name of his father, is to his credit. With his able management many new buildings were built and several new courses and distant education have been started. He is acclaimed to be a great administrator, a great educationist and philanthropist. The location of this University had added colour and importance to the temple city Chidambaram. My humble request to Dr. M.A.M. Ramasamy to use his influence as the Prochancellor of Annamalai University and Rajyasabha member and his personal influence for the early conversion of the meter gauge Railway line into broad gauge from Villupuram to Chidambaram and connecting line to Tanjore so that it would not only develop the town Chidambaram but also the entire region.

We are very fortunate for Dr. M.A.M. Ramasamy has been generous enough to grant us permission to have IMSA Branch Unit at Annamalai University premises and was kind enough to have consented to inaugurate the branch unit.

Dear Friends, we have assembled here for the inauguration of the new **IMSA branch unit**. I am extremely happy to be involved in the formation of the **IMSA branch unit** under IMSA Tamil Nadu Chapter at Annamalai Nagar, the first of its kind in the history of IMSA. The **IMSA branch unit** is being organized as a unit in a chapter of a region under the interpretation of the para (j) on page 7 of the memorandum of Association and Regulations of the constitution of IMSA. We had thought of starting IMSA branches under the IMSA Tamil Nadu Chapter after the annual conference at Cambridge where a decision had been taken to conduct rural CME programs. The work of Rural CME program was our priority which we have started organizing at various places far and near the city of Chennai. So far we have conducted nine CME programs. This is in addition to our regular monthly meetings which we have at K.J. Hospital Auditorium on second Sunday of every month. So far we have conducted 274 monthly meetings without a break. We have achieved this feat because of our strict norms, The speakers are happy with the system. We line up speakers in advance so that no failure occurs.

We have been conducting the activity of the IMSA Tamil Nadu Chapter with annual subscription of Rs.200 which a few fellows only contribute and the 30% of fellowship share money from IMSA HQ. We have to spent about three to four thousand rupees for a monthly meeting and about six to seven thousand rupees for a rural CME. Our financial position is not that sound. But for the support from our president Dr. K. Jagadeesan and K.J. Hospital, the IMSA TN Chapter would have become defunct. Their voluntary and ardent support in every way has kept the IMSA TN Chapter live and active. We owe so much to Dr. K. Jagadeesan and K.J. Hospital.

The work for the formation of the IMSA branch unit under IMSA TN Chapter had been started just before we had started the arrangement of IMSACON-2003. Many fellows in the districts of Tamil Nadu had come forward to take up the task of organizing the IMSA branch unit in their respective districts. Dr. Hayavadana Rao was first to offer and first to succeed. It is because of dynamic nature of Dr. Hayavadana Rao and his sincere work and perseverance, the formation of IMSA branch unit at Annamalai Nagar has become a reality. At the very outset he promised to enroll thirty fellows from Annamalai University and he had kept his promise. Dr. Hayavadana Rao deserves all appreciation; our congratulations to him.

We are extremely thankful to our president Dr. K. Jagadeesan for his help and guidance in the formation of the branch unit. We are immensely grateful to the respected Dr. M.A.M. Ramasamy Pro-Chancellor Annamalai University for having given us permission to start the branch at Annamalai University premises. We are also thankful to Dr. L.B. Venkatragan the vice chancellor of Annamalai University for having agreed to have the branch at Annamalai Nagar.

Hearty welcome to new fellows and members

Long live IMSA.

Thank You all

Dr. A. Govindan
Hon. Secretary

IMSA Tamil Nadu Chapter

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